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 (k = 0.171). This inconsistency persisted even in a more homogeneous subgroup of patients with only homozygote mutations of M694V, M680I and M694I (k = 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.

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...
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 ≤ 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 comorbid 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 k-coefficients. High k-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
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).

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 ($\kappa = 0.125$) (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
Severe disease based on the scoring system of Mor et al. [3] was found in 9 (60.0) patients, while 37 (59.7) patients were categorized as moderate disease. According to the scoring system of Pras et al. [4], 12 (15.7) patients were regarded as having severe disease, 19 (25.6) as moderate, and 54 (72.7) as mild. The correlation between the two scoring systems was defined as Spearman’s correlation = 0.196.

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.

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.

### Table 4: Relations between clinical severity and genetic mutation groups

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
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<tbody>
<tr>
<td>Mor et al. [3], a* n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>M694V, M680I, M694I</td>
<td>16 (15.4)</td>
<td>28 (26.9)</td>
<td>60 (57.7)</td>
<td>104 (100)</td>
</tr>
<tr>
<td>V726A, E148Q other</td>
<td>18 (25.4)</td>
<td>25 (35.2)</td>
<td>28 (39.4)</td>
<td>71 (100)</td>
</tr>
<tr>
<td>Heterozygote</td>
<td>25 (30.1)</td>
<td>28 (33.7)</td>
<td>30 (36.1)</td>
<td>83 (100)</td>
</tr>
<tr>
<td>Pras et al. [4], b* n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M694V, M680I, M694I</td>
<td>19 (18.3)</td>
<td>82 (78.8)</td>
<td>3 (2.9)</td>
<td>104 (100.0)</td>
</tr>
<tr>
<td>V772A, E148Q other</td>
<td>25 (35.2)</td>
<td>46 (64.8)</td>
<td>0 (0)</td>
<td>71 (100.0)</td>
</tr>
<tr>
<td>Heterozygote</td>
<td>27 (35.2)</td>
<td>56 (30.4)</td>
<td>0 (0)</td>
<td>83 (100.0)</td>
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aSpearman’s correlation = 0.196. bSpearman’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

<table>
<thead>
<tr>
<th>Scoring system of Pras et al. [4], n (%)</th>
<th>Scoring system of Mor et al. [3], n (%)</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>5 (33.3)</td>
<td>6 (9.7)</td>
</tr>
<tr>
<td>1 (6.7)</td>
<td>19 (30.6)</td>
</tr>
<tr>
<td>9 (60.0)</td>
<td>37 (59.7)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>15 (18.8)</td>
<td>62 (77.5)</td>
</tr>
<tr>
<td>3 (3.8)</td>
<td></td>
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<tr>
<td>80 (100.0)</td>
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</table>

κ = 0.125
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.

References


