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Concise report

Evaluation of the current disease severity scores in paediatric FMF: is it necessary to develop a new one?

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Abstract

Objectives. Modified adult disease severity scoring systems are being used for childhood FMF. We aim to test the clinical consistency of two common severity scoring systems and to evaluate the correlation of scores with the type of FMF mutations in paediatric FMF patients since certain mutations are prone to severe disease.

Methods. Two hundred and fifty-eight children with FMF were cross-sectionally studied. Assessment of the disease severity was performed by using the modified scoring systems of Mor *et al*. and Pras *et al*. Genetic analysis was performed using PCR and restriction endonuclease digestion methods for the presence of 15 FMF gene mutations. FMF mutations were grouped into three based on well-known genotypic–phenotypic associations. Correlation between the mutation groups and the severity scoring systems was assessed. The consistency of the severity scoring systems was evaluated.

Results. The results of two scoring systems were not statistically consistent with each other ($\kappa = 0.171$). This inconsistency persisted even in a more homogeneous subgroup of patients with only homozygote mutations of M694V, M680I and M694I ($\kappa = 0.125$). There was no correlation between the mutation groups and either of the scoring systems ($P = 0.002$, $r = 0{,}196$ for scoring systems of Mor *et al*.; $P = 0.009$, $r = 0.162$ for Pras *et al*.).

Conclusions. The inconsistency of the two scoring systems and lack of correlation between the scoring systems and mutation groups raises concerns about the reliability of these scoring systems in children. There is a need to develop a scoring system in children based on a prospective registry.

Key words: familial Mediterranean fever, children, outcome measurement, disease severity assessment.

CLINICAL SCIENCE

Introduction

FMF is an autosomal recessive disease characterized by recurrent inflammatory febrile attacks of serosal and synovial membranes along with increased acute-phase reactants. It is the most frequent periodic febrile syndrome and has been proposed as the prototype of the auto-inflammatory disorders [1]. Whereas there are many targeted therapies for FMF, there is no consensus on any outcome measures in FMF.

A group of experts on auto-inflammatory diseases has recently published preliminary activity scores for FMF, mevalonate kinase deficiency (MVK), TNF receptor-1-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS) [2]. Standardized disease activity and severity scores are required to assess new medications by using variables that can change over time. Severity scoring systems have been developed to objectively quantify disease severity for

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both therapeutic and prognostic purposes. Major severity scoring systems are composed of clinical features of patients and have been utilized for the adult clinical trials of FMF [3, 4], but there is no validated severity score assessment tool for childhood FMF. Instead, paediatric modifications of adult scoring systems based on expert opinion are being used for childhood FMF [5].

It is well known that patients carrying certain mutations are prone to more severe disease course, as evidenced by genotype–phenotype correlation studies [6, 7]. The results of most of these studies indicate a correlation between the M694V mutation and a more severe disease or the presence of amyloidosis across all affected ethnic groups with the exception of the Turkish patients with FMF [8–11]. We performed this study to test the clinical consistency of two severity scoring systems and to evaluate the correlation of these scores with the type of FMF mutations in paediatric FMF patients.

Materials and methods

This was a cross-sectional study including the patients diagnosed by their treating physician as FMF according to the Tel Hashomer criteria from four different tertiary care referral centres; the age at diagnosis were $\leqslant$16 years of age. All children fulfilled the diagnostic criteria for FMF (one major criterion or at least two minor criteria) [12]. In brief, the data include demographics, clinical diagnosis made by the attending physician, signs/symptoms, detailed features of attacks as well as laboratory values including ESR, CRP, white blood cell count, fibrinogen levels, course of the disease, treatment modalities and doses of colchicum given and response to therapy. Patients with concomitant chronic diseases were excluded from the study.

DNA analyses were done at local referral centres. DNA was isolated from peripheral blood lymphocytes by standard procedures and amplified with sequence-specific primers using the PCR technique. Patients were screened for 15 *MEFV* gene mutations including M694V, M680I, E148Q, V726A, R202Q, R761H, A744S, M694I, P369S, F479L, K695R, G138G, P365S, S141I and T267I.

Severity assessment

Assessment of the disease severity was performed using the scoring systems of Mor *et al*. [3] and Pras *et al*. [4] along with paediatric modifications through the integration of recommended age-related doses by Ozen *et al*. [5]. Since the variables of the Tel Hashomer severity scoring system [13] were comparable with Pras *et al*. [4], we did not consider the Tel Hashomer severity scoring system in our study.

The scoring system of Mor *et al*. [3] has six elements, including age of onset, dose of colchicine, number of involved sites in one attack and during the course of the disease, and the presence of pleuritic and erysipelas-like attacks during the course of the disease. The scoring system of Pras *et al*. [4] also has six elements, including age of onset, dose of colchicine, number of attacks per month, presence of arthritis, erysipelas-like erythema and amyloidosis. The scoring systems used in the study are provided as supplementary data in supplementary table S1 (available at *Rheumatology* Online). After assessing the severity scores of our patients according to the modified scoring systems of Mor *et al*. [3] and Pras *et al*. [4], patients were classified into three groups as mild, moderate and severe. FMF mutations were categorized into three groups based on well-known genotypic–phenotypic associations [6, 7]. The first group included homozygote or compound heterozygote mutations of M694V, M680I and M694I, which are associated with increased disease severity. The second group included all homozygote mutations and the compound heterozygote mutations of other genes except the ones in the first group. The third group was composed of patients with a clinical diagnosis of FMF carrying a heterozygote mutation. We checked the correlation between these mutation groups and the severity scoring systems of Mor *et al*. [3] and Pras *et al*. [4] separately.

We also tested the consistency between these two severity scoring systems on patients with only homozygote mutations of M694V, M680I and M694I, those which are known to have the most severe disease course. Informed consent was obtained from the parents of each patient and the study was approved by the institutional ethics committee (Gulhane Military Academy, School of Medicine, Local Ethics Committee).

Statistical analysis

Descriptive statistics are shown as means (S.D.) for continuous variables, and frequencies and percentages for categorical variables. The consistency of the clinical severity scoring systems of Mor *et al*. [3] and Pras *et al*. [4] was evaluated by κ-coefficients. High κ-coefficients were considered to be values $>$0.7. Spearman's rank correlations were calculated to evaluate the correlation between clinical scoring systems and genotyping results, where a Spearman's correlation coefficient value of $>$0.7 was considered high, a value of 0.4–0.7 was considered moderate and a value of $<$0.4 was considered low [14]. The statistical significance of alpha error was set at $P < 0.05$.

Results

Demographics and clinical features

A total of 279 patients were studied. Twenty-one patients were excluded from the study due to lack of clinical information, incomplete chart data or missing FMF mutation analysis. Of the remaining 258 patients, 141 were males and 117 were females. The mean age of disease onset was 6.2 (3.4) years. The mean age at diagnosis was 11.3 (7.6) years. The most common clinical features during the attacks were fever (90.3%), abdominal pain (82.9%) and arthralgia (44.1%). The mean number of attacks per year was 9.9 (8.0) and the mean duration of attacks was 2.9 (2.0) days. Other demographic and clinical features of the remaining 258 patients are illustrated in Table 1. Fifteen mutations in the *MEFV* gene were screened and the most

Table 1 Demographic and clinical features of patients with FMF

Characteristics	Patients ($n = 258$)
Demographic status	
Male/female, *n*	141/117
Age of onset, mean (S.D.), years	6.2 (3.4)
Age at diagnosis, mean (S.D.), years	11.3 (7.6)
Number of attacks per year, mean (S.D.)	9.9 (8.0)
Duration of attacks, mean (S.D.), days	2.9 (2.0)
Clinical features, *n* (%)	
Fever	214 (90.3)
Abdominal pain, *n* (%)	211 (82.9)
Arthritis	45 (17.4)
Arthralgia	104 (44.1)
Chest pain	16 (6.8)
Myalgia	45 (19.0)
Erysipelas-like erythema	8 (3.4)
Patients with one *MEFV* mutations	83 (32.1)
Patients with two *MEFV* mutations	175 (67.9)

Table 2 Allele frequencies of FMF mutations

Mutation	Frequency (%)
M694V	225 (52.0)
M680I	77 (17.8)
E148Q	45 (10.4)
V726A	38 (8.8)
R202Q	17 (3.9)
R761H	9 (2.1)
A744S	5 (1.2)
M694I	5 (1.2)
P369S	4 (0.9)
F479L	2 (0.5)
K695R	2 (0.5)
G138G	1 (0.2)
P365S	1 (0.2)
S141I	1 (0.2)
T267I	1 (0.2)
Total	433 (100.0)

common mutations were M694V, M680I and E148Q. The allele frequencies of all the mutations are provided in Table 2.

Disease severity

Disease severity was evaluated using paediatric modified versions of the severity scoring systems of Mor *et al*. [3] and Pras *et al*. [4]. A total of 59 (22.9%), 81 (31.4%) and 118 (45.7%) patients were mild, moderate and severe, respectively, according to the scoring system of Mor *et al*. [3], whereas this was 71 (27.5%), 184 (71.3%) and 3 (1.2%), respectively, according to the scoring system of Pras *et al*. [4]. The results of these two scoring systems were not statistically consistent with each other ($\kappa = 0.171$) (Table 3).

Table 3 Consistency of clinical severity according to scoring systems of Mor *et al*. [3] and Pras *et al*. [4] in our cohort

Scoring system of Pras *et al*. [4], *n* (%)	Scoring system of Mor *et al*. [3], *n* (%)			
	Mild	Moderate	Severe	Total
Mild	33 (55.9)	10 (12.3)	28 (23.7)	71 (27.5)
Moderate	26 (44.1)	71 (87.7)	87 (73.7)	184 (71.3)
Severe	0 (0)	0 (0)	3 (2.5)	3 (1.2)
Total	59 (22.9)	81 (31.4)	118 (45.7)	258

$\kappa = 0.171$.

Well-known genotypic–phenotypic associations were evaluated with the severity scoring systems for the presence of correlation [6]. Mutations were collected into three groups as described in the 'Materials and methods' section. There was not any correlation between the mutation groups and neither of the scoring systems ($P = 0.002$, $r = 0.196$ for modified scoring systems of Mor *et al*. [3]; $P = 0.009$, $r = 0.162$ for Pras *et al*. [4]) (Table 4).

Further evaluation of the consistency of the two scoring systems was assessed in a subgroup of patients with homozygote mutations of M694V, M680I and M694I, which are known for the most severe genotypic–phenotypic associations (Table 5). Only 3 (3.8%) patients had severe disease according to the modified scoring system of Mor *et al*. [3], whereas this was 49 (61.3%) with the modified scoring system of Pras *et al*. [4]. The number of patients with moderate disease was 62 (77.5%) and 20 (25.0%) by the scoring systems of Mor *et al*. [3] and Pras *et al*. [4], respectively. The number of patients with mild disease was 15 (18.8%) based on the scoring system of Mor *et al*. [3] and 11 (13.8%) according to the Pras *et al*. system [4]. The two scoring systems failed to show consistency even when evaluated in a subgroup of patients with homozygote mutations of M694V, M680I and M694I, which are known for the most severe genotypic–phenotypic associations ($\kappa = 0.125$) (Table 5).

Discussion

Although there is plenty of literature on FMF, there are only a few studies about the outcome measurements of this disorder. Moreover, the tools to assess the outcome have been developed for adult patients. Paediatric rheumatologists have been using these assessment tools or their modified versions in clinical trials [5, 15, 16]. Therefore, this study was performed to test the clinical consistency of two common severity scoring systems that have not been validated statistically in either paediatric or adult FMF patients. Our study has yielded three key findings: first, the results of these two scoring systems were not statistically consistent with each other. Second, no

Table 4 Relations between clinical severity and genetic mutation groups

	Mild	Moderate	Severe	Total
Mor *et al*. [3],[a,*] *n* (%)				
M694V, M680I, M694I	16 (15.4)	28 (26.9)	60 (57.7)	104 (100)
V726A, E148Q other	18 (25.4)	25 (35.2)	28 (39.4)	71 (100)
Heterozygote	25 (30.1)	28 (33.7)	30 (36.1)	83 (100)
Pras *et al*. [4],[b,**] *n* (%)				
M694V, M680I, M694I	19 (18.3)	82 (78.8)	3 (2.9)	104 (100.0)
V772A, E148Q other	25 (35.2)	46 (64.8)	0 (0)	71 (100.0)
Heterozygote	27 (35.2)	56 (30.4)	0 (0)	83 (100.0)

[a]Spearman's correlation = 0.196. [b]Spearman's correlation = 0.162. *P = 0.002, **P = 0.009.

Table 5 Consistency of severity scoring systems of Mor *et al*. [3] and Pras *et al*. [4] in patients with homozygote mutations of M694V, M680I and M694I

Scoring system of Pras *et al*. [4], *n* (%)	Scoring system of Mor *et al*. [3], *n* (%)			
	Mild	Moderate	Severe	Total
Mild	5 (33.3)	6 (9.7)	0 (0)	11 (13.8)
Moderate	1 (6.7)	19 (30.6)	0 (0)	20 (25.0)
Severe	9 (60.0)	37 (59.7)	3 (100.0)	49 (61.3)
Total	15 (18.8)	62 (77.5)	3 (3.8)	80 (100.0)

$\kappa = 0.125$

correlation was defined between the scoring systems and the mutation groups. Third, these two scoring systems failed to show consistency on the subgroup of patients with homozygote mutations of M694V, M680I and M694I, which are known to have the most severe disease course [7, 17].

Since we do not have validated measures to assess the severity in paediatric FMF patients, we attempted to test the reliability of the modified version of scoring systems of Mor *et al*. [3] and Pras *et al*. [4] suitable for paediatric patients. We assessed the consistency of these two severity scoring systems in a cohort of patients collected from four different centres and found no consistency between them. For instance, 28 (23.7%) patients with mild disease based on the scoring system of Pras *et al*. [4] were regarded as having severe disease according to the scoring system of Mor *et al*. [3] (Table 3). On the other hand, 87 (73.7%) patients with severe disease according to the scoring system of Mor *et al*. [3] had moderate disease according to the scoring system of Pras *et al*. [4]. Moreover, there were only three patients with severe disease based on the scoring system of Mor *et al*. [3], whereas this was 118 with the scoring system of Pras *et al.* [4] (Table 3).

The lack of consistency of these two scoring systems could be related to the fact that they investigate different aspects of the disease. Although the scoring systems have common elements such as the age of onset, dose of colchicine and the presence of erysipelas-like erythema, the scoring system of Mor *et al*. [3] focuses more on the number of involved sites during attacks. However, the scoring system of Pras *et al*. [4] emphasizes the number of attacks per month and the presence of amyloidosis. The inconsistency of these scoring systems demonstrates that severity assessment should be different in the paediatric population. Moreover, the consistency of these instruments should be further evaluated in the adult population with FMF. It is well understood that subjective complaints may constitute some of the criteria of the severity scoring systems in the adult population. It is clear that objective evaluation of the pain and its relation to a specific organ system may be vague in children. For instance, abdominal pain or pleuritic pain can easily be missed in children. Therefore there is a need to construct a severity scoring system based on more objective criteria that is also suitable for children.

Furthermore, we were not able to show a satisfactory correlation of the scoring systems with mutation groups of well-known genotypic–phenotypic associations. We suggest that this lack of correlation raises concerns as well in the reliability of these scoring systems in children.

Phenotype–genotype correlation in FMF has not been explained definitely, but several researchers have observed more severe disease expressions and increased susceptibility to amyloidosis in patients with specific *MEFV* mutations [18, 19]. Moreover, standardized disease severity scores are required for the assessment of new therapies in constant development.

Long-term colchicine treatment leads to complete remission in two-thirds of the patients. However, 10% of the patients are reported to be resistant or non-responsive to colchicine and in these cases there is no consensus as to which second-line agents should be used. These observations highlight the need for controlled trials to further evaluate the safety and efficacy of new biological agents in FMF patients [20]. Consequently, new treatment strategies such as blockade of either IL-1 signalling or nuclear factor κB (NF-κB) activation represents possible targets for the treatment of FMF [21–23]. This ranking of severity is implicit in reasonable treatment programmes.

In addition, we also evaluated the consistency in a subgroup of patients with so-called severe mutations (those with homozygote mutations between 680 and 694 on the 10th exon), and again no consistency was observed between the scoring systems when applied to this group of patients.

FMF is the prototype of the monogenic auto-inflammatory syndromes. A common definition of disease severity would be rational and useful in the management of these lifelong diseases. Frequent and severe FMF attacks may severely compromise the quality of life and increase the risk for secondary amyloidosis. Treatment with colchicine decreases the frequency and the intensity of attacks and prevents secondary amyloidosis in the majority of patients. However, there is a subgroup of patients that fail to respond to usual doses of the drug. Assessment of severity may be crucial in defining such patients and adjusting treatment.

Potential uses of severity scoring systems are as follows. These systems can be used to compare the study population in randomized controlled trials and clinical research, to assess daily care performance or assess individual patient prognosis and guide care, and also for administrative purposes. Therefore there is a need to develop a new scoring system in children based on a prospective registry. Multinational collaboration is crucial for the development of such criteria, since ethnic and environmental effects are evident in FMF. We believe that further specific modifications to the adult instruments would enhance their use in children until a true paediatric severity scoring system is constructed, which is currently under way as a part of the Eurofever Project [24].

Rheumatology key messages

- Current severity scoring tools for FMF showed no consistency when applied to the paediatric FMF population.
- There is a need to develop an evidence-based severity assessment tool for childhood FMF.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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