A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin

Seza Ozen and Yelda Bilginer

Abstract | Autoinflammatory diseases are associated with abnormal activation of the innate immune system, leading to clinical inflammation and high levels of acute-phase reactants. The first group to be identified was the periodic fever diseases, of which familial Mediterranean fever (FMF) is the most common. In FMF, genetic results are not always straightforward; thus, flowcharts to guide the physician in requesting mutation analyses and interpreting the findings are presented in this Review. The other periodic fever diseases, which include cryopyrin-associated periodic syndromes (CAPS), TNF receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), have distinguishing features that should be sought for carefully during diagnosis. Among this group of diseases, increasing evidence exists for the efficacy of anti-IL-1 treatment, suggesting a major role of IL-1 in their pathogenesis. In the past decade, we have started to learn about the other rare autoinflammatory diseases in which fever is less pronounced. Among them are diseases manifesting with pyogenic lesions of the skin and bone; diseases associated with granulomatous lesions; diseases associated with psoriasis; and diseases associated with defects in the immunoproteasome. A better understanding of the pathogenesis of these autoinflammatory diseases has enabled us to provide targeted biologic treatment at least for some of these conditions.

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Introduction

When the gene mutated in patients with familial Mediterranean fever (FMF; MIM 249100) was identified in 1997,[1,2] none could have expected it to start such an exciting chapter in rheumatology. New technologies at the time enabled the rapid discovery of other diseases with similar clinical symptoms but differing genetic bases to FMF and led to the description of the group as autoinflammatory diseases.[3] Autoinflammatory diseases are disorders of the innate immune system; thus, unravelling the molecular pathways in these diseases not only enlightens the pathogenesis of the respective diseases but also improves our understanding of the general mechanisms of inflammation.

Pattern-recognition receptors (PRRs) are crucial in the innate immune response. They recognize exogenous pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) and initiate downstream signalling pathways that regulate the transcription of proinflammatory cytokines mainly via nuclear factor κB (NFκB) and interferon-regulatory factors (IRFs).[4] One important class of PRRs is the NOD-like receptor (NLR) family. One of the NLR molecules, NLRP3, is a crucial element of the NLRP3 inflammasome, a molecular complex that is responsible for the activation of caspase 1 (Figure 1).[4] Activation of caspase 1 through inflammasomes leads to the production of active IL-1β, a potent proinflammatory cytokine. Most autoinflammatory diseases, including FMF, are monogenic diseases caused by mutations of genes that function in this system or in related pathways (Figure 1).

As these diseases are rare, collaborations are required to analyse them in depth. A multicentre registry in Europe, the Eurofever registry, has been established in the hope of determining the general demographics of the main monogenic autoinflammatory diseases that have been defined. Establishing such a large cohort enables statistically robust analyses of phenotype–genotype correlations, complications and response to treatment.[5] About three-quarters of the patients in this registry were from Western Europe,[5] and 76% of the registry patients were children (under 18 years of age).[5] Data obtained from this registry are referred to in this Review as we assess the recent data on these diseases.

Classification

New monogenic autoinflammatory diseases continue to be defined. However, we suggest two possible classification systems: one according to the leading clinical features and the other according to the pathogenesis (Boxes 1 and 2).

We now know that some common diseases are also autoinflammatory in nature but do not have a monogenic inheritance and are therefore classified as polygenic (complex genetic trait) autoinflammatory diseases. Among these conditions are gout, Schnitzler syndrome (although sporadic, acquired cases are also possible),

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S. Ozen declares associations with the following companies: Novartis and Biovitrium. See the article online for full details of the relationships. Y. Bilginer declares no competing interests.

Key points

- Monogenic autoinflammatory diseases can be classified on the basis of their dominating clinical feature (for example, periodic fever) or their pathogenesis (for example, as IL-1 or NFκB activation disorders)
- Among the monogenic autoinflammatory diseases, clinical diagnostic criteria have already been suggested for familial Mediterranean fever (FMF), and we suggest a flowchart to guide requests for mutation analysis of the associated gene
- FMF is an autosomal recessive disease; however, a single mutation, or a clear disease-causing mutation together with a variant with low penetrance, can be associated with the clinical phenotype
- Clinical classification criteria and flowcharts to guide physicians in decision-making and asking for specific genetic testing are also needed for other autoinflammatory diseases
- Anti-IL-1 treatment has shown promising results in many of the autoinflammatory diseases

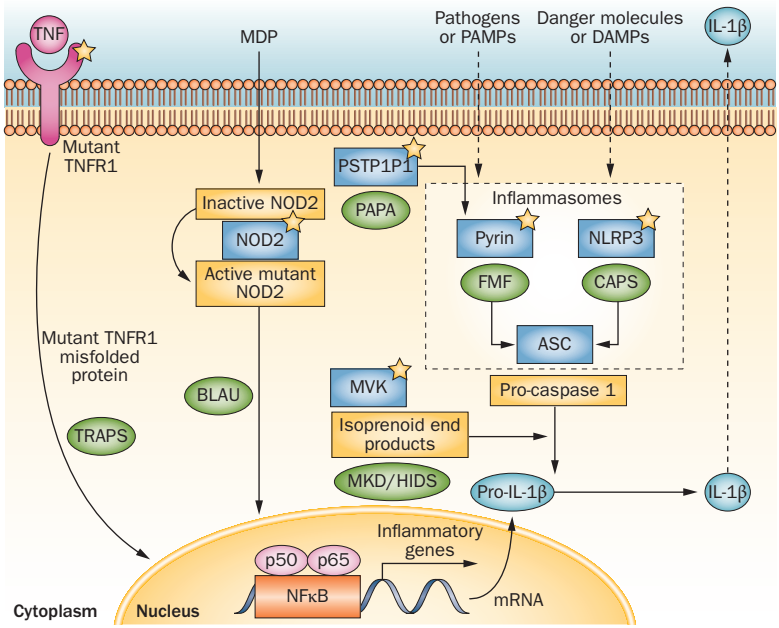

Figure 1 | A schematic showing a simplified view of the pathogenesis of the main monogenic autoinflammatory syndromes. Mutated proteins are denoted by stars, and the terms in green circles denote the diseases with which they are associated. In TRAPS, mutant TNFR1 (misfolded protein) leads to an abnormal inflammatory response through NFκB activation. In Blau syndrome, mutant NOD2 that is activated after stimulation with MDP induces NFκB activation. In FMF, mutant pyrin is suggested to associate with the inflammasome adaptor protein ASC and increase IL-1β processing. In CAPS, activated NLRP3 oligomerizes and interacts with the adaptor protein ASC and caspase 1 to form macromolecular complexes (inflammasomes) that process IL-1β into its active form. In PAPA syndrome, PTSPIP1 has been implicated through its binding to pyrin. In MKD/HIDS, a shortage of nonsterol isoprenoid end products results in increased IL-1β production. Abbreviations: CAPS, cryopyrin-associated periodic syndromes; DAMP, damage-associated molecular pattern; FMF, familial Mediterranean fever; MDP, muramyl dipeptide; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; MVK, mevalonate kinase; NFκB, nuclear factor κB; NLRP, NOD, LRR and pyrin domain-containing protein; NOD2, nucleotide-binding oligomerization domain protein 2; PAMP, pathogen-associated molecular pattern; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PSTPIP1, proline-serine-threonine phosphatase interacting protein 1; TNFR1, TNF receptor 1; TRAPS, TNF receptor-associated periodic syndrome.

Behçet disease, systemic-onset juvenile idiopathic arthritis (JIA), spondyloarthritis, type 2 diabetes mellitus and periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. Polygenic diseases are outside the scope of this Review; however, PFAPA syndrome is discussed as a differential diagnosis.

Periodic fever diseases

Familial Mediterranean fever

FMF is the most common monogenic autoinflammatory disease worldwide,[3,5,6] and has an autosomal recessive inheritance. The gene mutated in patients with FMF is the *MEFV* gene, which encodes pyrin. Pyrin may form part of the NLRP3 inflammasome complex, and mutations in *MEFV* are associated with excess inflammation through increased IL-1β production.[7] Thus, FMF may be classified as an inflammasomeopathy. Pyrin has been suggested to associate with the inflammasome adaptor protein ASC and increase IL-1β processing.[4] On the other hand, however, some findings have indicated that pyrin might act as a negative regulator of inflammasome function.[4,8,9] By contrast, findings from study in mice indicated that gain-of-function mutations in pyrin might exert their effects independently of NLRP3, possibly through another type of inflammasome (Figure 1).[10] As pathogens act as signals that activate this part of the innate immune system, it is not surprising that infections in childhood trigger exaggerated inflammation in patients with FMF, above the level of subclinical inflammation that is present in these patients.[6] Moreover, the finding that sterile activators can provide proinflammatory signals through DAMPs might explain why patients have attacks triggered by stress as well.

Convincing data indicate that subclinical inflammation continues in untreated patients with FMF.[6] This subclinical inflammation underlies the association of FMF with certain rheumatic diseases. Indeed, these patients have an increased propensity to develop diseases such as vasculitides,[6,11] and in the eastern Mediterranean the frequency of *MEFV* mutations (carrier rate) is higher among patients with rheumatic diseases than in the general population.[12,13] Associations have also been shown with two polygenic autoinflammatory diseases: our group has identified an increased carrier rate for *MEFV* mutations in systemic-onset JIA;[14] and Berkun *et al.* have demonstrated an increased carrier rate in PFAPA syndrome.[15]

Epidemiology

FMF is most frequent among people originating from the eastern Mediterranean area, including the Jewish, Turkish, Armenian and Arab populations from this region. In these ethnic groups, the prevalence of FMF is between 1 in 500 and 1 in 1000,[17,18] and *MEFV* mutations are very common, with the carrier rate reaching 1 in 5.[16,12] The disease has spread over the world with the migrations of these populations over the past century.

However, the disease is definitely not confined to these groups. Studies have shown that the disease is not rare among Greeks and Sicilians.[19] Furthermore, the Eurofever registry, which has established a large collection of patients from 76 centres in 31 countries across Europe and the eastern Mediterranean,[5] has identified at least 60 cases of pure European ancestry, with more to be confirmed.[5] European patients with FMF in this

Box 1 | Monogenic autoinflammatory diseases classified by leading clinical features

Periodic fever diseases
FMF (familial Mediterranean fever);
MKD/HIDS (mevalonate kinase deficiency/hyperimmunoglobulin D syndrome);
CAPS (cryopyrin-associated periodic syndromes);
TRAPS (TNF receptor-associated periodic syndrome);
FCAS2 (familial cold autoinflammatory syndrome 2)

Diseases with pyogenic lesions
DIRA (deficiency of IL-1 receptor antagonist);
PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome;
Majeed syndrome

Diseases with granulomatous lesions
Blau syndrome

Diseases with psoriasis
DITRA (deficiency of IL-36 receptor antagonist)

Diseases with panniculitis-induced lipodystrophy
JMP (joint contractures, muscle atrophy and panniculitis-induced lipodystrophy) syndrome;
CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome;
NNS (Nakajo–Nishimura syndrome)

Others
APLAID (PLCγ2-associated antibody deficiency and immune dysregulation) syndrome

Box 2 | Monogenic autoinflammatory diseases alternatively classified by pathogenesis

Defects of IL-1β family regulation
FMF (familial Mediterranean fever);
CAPS (cryopyrin-associated periodic syndromes);
MKD/HIDS (mevalonate kinase deficiency/hyperimmunoglobulin D syndrome);
PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome;
Majeed syndrome;
DIRA (deficiency of IL-1 receptor antagonist)

Diseases linked to NFκB activation
Blau syndrome;
FCAS2 (familial cold autoinflammatory syndrome 2)

Protein-misfolding disorders
TRAPS (TNF receptor-associated periodic syndrome)

Diseases linked to IL-36 regulation
DITRA (deficiency of IL-36 receptor antagonist)

Diseases linked to the proteasome and/or IFN-γ
JMP (joint contractures, muscle atrophy and panniculitis-induced lipodystrophy) syndrome;
CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome;
NNS (Nakajo–Nishimura syndrome)

Others
APLAID (PLCγ2-associated antibody deficiency and immune dysregulation) syndrome

registry display similar features to those in the eastern Mediterranean; however, further evaluation of these patients suggests a less severe disease in patients with a European ancestry.[20] Interestingly, the registry findings also indicate that eastern Mediterranean patients have a milder disease if they have migrated to Europe,[20] clearly indicating that the environment might have an effect on the phenotypic expression of the disease.

In addition to Europeans, 292 Japanese patients with FMF have also been reported.[21] These Japanese patients had the same general features as other patients with FMF, although the age of onset seemed to be later than in eastern Mediterranean patients and the most common *MEFV* mutation genotype was Glu148Gln/Met694Ile (which occurred in 19.8% of cases).[21] We now know that some variants of the *MEFV* gene are also present in other ethnic groups. For example, a carrier rate for the Glu148Gln variant of almost 1 in 5 has been reported in the Chinese and Indian populations.[22,23] The role of Glu148Gln in inflammation and the FMF phenotype is very intriguing, and the high carrier rate in other groups adds a new dimension to this issue (discussed below).

Clinical presentation

FMF usually has a childhood onset. Indeed, in a combined multicentre study of adults and children, the mean ages of onset and diagnosis were reported as 9.6 ± 8.6 years and 16.4 ± 11.6 years, respectively.[11] The age of onset was lower in populations in whom the disease is frequent, probably owing to the increased awareness of the paediatricians in those areas.[5]

FMF is characterized by recurrent attacks that occur at irregular intervals, last 0.5–3 days on average and resolve spontaneously. Fever can sometimes be the only manifestation of an attack, especially in preschool-aged children. Thus, FMF should be considered in the differential diagnosis of all children who present with recurrent fevers. In a study of 2,838 Turkish patients, the cardinal signs and symptoms of FMF and their frequencies were fever (92.5%), peritonitis (93.7%), arthritis (47.4%), pleurisy (31.2%), amyloidosis (in inadequately treated patients; 12.9%) and nonamyloid glomerular disease (0.8%).[11] Patients can also have symptoms that are not related to attacks, such as prolonged myalgia, exercise-induced leg pain, erysipelas-like erythema after exercise and sacroiliitis.[24]

Diagnosis

The developed sets of classification and diagnostic criteria for FMF aid the diagnostic work-up and the decision for genetic testing. The first set of criteria was suggested for adults, and includes major and minor criteria as well as supportive criteria.[25] The four major criteria are typical attacks (defined as ≥3 attacks of the same type, with rectal temperature ≥38 °C, lasting 12–72 h) with any one of peritonitis, pleuritis, monoarthritis (of the hip, knee or ankle), or fever alone. The minor criteria were defined as incomplete attacks, exertional leg pain and favourable response to colchicine.[25] The authors suggested that 1 major or 2 minor criteria, or 1 minor plus 5 supportive criteria, should be satisfied to establish a diagnosis.[25]

We have subsequently attempted to define criteria for children as well.[26] According to these criteria, the presence of at least two of the following characteristics is required for FMF classification: fever (lasting 6–72 h, ≥3 attacks), abdominal pain (lasting 6–72 h, ≥3 attacks), chest pain (lasting 6–72 h, ≥3 attacks, unilateral), arthritis (lasting 6–72 h, ≥3 attacks, monoarthritis), exertional leg pain and family history of FMF. These criteria reached a sensitivity and specificity of 88.8% and 92.2%, respectively, among Turkish children.[26] However, the control group of this study included patients of all ages; if the

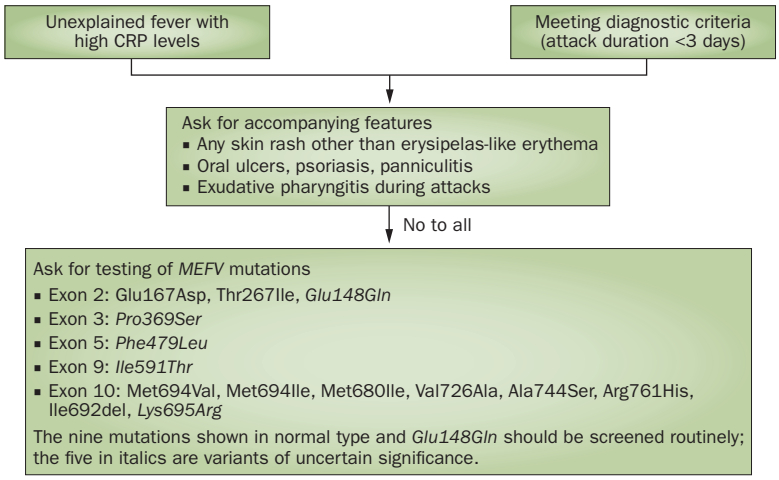

Figure 2 | A flowchart to guide requests for *MEFV* mutation analysis. In a patient with recurrent attacks of <3 days duration and unexplained high CRP levels, a mutation analysis of the *MEFV* gene is indicated, in the absence of skin rash or other features that are suggestive of the other periodic fever syndromes or PFAPA syndrome. Abbreviations: CRP, C-reactive protein; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis. Recommendations revised from Shinar *et al.* (2012).[29]

study group had included a larger proportion of young children with FMF characterized by fever attacks only (without serositis) and more controls with PFAPA syndrome, the sensitivity or the specificity might have decreased. When the paediatric criteria were assessed in French children, the presence of three instead of two characteristics yielded a better specificity of 95%.[27] Validation in a large multiethnic population is underway.

Genetic testing

Although we often claim that the diagnosis of FMF is a clinical one, it is hard to make a clinical diagnosis given the similarities with all the more recently identified autoinflammatory diseases, and the family and the physician often seek confirmation with genetic diagnosis. Moreover, the diagnosis of a child with periodic fever is much more challenging in a multiethnic population than in regions of high FMF prevalence. Thus, the first step is to decide on who to test, and then it is crucial to correctly analyse the genetic data. On the basis of our common practice and literature search, we have defined a recommendation flowchart for *MEFV* screening (Figure 2). This flowchart has proved useful to us in our periodic fever clinic, although it now needs to be tested in individuals of European descent and in multiethnic populations. Such charts are also needed for other monogenic autoinflammatory diseases, to help health authorities and save unnecessary time and cost in the diagnosis of these diseases.

Although not included in our chart, the ethnicity of the patient is also a factor when considering conducting an *MEFV* mutation analysis, given the variation in mutation rates between different ethnic groups, although it is not expected to have an effect on the decision flow after the result of the genetic analysis. A family history of secondary amyloidosis might also be considered in the decision, as studies have shown that this history introduces a substantial risk of amyloidosis for the patient.[28]

Interpretation of genetic test results

The diagnosis of FMF is straightforward in a patient with a suggestive phenotype and a mutation in both *MEFV* alleles. However, decisions are not so straightforward when dealing with patients with ambiguous clinical symptoms and equivocal results from mutational screening. Interpretation of FMF genetic testing is difficult, as there are many common variants as well as rare variants with unknown disease-causing capabilities. A group of molecular geneticists and clinicians working in the field of autoinflammatory diseases met for a 'best clinical practice' workshop in 2011,[29] and subsequently published guidelines for reporting the genetic results and definitions for clinical significance.[29] A revised flowchart for recommendations according to the genetic results is presented in Figure 3. These recommendations are based on the assumption that the patient already had symptoms that led you to suspect FMF, at least unexplained fever attacks.

Two different pathogenic mutations are as definitive as a homozygous mutation. However, one has to check whether these mutations have ever been reported in *cis* (that is, whether they can occur on the same allele). If they have been previously reported in *cis*, one needs to ask for parental testing of at least one of the parents, to see whether these single-nucleotide polymorphisms (SNPs) are from different alleles (one from each parent) (Figure 3). The mutation associated with the most severe disease course is Met694Val. In some cases, interpretation of the genetic tests on *MEFV* is still complicated, despite the recommendations, and experts might need to be consulted.

Another point to consider is the mutations and variants of uncertain significance. Whether these variants, such as Glu148Gln, cause the FMF phenotype remains controversial. Although Glu148Gln results in an amino acid substitution, it is present in >1% of the healthy population and is known to have a low penetrance, suggesting that it might be a polymorphism.[16] However, occasional reports have described patients homozygous for Glu148Gln who have an FMF-like illness.[30,31] Furthermore, when patients carry an uncertain variant together with a clearly pathogenic mutation (such as Met694Val) on the other allele, they often do display the FMF phenotype. It is also noteworthy that these *MEFV* variants have been identified at increased frequencies in the context of other inflammatory and/or rheumatic diseases.[13,32] Thus, it has been suggested that these variants can be classified as susceptibility alleles to inflammation but are not causal of typical FMF.[33] If colchicine is started, we recommend that patients in the third and fourth arms of Figure 3 are re-evaluated for their diagnosis after 6 months.

Approach to a patient with only one mutation

Given the autosomal recessive inheritance of FMF, a patient with only one mutation is a carrier and should not display the disease phenotype. However, we fail to define the second mutation in at least 20% of patients.[28,34–36] Much debate has focused on how a genetic carrier can express the phenotype. Two elegant studies have addressed the possible explanations for this conundrum.[34–36] These

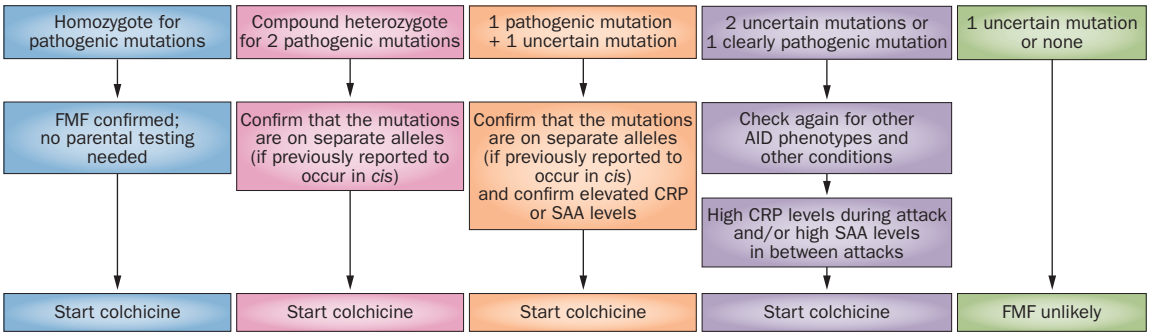

Figure 3 | Algorithm to guide diagnosis and treatment decisions after *MEFV* genotype analysis. In patients homozygous for an FMF-associated mutation (first path), disease is confirmed and treatment should be initiated. Compound heterozygotes for pathogenic mutations known to be on separate alleles should be treated in the same manner (second path). If one of these variants is of unknown significance, further clinical confirmation—high CRP levels during attacks and/or high SAA levels in between attacks—is required before starting colchicine (third path). If two variants of unknown significance are reported or if there is only one clearly pathogenic mutation, one needs to carefully reconsider other periodic fever syndromes as well as testing acute-phase reactant levels (fourth path). Finally, if only one variant of uncertain significance has been reported, FMF is unlikely (final path). Patients in the last three paths should be re-evaluated after 6 months. Abbreviations: AID, autoinflammatory disease; CRP, C-reactive protein; FMF, familial Mediterranean fever; SAA, serum amyloid A. Recommendations revised from Shinar *et al.* (2012).[29]

studies have ruled out several possible explanations, such as loss of expression of one allele, additional mutations, large genomic deletions, duplications, or interactions with several relevant proteins.[35,36] It is tempting to speculate that a single mutation can cause unexpected inflammation in the setting of a number of polymorphisms in genes encoding relevant proinflammatory proteins or cytokines.[34]

Clinically, a patient with periodic fever and only one mutation can be challenging, especially in countries with multiethnic populations. A thorough clinical evaluation for other monogenic and polygenic autoinflammatory diseases is warranted (see below). If any features suggestive of these diseases are present, further genetic analyses of the respective genes are recommended. If not, our practice is to start colchicine treatment if C-reactive protein (CRP) or serum amyloid A (SAA) levels are elevated during the attack-free period and typical attacks are described (Figure 3). However, in selected cases, a trial of colchicine might be indicated by the demonstration of high levels of acute-phase reactants during an attack, without requiring high levels in between attacks.

Treatment and management

The treatment of patients with FMF is aimed at suppressing the inflammation, as indicated by laboratory measures such as CRP levels, and providing an acceptable quality of life. Uncontrolled studies have provided us with grade II evidence that colchicine is efficient in preventing the development of amyloidosis in the majority of the patients who are compliant with the drug.[28,37] Indeed, the mainstay of treatment for FMF is colchicine, which is effective not only in controlling the attacks but also in preventing secondary amyloidosis.

The management of these patients also requires the adjustment of the dose to prevent adverse effects during this life-long treatment. In 2007, we held a consensus conference based on a literature review for the use of colchicine with respect to its indication, efficacy, mode of application, and safety in children and adolescents with FMF.[38] It was agreed that 0.5 mg per day should be used as a starting dose for children <5 years of age, 1 mg per day for children between 5 and 10 years of age, and 1.5 mg per day for children >10 years of age.[38] However, the dose needs to be adjusted according to the clinical symptoms and CRP or SAA levels in between attacks. The main adverse effects of colchicine are diarrhoea and gastrointestinal intolerance. Rare adverse effects include liver dysfunction, leukopenia and neuromyopathy.[39] The dose needs to be adjusted in patients with renal or liver failure. Other medications can affect the metabolism of colchicine either by inhibiting cytochrome P450 3A4 (particularly in the case of clarithromycin) or by disrupting the efflux pump ATP-binding cassette subfamily B member 1 (ABCB1).[39,44] Thus, drug interactions should also be checked to avoid increasing the toxicity of colchicine.[39]

The follow up of patients with FMF should include the management of possible complications that arise from chronic inflammation. For example, quality of life will be impaired in patients with frequent attacks, and thus depression might ensue. In untreated patients, uncontrolled inflammation can result in splenomegaly, growth retardation, decreased bone density, premature atherosclerosis and, ultimately, secondary amyloidosis.[40] Frequent attacks might also lead to female or male infertility owing to adhesions in reproductive organs.[39]

Patients with FMF should also be followed up for the efficacy of the treatment, dose adjustment, complications, and possible adverse effects. Young children should be seen twice yearly, whereas annual visits might suffice in older children and adults. An activity score has been developed to assess these patients, and the development of severity scores is underway.[41] On a practical level, treatment aims to stop or drastically reduce attacks and normalize levels of acute-phase reactants. Although we do

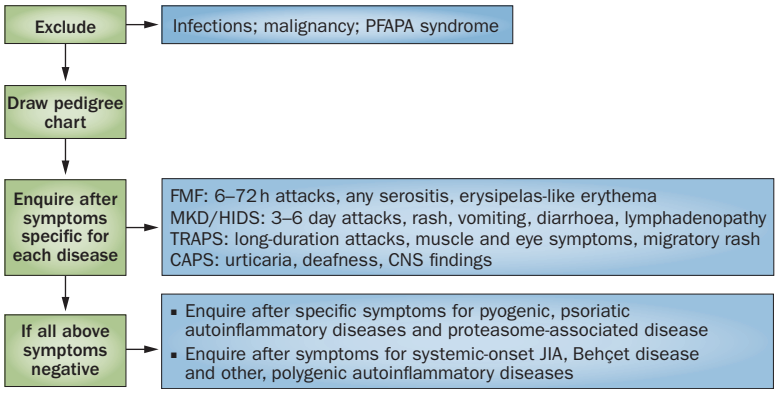

Figure 4 | Differential diagnosis in a child referred with fever. The first step is to exclude infections, malignancies and PFAPA syndrome (see main text for symptoms of PFAPA syndrome). Then one needs to draw a pedigree chart to define the manner of inheritance. If a hereditary periodic fever disease is suspected, the differentiating features of each should be considered. If no specific features are met, one needs to consider the polygenic autoinflammatory diseases such as systemic-onset JIA or other newly identified rare diseases. Abbreviations: CAPS, cryopyrin-associated periodic syndromes; CNS, central nervous system; FMF, familial Mediterranean fever; JIA, juvenile idiopathic arthritis; MKD/HIDS, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; TRAPS, TNF receptor-associated periodic syndrome.

not yet have a validated definition of resistance, patients with FMF are considered to be resistant to colchicine if they continue to have >1 attack per month and have elevated CRP and SAA levels in between the attacks (during the attack-free period).[42] In addition to CRP and SAA, S100A12 might also serve as a biomarker for monitoring disease activity, although commercial tests for this molecule are not widely available.[43] An important point to consider is the compliance to treatment of the patient. In fact, a study has shown that >40% of adult patients fail to take their medication.[44] Thus, one has to make sure of compliance before defining resistance. In patients resistant to colchicine, anti-IL-1 treatment has proven beneficial in suppressing clinical and laboratory measures of inflammation.[42,45–47] Indeed, in two small series reported in 2011, five and seven patients were treated with anakinra (a recombinant form of IL-1 receptor antagonist) and/or canakinumab (an anti-IL-1β monoclonal antibody), and the drugs were effective in all patients.[42,46] Moreover, rilonacept (IL-1Trap) was subsequently shown to reduce the frequency of attacks compared with placebo in a crossover study of ten patients.[45] In our experience, corticosteroids can also be beneficial during FMF attacks.

Differential diagnosis

A child with fever should initially be investigated for infections (Figure 4). Recurrent severe and/or opportunistic infections would lead one to consider immunodeficiencies. Recurrent fever can also be the leading manifestation of a malignant disease, such as the most frequent malignancy of childhood, leukaemia. On the other hand, the differential diagnosis of a child with suspected FMF includes all the monogenic diseases summarized in Box 1. In dealing with diseases that are rare in the patient's population, it is important to start the differential diagnosis with a pedigree to search for familial cases and define the mode of transmission. If the inheritance suggests an autosomal recessive route, one should consider FMF, mevalonate kinase deficiency/hyperimmunoglobulin D syndrome (MKD/HIDS), Majeed syndrome, deficiency of IL-1 receptor antagonist (DIRA), and joint contractures, muscle atrophy, and panniculitis-induced lipodystrophy (JMP) syndrome, and search for the clinical features of these diseases. If a dominant route is likely, one would consider TNF receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, familial cold autoinflammatory syndrome 2 (FCAS2), and Blau syndrome, and enquire after the clinical features of these diseases. In fact, these diseases do have distinguishing clinical features that would justify a specific genetic analysis (see below).[3,24]

When questioning a patient with periodic fevers, it is practical to start checking for the distinguishing symptoms of various periodic fever diseases, including urticaria or neurological symptoms for CAPS, lymphadenopathy, vomiting and non-urticarial rash for MKD/HIDS, and long-duration attacks as well as eye symptoms in TRAPS (Figure 4).[48] Subsequently, it is essential to enquire after the characteristic features of specific groups of autoinflammatory diseases, including pyogenic lesions, panniculitis and psoriasis. Occasionally, one might also need to consider systemic-onset JIA and Behçet disease. Moreover, in preschool children, paediatricians specifically need to consider PFAPA syndrome. As discussed below, it can be quite difficult to differentiate PFAPA syndrome from FMF, and from the other autoinflammatory diseases.

Cryopyrin-associated periodic syndromes

CAPS are definitely some of the most interesting autoinflammatory periodic fever diseases. The term CAPS encompasses three diseases: familial cold autoinflammatory syndrome (FCAS; MIM 120100), Muckle–Wells syndrome (MWS; MIM 191900) and neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic cutaneous articular [CINCA] syndrome; MIM 607115).[49–51] All three are associated with mutations in *NLRP3*. NLRP3 is a key protein of the NLRP3 inflammasome, which can activate caspase 1. Several stimuli can gain access to the cytoplasmic NLRP3 inflammasome and trigger its activation. Activated NLRP3 oligomerizes and interacts with the adaptor protein ASC and pro-caspase 1, resulting in the enzymatic activation of caspase 1, which in turn converts pro-IL-1β to its mature form.[4] The reader is referred to an excellent review for understanding the mechanisms of inflammasome activation.[4]

Clinical presentation

The common symptoms observed in patients with CAPS are fever, urticarial rash (Figure 5), musculoskeletal symptoms, high levels of acute-phase reactants, and conjunctivitis. Among the three diseases, FCAS is the mildest in the clinical spectrum. It is characterized by

cold-induced episodes of inflammation, associated with fever, chills, urticaria and joint symptoms, and sometimes accompanied by conjunctivitis, that last <2 days. The quality of life is good in most cases if cold is avoided, and the condition might not necessitate lifelong treatment.[48] However, a survey of 30 patients reported by Stych and Dobrovolony suggested that FCAS has lifelong debilitating effects that restrict patients' lives, such as impaired job advancement.[53]

Patients with MWS present with fever, urticarial rash and arthritis, as well as subsequent hearing loss, and often also have eye manifestations, namely conjunctivitis and episcleritis. In addition, amyloidosis develops in one-quarter of patients with MWS.[49] The spectrum of presentation of MWS can vary: patients can have more intense attacks and earlier hearing loss or can present with vague symptoms that would be hard to differentiate from FMF and MKD/HIDS if not for the presence of urticaria.

NOMID is one of the most severe monogenic autoinflammatory diseases. It has a more chronic and persistent course than FCAS and MWS, rather than clear-cut episodes. Patients display ongoing fever, continuous rash (Figure 5), optic disc oedema, uveitis, abnormal bony overgrowth of the knees, and a variety of central nervous system (CNS) manifestations. The CNS features can vary, but include severe headaches, chronic meningitis, hydrocephalus, mental retardation, hearing loss and lymphadenopathy.[50,51] Mortality is high in untreated patients.[5,48]

Diagnosis

When clinical features suggest a diagnosis of CAPS, a mutation analysis of the *NLRP3* gene should be requested to provide genetic confirmation. Routine genetic testing should screen the common mutations in exon 3. The same mutation can be associated with different forms of CAPS, and thus genetic testing may not be able to distinguish between FCAS, MWS and NOMID.[51,54] Gain-of-function missense mutations in *NLRP3* have been identified in the majority of patients with CAPS.[4] Unfortunately, however, a substantial proportion of patients fail to display the defined mutations.[52] In this case, the diagnosis mainly relies on the clinical features, although no validated criteria have been developed so far. One study has indicated that a low level of *NLRP3* mosaicism might explain the aetiology in mutation-negative patients, and thus mosaicism might need to be assessed in selected cases.[52]

Treatment and management

Elucidation of the role of IL-1 in the pathogenesis of CAPS has led to specific treatment with anti-IL-1 drugs.[54] In fact, randomized placebo-controlled trials show a clear beneficial role of anti-IL-1 treatment in CAPS for the control of clinical features and laboratory-assessed inflammation.[54–56] Moreover, analyses of data from the Eurofever registry have shown that IL-1 inhibitors are the first treatment option in most centres and that 70% of patients respond to anti-IL-1 treatment.[56] These patients might also need specific treatment for their hearing defects and complications of CNS involvement, such as hearing aids or shunt surgery, although early treatment might enable the prevention of such permanent defects.

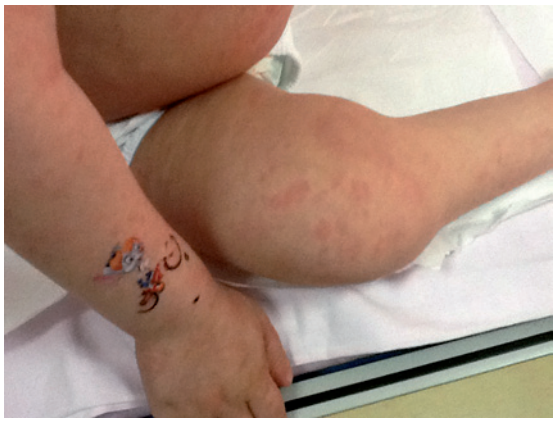

Figure 5 | Urticarial rash of a patient with neonatal-onset multisystem inflammatory disease.

TNF receptor-associated periodic syndrome

TRAPS (MIM 142680) is an autosomal dominant disease that was first reported in a large family of Irish/Scottish ancestry and was originally named Hibernian fever.[57] Recognition of the molecular basis of the disease and the description in different ethnic groups led to the introduction of the term TRAPS.[58]

TRAPS is caused by mutations in the *TNFRSF1A* gene encoding TNF receptor 1 (TNFR1).[58] To date, 75 mutations have been suggested to be associated with TRAPS.[59,60] Approximately 50% of these mutations affect highly conserved cysteines and other conserved residues that are important for maintaining the secondary structure of the TNFR1 extracellular domain.[4] These mutations resulting in cysteine substitutions demonstrate a higher penetrance than the other identified mutations and are usually associated with a more aggressive disease and an increased risk of renal amyloidosis. Other identified mutations in patients with TRAPS include those causing Arg92Gln and Pro46Leu amino acid substitutions; however, these mutations also occur in 1–3% of asymptomatic individuals.[4] Pro46Leu seems to be a benign polymorphism, whereas Arg92Gln behaves as a variant of incomplete penetrance and results in atypical attacks of shorter duration.[61]

TNF is a major cytokine involved in systemic inflammation. Although it had originally been proposed that reduced proteolytic cleavage of the soluble extracellular domain of TNFR1, causing impaired receptor shedding, was responsible for the pathogenesis of TRAPS, data now suggest that additional or alternative mechanisms could be involved.[4,62] Indeed, it is now proposed that an abnormal oligomerization or misfolding of TNFR1, leading to retention in the endoplasmic reticulum (ER), decreased binding to TNF, ligand-independent signalling and a reduction in TNF-induced apoptosis, underlies the pathogenesis of the disease (Figure 1).[4,56] Increased activation of proinflammatory mitogen-activated protein kinases (MAPKs) secondary to stress-induced overproduction

of mitochondrial oxygen species has also been demonstrated.[63] Furthermore, failure of mutant TNFR1 to be localized at the plasma membrane is associated with TNFR1 accumulation and aggregation both in cell lines *in vitro* and in peripheral blood mononuclear cells.[64] As autophagy is suggested to be the only mechanism effective in the clearance of TNFR1 aggregates, it has been suggested that this process is overwhelmed by the TNFR1 aggregation,[64] and the resulting autophagy defect might underlie the TRAPS-associated induction of NFκB and trigger innate immune responses and excessive IL-1β secretion, leading to chronic inflammation.[64] In addition, it has been reported that increased levels of the ER stress response protein X box binding protein 1 together with high reactive oxygen species (ROS) generation might contribute to the proinflammatory state associated with TRAPS.[65]

Clinical presentation

TRAPS is characterized by prolonged attacks of fever and inflammation with serosal, synovial, cutaneous, muscular, abdominal and ocular manifestations.[66] The age of onset is variable, ranging from infancy into adulthood, but tends to be in early childhood. TRAPS attacks usually last 1–4 weeks and recur at least 2–6 times each year. These recurrent inflammatory episodes occur either spontaneously or after minor triggers, such as stress.

Muscle involvement in TRAPS is frequent, and is characterized by muscle cramps or myalgia that migrates in a centrifugal pattern.[66] The most common skin manifestation is a migrating erythematous rash, which usually appears on an extremity. Urticaria-like lesions, plaques and patches can also be observed. Abdominal pain can be severe, and pleurisy, scrotal pain, arthritis, arthralgia and pericarditis can also be observed during attacks. Ocular inflammation is another common feature, with periorbital oedema or conjunctivitis.[58,68] Levels of acute-phase reactants are often elevated in patients with TRAPS even between fever attacks. The long duration of attacks, together with the skin and eye manifestations, are the features that distinguish TRAPS from FMF.[56,66–68] For confirmation of the diagnosis, genetic testing of the *TNFRSF1A* gene is suggested.

Treatment and management

The treatment of TRAPS depends on the severity of the disease. For some patients with mild disease and reasonably infrequent attacks, use of corticosteroids on demand (during the attacks) can be an option.[56] Inflammatory attacks usually respond to corticosteroid administration, but often require progressively higher doses over time, and steroid withdrawal is difficult in these patients owing to frequent relapses or continuous symptoms. Anti-TNF therapy with etanercept, a recombinant human TNFR2–Fc fusion protein, has been regarded as the treatment of choice.[70] By contrast, the administration of other anti-TNF agents might lead to exacerbation of the disease.[69] Etanercept has been reported to be effective in 87% of patients in the Eurofever registry.[56] However, a decrease in responsiveness to etanercept over time has been described.[71] Thus, a substantial proportion of patients need to switch to anti-IL-1β therapy.[72] Anakinra has been shown to induce a stable disease remission in a study of five patients with TRAPS.[72] Furthermore, the anti-IL-1β monoclonal antibody canakinumab has also produced rapid clinical and serological benefits.[73]

MKD/HIDS

MKD/HIDS (MIM 260920) is an autosomal recessive autoinflammatory disease caused by mutations of the *MVK* gene, which encodes mevalonate kinase, an enzyme involved in cholesterol and isoprene biosynthesis.[74,75] Isoprenes are involved in a variety of cellular functions, and the pathogenic mechanism leading to autoinflammatory disease remains poorly understood. Depending on the level of residual MVK activity, the clinical spectrum ranges from mild forms of disease to lethal forms of mevalonic aciduria. Although it has been suggested that inflammation in MKD is related to elevated mevalonic acid levels, a shortage of nonsterol isoprenoid end products has also been shown to result in a caspase-mediated increase in IL-1β production.[75–77]

Clinical presentation

MKD/HIDS is characterized by recurrent episodes of inflammation with high spiking fevers and a variety of symptoms that can include abdominal pain, skin rash, diarrhoea, vomiting, aphthous ulcers, arthralgia and lymphadenopathy lasting ~3–6 days. The onset is very early in life, often in infancy. Attacks are precipitated by immunizations, surgery, trauma and infections. Headache, cervical lymphadenopathy and splenomegaly are common features of MKD/HIDS. The skin manifestations observed during the attacks are erythematous macules that can be painful.[76,78,79] However, many types of rash, such as diffuse maculopapular, nodular, urticarial and morbilliform rashes, have been reported.[79] In a series of 50 patients with MKD/HIDS, recurrent and/or severe pulmonary or ear, nose and throat diseases were observed in one-quarter of cases, suggesting susceptibility to bacterial infections.[80] In addition, secondary amyloidosis has been reported in two patients.[81]

Most patients have increased levels of IgD (over three times the upper limit of the normal range) both during the fever episodes and under basal conditions, but 20% of patients show no increase in IgD levels. Furthermore, IgD levels are normal in very young infants with MKD/HIDS; thus, the name 'hyperimmunoglobulin D syndrome' is not completely appropriate. Moreover, the level of IgD is not related to the severity of the disease.[82,83] By contrast, the increased urinary excretion of mevalonic acid during attacks can be used as a diagnostic tool and regarded as a biomarker for these patients. Thus, MKD/HIDS is the only autoinflammatory disease in which a laboratory test other than genetic screening is useful.

Treatment and management

Fever attacks in patients with MKD/HIDS usually respond dramatically to corticosteroids. Some patients might need continuous therapy, but treatment on demand

(during attacks) is also recommended.[56] In patients with severe disease, anti-TNF and anti-IL-1 treatments have been used.[84,85] Indeed, in the Eurofever registry, etanercept has been reported to be effective in 51% of patients, whereas 80% responded to anakinra.[56] Furthermore, as the mutant enzyme in MKD/HIDS is involved in the cholesterol and isoprene pathway, statins have been used for treatment; however, the treatment results with statins have not been impressive.[56]

Familial cold autoinflammatory syndrome 2

FCAS2 (MIM 611762) is much rarer than the four diseases discussed above. The causative mutations have been defined in *NLRP12* (also known as *NALP12*), which encodes another member of the NLR family.[86] The clinical features of these patients somewhat resemble FCAS. The reported patients describe attacks of fever and arthralgia lasting 2–10 days that are induced by exposure to cold. Some attacks can be accompanied by urticaria, abdominal pain and lymphadenopathy, and hearing loss has been observed in at least two patients. CRP levels are normal between episodes.[86,87]

Diseases with pyogenic lesions

Deficiency of IL-1 receptor antagonist

DIRA (MIM 612852) is an autosomal recessive disease associated with excessive IL-1 activity.[88] Only a few families with the condition have been reported so far. The identification of *IL1RN* (which encodes IL-1 receptor antagonist) as the associated gene was achieved through a remarkable international collaboration. The mutations in *IL1RN* result in a truncated protein that is not secreted; thus, in the absence of IL-1RN-meditated inhibition, responsiveness to IL-1β is increased.[88]

Clinically, DIRA is characterized by pustular skin lesions, together with bone lesions. The pyogenic bone lesions are in the form of osteomyelitis or periostitis.[88] Some of the reported patients experienced marked joint pain and swelling, and one had cerebral vasculitis. However, unlike in the diseases described above, fever has not been observed in patients with DIRA.

Treatment with anakinra has resulted in a dramatic response of the skin and other features in the few patients studied.[54] Lifelong treatment is required, however, and thus daily injections of anakinra might pose a problem because of the pain at the injection site.

PAPA syndrome

PAPA syndrome (MIM 604416) is associated with mutations in the gene encoding proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1; also known as CD2BP1), which interacts with pyrin.[89] Two mutations (Ala230Thr and Glu250Gln) have been identified. Increased IL-1β production is evident, as demonstrated in peripheral blood leukocytes from a patient with clinically active PAPA syndrome caused by the Ala230Thr PSTPIP1 mutation and in cell lines transfected with both PAPA-syndrome-associated mutants.[89]

PAPA syndrome is inherited through an autosomal dominant route.[89] The disease is clinically characterized by pyogenic arthritis, pyoderma gangrenosum and acne. The pyodermic lesions can be disturbing and have a great impact on the quality of life of the patients. With regard to treatment, at least a partial response has been observed in the few patients treated with anti-TNF and anti-IL-1 therapies.[56,90]

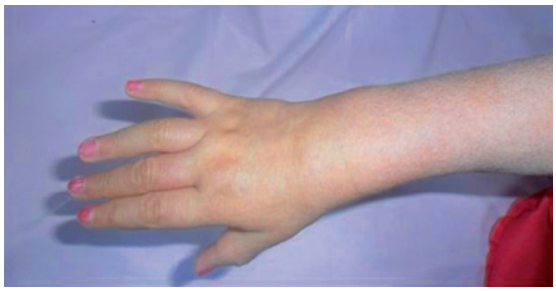

Figure 6 | Typical boggy arthritis of a child with demonstrated mutations for Blau syndrome.

Majeed syndrome

Majeed syndrome (MIM 609628) is the autosomal recessive form of chronic recurrent multifocal osteomyelitis (CRMO). Homozygous mutations in the gene encoding the phosphatidate phosphatase LPIN2 have been identified in affected individuals from two families.[91]

Clinically, patients manifest with inflammation of the bone and skin, recurrent fevers and dyserythropoietic anaemia.[91] Treatment approach is similar to that for CRMO. In addition, anti-IL-1 treatment was reported to be effective in Majeed syndrome, supporting the importance of IL-1 in the sterile bone inflammation.[92]

Diseases with granulomatous lesions

Blau syndrome

Blau syndrome (also known as early-onset familial sarcoidosis; MIM 186580) is an autosomal dominant disease caused by mutations in the gene encoding the NLR family protein NOD2 (also known as CARD15) (Figure 1).[93] Clinically, the condition is characterized by the triad of dermatitis, granulomatous uveitis and arthritis (which is often symmetrical) (Figure 6).[94] The age of onset is early, typically before 3 to 4 years of age. The characteristic arthritis involves a thick granulomatous tenosynovitis, causing a boggy appearance. In addition, fever and other organ manifestations have been reported.[94] Blau syndrome and early-onset sarcoidosis constitute the familial and sporadic forms of the disease, and thus the term paediatric granulomatous arthritis has been proposed for both conditions.

Blau syndrome is another rare disease; thus, we lack evidence for effective treatment. However, studies have suggested a clear beneficial effect of anti-TNF (infliximab) and anti-IL-1 treatment in a few patients.[95,96]

Diseases with psoriasis

Deficiency of IL-36 receptor antagonist

Deficiency of IL-36 receptor antagonist (DITRA; MIM 614204) is an autosomal recessive autoinflammatory disease characterized by generalized psoriasis that was

defined in 2011.[97] The identification of DITRA as an autoinflammatory disease adds a new dermatological feature—psoriasis—to the range of manifestations observed in patients with these conditions.

DITRA is associated with mutations in the gene encoding IL-36 receptor antagonist (IL-36RN), a protein that inhibits proinflammatory IL-36 signalling. IL-36 is a member of the IL-1 family and might have a role in the innate immune response to pathogens.[97] The mutation affects both the stability of IL-36RN and its interaction with its receptor, IL-1 receptor-like 2.

Patients with DITRA, in contrast to those with DIRA, have a high-grade fever and general malaise during an attack. However, the disease mainly affects the skin, and its hallmark is pustular psoriasis.[97] The reported patients have flares of typical skin eruption rapidly covered with pustules, together with fever and elevated CRP levels. The age of onset has varied among the reported patients, even within the same family.[97]

Diseases with panniculitis-induced lipodystrophy

The identification of the group of diseases with panniculitis-induced lipodystrophy (MIM 256040) has again introduced a completely new set of symptoms for diseases associated with autoinflammation, as well as a new pathogenic basis. The diseases described above are caused by defects in the production or downstream signalling of IL-1 family members or TNF, which are key cytokines of the innate immune system. By contrast, in the diseases with panniculitis-induced lipodystrophy, interferon-γ (IFN-γ) is the crucial mediator. These syndromes are caused by mutations in the gene encoding the immunoproteasome subunit PSMB8. Such mutations seem to result in an abnormal accumulation of ubiquitylated protein aggregates, leading to increased cellular stress and sensitivity to apoptosis.[98]

The spectrum of disease associated with *PSMB8* mutations comprises three conditions: JMP syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, and Nakajo–Nishimura syndrome.[99] The disease was initially described as 'joint contractures, muscle atrophy, microcytic anaemia, and panniculitis-induced lipodystrophy',[100] and Liu *et al.*[101] subsequently expanded this description of JMP syndrome in children and termed it CANDLE syndrome. These immunoproteasome-related diseases have some differences. JMP syndrome is described in adults and manifests with joint contractures, muscle atrophy and panniculitis-induced lipodystrophy.[100] By contrast, CANDLE syndrome has a childhood onset (that can be during the first year of life), and patients present with fever as well as neutrophilic dermatosis with a mononuclear interstitial infiltrate comprising 'immature' neutrophils in the dermis that seems to be pathognomonic for this disease.[100,101] Other features of CANDLE syndrome include purpuric skin lesions, violaceous swollen eyelids, arthralgias, progressive lipodystrophy, hypochromic or normocytic anaemia, delayed physical development, and increased levels of acute-phase reactants.[100]

Although Nakajo–Nishimura syndrome is associated with defects in the same gene as JMP syndrome and CANDLE syndrome, it differs in that IFN-γ levels may be in the normal range. The clinical features are also quite distinct, although in all cases the main symptoms are panniculitis or nodular skin lesions and lipodystrophy. Nakajo–Nishimura syndrome is characterized by periodic fever, skin rash, partial lipomuscular atrophy and joint contracture starting in early infancy.[99]

The outcome of patients with these diseases is poor. Reduced life expectancy seems to be related to early cardiovascular disease as a consequence of chronic inflammation and metabolic dysfunction.[102] Only a partial response has been achieved with each of the available biologic agents, including anti-IL-1, anti-TNF and anti-IL-6 therapies.[101]

Others

APLAID syndrome

PLCγ2-associated antibody deficiency and immune dysregulation (APLAID) syndrome (MIM 614878) has been defined in patients with cold urticaria. These patients often present with recurrent sinopulmonary infections, varying immune deficiency features, vitiligo, autoimmune thyroiditis and arthritis, and test positive for antinuclear antibodies. This autosomal dominant syndrome is caused by deletions in the gene encoding phospholipase Cγ2 (PLCγ2), resulting in abnormal B-cell functions.[103]

Undefined diseases

Despite the definition of multiple autoinflammatory diseases, centres caring for individuals with such conditions still have a number of patients with less clear-cut manifestations, whose condition is yet to be associated with specific mutations. The field of monogenic autoinflammatory diseases will thus surely continue to expand.

Polygenic autoinflammatory diseases

In a patient with fever and high levels of acute-phase reactants, if the pedigree fails to suggest a monogenic disease and the clinical features are suggestive, then the polygenic autoinflammatory syndromes should be considered. The differential diagnosis can sometimes be challenging, even for an experienced physician. For example, the ulcers, arthralgia and high erythrocyte sedimentation rate in MKD/HIDS might be mistaken for Behçet disease or vice versa. Moreover, differentiating the long-lasting fever and rash attacks of TRAPS from systemic JIA might pose a problem for a paediatrician. Thus, the physician should be aware of the distinguishing features of these polygenic diseases as well.

PFAPA syndrome is another disease that complicates the differential diagnosis of a young child with periodic fevers; its symptoms are similar to those of FMF and MKD/HIDS in particular. PFAPA syndrome is characterized by almost regular periodic attacks of fever, adenitis, pharyngitis and aphthae.[104] FMF, MKD/HIDS and PFAPA syndrome are all associated with periodic fevers and may involve lymphadenopathy, and it is difficult to

specify aphthae in young children. To further complicate the differential diagnosis, at younger ages children with FMF often do not have serositis but only fever. Furthermore, the attacks do not stay periodic in all patients with PFAPA syndrome, and familial cases have been defined. Last but not least, an increased prevalence of the *MEFV* mutation carrier state and the Arg92Gln mutation in *TNFRSF1A* that is usually associated with mild TRAPS has been defined in these patients, at least in some ethnic groups.[104] In the differential diagnosis of PFAPA syndrome, we find that evidence of pharyngitis (usually exudative) during the attacks and the regularity of attacks are the most useful characteristics. It should be remembered that medications including corticosteroids change the regularity of the attacks. Prednisone might also prevent monogenic disease attacks, although one dose might not be sufficient. These factors should be discussed with the family when considering tonsillectomy.[104]

Conclusions

Understanding the pathogenesis of the autoinflammatory diseases not only has provided us with data on their pathogenesis but also has introduced new perspectives on the inflammatory pathways of more common diseases, ranging from JIA to atherosclerosis. The clinical side of this learning exercise has been exciting as well. We witness the body's reaction to inflammation in so many ways, and the identification of molecular targets has provided the opportunity to treat these patients with biologic agents.

Yet, a lot remains to be done. We all have patients with less clear-cut clinical features of inflammation, and unidentified mutations. International registries are of utmost importance to collect patients with similar symptoms for efficient genetic analyses. The definition of DIRA has been an example of an effective overseas collaboration. We also need close collaboration between clinicians and molecular genetics teams, and the aforementioned workshop is a nice example of the work that can be produced through such partnerships.[29] On the clinical side, we need to define flowcharts to aid physicians in the consideration of genetic work-up for each disease, as all such genetic tests are expensive and should be conducted selectively to prevent unnecessary costs and ensure that health authorities continue to fund them. It is clear that the field of autoinflammatory diseases will continue to intrigue and challenge us.

Review criteria

PubMed was searched for articles published between 2000 and 2013. In addition, older references were included if they described the identification of disease-associated mutations or key case studies. The search terms used in combination were "familial Mediterranean fever" and the names of the other autoinflammatory diseases included in this text, "pathogenesis", "clinical findings" and "treatment options". A number of case reports were excluded if novel aspects were not introduced. The reference lists of the identified articles were also searched. All of the identified manuscripts were full-text English-language papers.

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