Not easy-peasy to diagnose: familial Mediterranean fever unaccompanied by fever as neither always Mediterranean

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Research Article

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Abstract

Purpose

Classical attacks of familial Mediterranean fever (FMF) are often accompanied by fever, but some of the patients have attacks without fever. This study aimed to compare the characteristics of FMF patients with and without fever during their attacks and draw attention to the different clinical presentations of FMF in children.

Methods

Medical files of patients aged 0–18 years who were followed up with the diagnosis of FMF in two reference pediatric rheumatology centers were reviewed retrospectively. The patients were divided into two groups: Children who had had no fever in any of their attacks were assigned as group 1, and those who had fever during their attacks were classified as group 2.

Results

Out of 2003 patients evaluated, 191 (9.53%) patients had attacks not accompanied by fever and their median age at onset of symptoms (7.0 vs. 4.0 years, p < 0.001) and the median age at diagnosis (8.6 vs. 6.0 years, p < 0.001) were significantly higher, however group 2 had delay in diagnosis. The annual number of attacks and abdominal attacks were more common in group 2, arthritis, arthralgia, erysipelas-like rash, exercise-induced leg pain, and myalgia were more common in group 1.

Conclusion

The data from the assessment of children with FMF attacks not accompanied with fever were presented for the first time. Children with late age onset of FMF and dominance of musculoskeletal features may display attacks not accompanied with fever.

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most common inherited autoinflammatory disease in the world and is frequent among people of the Mediterranean basin such as Turks, Arabs, non-Ashkenazi Jews, and Armenians [1]. It is caused by gain of function mutations in the MEFV gene encoding the pyrin protein [2]. Activation of the pyrin leads to the assembly of the inflammatory complex and through excessive stimulation of caspase-1, overproduction of IL-1β and IL-18 that create an inflammatory environment and act as fever inducing endogenous pyrogens which is the main characteristic feature of FMF [3].

The diagnosis of FMF is based on the demonstration of recurrent episodes of peritonitis, pleuritis, pericarditis, and arthritis usually accompanied by fever and supported by the presence of MEFV gene variants. Fever is the most common symptom during attacks. According to the largest pediatric FMF cohort published by our group, 86.7% of patients reported attacks with fever [4]. However, the type and
frequency of attacks, development of amyloidosis, and colchicine resistance display significant heterogeneity among patients and populations [5–7]. Although fever is the major symptom, there are case reports in the literature that FMF patients have exacerbations without fever [8–11].

Nonetheless, it is unclear whether patients without fever during episodes reflect a distinct clinical entity. So, making the diagnosis of FMF in these patients may be challenging. From this point of view, we evaluated and compared the genotype-phenotype characteristics of patients diagnosed with FMF between two groups in a large pediatric cohort of FMF: patients without fever during attacks and patients who had fever during attacks.

The aim of this study was to identify patients with FMF but without fever during attacks and to demonstrate their distinctive presentations.

**MATERIALS and METHODS**

**Patients and methods**

The medical files of children with FMF who were followed up regularly every 3–6 months in the Pediatric Rheumatology Units of Istanbul University, Istanbul Faculty of Medicine and Health Sciences University Umraniye Training and Research Hospital were analyzed retrospectively. The study included 2003 patients aged 0–18 years who met at least one of the Tel-Hashomer and Eurofever/PRINTO 2019 diagnostic criteria for FMF and carried at least one mutation in exon 2, 3, 5, or 10 in the *MEFV* gene [12]. Patients with the concomitant disease were excluded from the study.

The entire cohort was grouped as follows: Group 1, included patients who had no fever during any of the attacks and Group 2, included patients with fever during the attacks.

Patients’ files were evaluated and the demographic data, clinical manifestations during attacks, presence of fever during attacks, family history of FMF and amyloidosis, parental consanguinity, genetic test results, treatments used, and presence of colchicine resistance were recorded for both groups. The colchicine dose was as follows: for children under 5 years of age, the dose is 0.5 mg/day; 0.5–1 mg/day for 5–10 years old, and 1.5 mg/day for children over 10 years old [13]. In cases not responding to colchicine, side effects of the drug were carefully monitored and the maximum tolerated doses were given (maximum 1.5 mg/day in patients aged 5–10 years, maximum 2 mg/day in patients older than 10 years). Colchicine resistance was defined as having one or more attacks per month (over three months) and/or the presence of subclinical inflammation despite treatment with the maximum tolerable doses of colchicine [13]. Anti-IL1 biological agents (anakinra or canakinumab) were started in case of colchicine resistance.

The study was approved by the ethical committee of Istanbul University, Istanbul Medicinal Faculty (Date:21/05/2020; No:19). The study was carried out and complied with the Declaration of Helsinki. Informed consent was obtained from all parents/patients before inclusion in the study.
Statistical analysis

Data was collected for analysis using Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS 28.0 (IBM, Armonk, NY). The distribution of numerical variables was investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk). For numerical variables, descriptive statistics were made with minimum, maximum, mean, standard deviation, and median according to their distribution. Categorical variables were evaluated as frequencies and ratios. Where appropriate, categorical variables were compared with the Chi-square test or Fisher's exact test. Numerical data were compared with the Mann-Whitney U test or Student t-test according to their distribution. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 2003 patients from two centers were involved in this study. Among them, 1016 (50.7%) were female. The median age at symptom onset was 4 (min-max: 0.1–17) years, and the median age at diagnosis was 6 (min-max: 0.5–18) years. Consanguinity was present in 650 patients (32.5%). Family history of FMF and amyloidosis was present in 1216 (60.6%) and 153 (7.6%) patients, respectively.

Group 1 consists of 191 (9.53%) patients without fever during any attacks and group 2 consists of 1812 (90.47%) patients with fever during attacks. Demographic data and clinical findings of both groups were evaluated separately. Group 1 and 2 were similar in terms of gender (female 49.7% vs. 50.8%; p < 0.77). The median age at symptom onset was higher in group 1 than in Group 2 (p < 0.001). Patients in group 1 were diagnosed with FMF at a later age than group 2 (p < 0.001). Additionally, the median duration between symptom onset and the diagnosis was longer in group 2 (12 months (range 0-192) than in group 1; 12 (range 0-108) in group 2; p = 0.04).

When patients were evaluated according to the number of attacks per year, the median was 6 (range 0–48) for group 1, whereas in group 2, it was 12 (range 0–48) attacks (p < 0.001). In group 1, the most common symptom during the attacks was abdominal pain (63.9%), followed by arthritis (60.7%), arthritis (45.3%), myalgia (32.5%), exertional leg pain (26.2%), and erysipelas-like erythema (25.1%). Similarly, the most common symptom during the attacks was abdominal pain (94%) in group 2. The following symptoms were arthralgia (37.9%), myalgia (21.2%), arthritis (19.6%) and chest pain (18.6%). The clinical features of both groups are depicted in Table 1.
<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Group 1 (n = 191)</th>
<th>Group 2 (n = 1812)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>Female</td>
<td>95 (49.7)</td>
<td>921 (50.8)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>96 (50.3)</td>
<td>891 (49.2)</td>
<td></td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>Min-max (median)</td>
<td>0.5–17 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>Min-max (median)</td>
<td>1–18 (8.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Delay in diagnosis (months)</td>
<td>Min-max (median)</td>
<td>0-108 (12)</td>
<td>0.04</td>
</tr>
<tr>
<td>Presence of FMF in the family of the patients</td>
<td>n (%)</td>
<td>114 (59.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Presence of amyloidosis in the family of the patients</td>
<td>n (%)</td>
<td>12 (6.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The annual number of attacks</td>
<td>Min-max (median)</td>
<td>0–48 (6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>n (%)</td>
<td>122 (63.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>n (%)</td>
<td>28 (14.7)</td>
<td>0.180</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>n (%)</td>
<td>116 (60.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arthritis</td>
<td>n (%)</td>
<td>83 (43.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Erysipelas like erythema</td>
<td>n (%)</td>
<td>48 (25.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>n (%)</td>
<td>2 (1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Exertional leg pain</td>
<td>n (%)</td>
<td>50 (26.2)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*FMF; Familial Mediterranean fever*
The frequency of symptoms was compared and arthritis (43.5% vs. 19.6%; p < 0.001), arthralgia (60.7% vs. 37.9%; p < 0.001), erysipelas-like rash (25.1% vs. 8.2%; p < 0.001), exercise-induced leg pain (26.2% vs. 17.6%; p:0.04), and myalgia (32.5% vs. 21.2%; p < 0.001) were significantly more common in group 1 than group 2. However, patients in group 2 had a higher prevalence of abdominal pain compared to group 1 (94% in group 1 and 63.9% in group 2; p < 0.001). The colchicine treatment resistance in group 1 and group 2 were similar (2.6% vs. 5.6%) (p < 0.078).

The most commonly observed MEFV mutation patterns in group 1 were homozygous (27.2%) and heterozygous (23.6%) mutations of M694V, it was homozygous (30.2%) and heterozygous (19.7%) mutations of M694V in group 2 and frequencies of M694V mutations were similar between groups. Carrying one pathogenic mutation or biallelic pathogenic mutations (compound heterozygote and homozygote) of the two groups were evaluated and no significant difference was found (Table 2). MEFV gene variants in group 1 are shown as supplementary table 1.

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Group 1 (n = 191)</th>
<th>Group 2 (n = 1812)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>62 (32.5)</td>
<td>385 (21.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>0 (0)</td>
<td>6 (0.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Colchicine resistance</td>
<td>5 (2.6)</td>
<td>102 (5.6)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

The family history for FMF and amyloidosis were similar between group 1 and group 2 (59.7% vs. 60.7%; p:0.78 6.3% vs. 7.8%; p:0.45, respectively).

**DISCUSSION**

To the best of our knowledge, our study is the first to compare the demographic data and characteristics of children with FMF who had no fever during any of their attacks with a large cohort of children with
FMF who had fever during attacks. Musculoskeletal symptoms such as arthritis, arthralgia, exertional leg pain and myalgia were found more commonly in group 1 than in group 2. Similarly, Avar-Aydin et al. reported fever as a less pronounced feature of patients with arthritis during attacks in their cohort [14]. ELE was seen more commonly in patients without fever during attacks in our cohort. In line with our study, Yıldırım et al. evaluated 782 FMF patients and they reported 59 patients with ELE with higher frequency of arthritis, but with a significantly lower prevalence of fever during attacks [15]. It is well known that the key feature of FMF is recurrent acute attacks of febrile peritonitis, and abdominal attacks are encountered by 95% of FMF patients at least during some of their attacks [16]. Abdominal pain was the most common symptom during attacks of both groups in our cohort, but it was significantly more common in group 2. The frequency of chest pain and pericarditis did not differ between two groups. Both groups were similar in terms of gender, family history of FMF, and amyloidosis. Six patients in group 2 had amyloidosis while none of the patients in group 1 had. Our patients in group 2 had more frequent number of attacks per year, so amyloidosis present in this group may be related to the frequency and severity of the attacks in group 2. However, FMF severity was not evaluated in the entire cohort, so this remains only as a potential cause.

In our study, patients with febrile attacks had a lower age of onset and they were diagnosed at earlier ages as well. However, when the duration to diagnosis was evaluated, the delay in diagnosis was more pronounced in patients with fever during their attacks. In recent studies, a negative correlation was shown between the age at onset of FMF and the duration until the diagnosis [17, 18]. Fever may be the unique symptom at younger children with FMF, and recurrence of fever may be attributed to the infections in infancy and early childhood by the pediatricians following these patients. This may be an explanation for the delay in diagnosis in this age group. Ozdel et al. showed that the frequency of fever and attacks was lower in patients who experienced their first attack after the age of eight [19]. Similarly, in our study, we observed that the frequency of attacks was lower in the afebrile group, and their median age at diagnosis was 8 years.

In a study by Tanatar A. et al. the frequency of fever and peritonitis was higher in patients with FMF whose disease onset was before 3 years of age while, arthritis, ELE, and arthralgia were more common in older patients [20]. In our cohort, patients with afebrile attacks had a significantly higher rate of arthritis and older age of onset, but they had a shorter delay in diagnosis. An earlier referral to the pediatric rheumatology clinics for musculoskeletal complaints, as a specific feature, may be the explanation for the timely diagnosis.

When we evaluated patients according to their mutations, the presence of two pathogenic alleles, the M694V variant at least in one allele, or one pathogenic allele made no difference in terms of concomitant fever during attacks. Although there are studies showing that genotype is correlated with clinical findings and severity of FMF, the relationship between fever and genotype has not been fully demonstrated yet [21–24]. In a study by Kondi et al. it was shown that genetic status had no influence on clinical findings, no relationship was found between having heterozygous or homozygous mutations and the presence of fever [25]. In our previous study in children with FMF, we could not show an association between fever
and having heterozygous or homozygous M694V mutation, there was a relation between the presence of musculoskeletal features like arthritis, arthralgia, myalgia, and M694V mutations [26]. Kısaoğlu et al. showed that clinical features such as fever, abdominal pain, chest pain, arthritis and erysipelas-like erythema did not differ according to the homozygous or heterozygous M694V mutation [27]. However, in an adult study published by Balta et al., FMF patients revealed genotype-phenotype correlation, and fever was most prevalent in patients with homozygous exon 10 mutations [28].

When patients were evaluated for colchicine resistance, even though resistance was more frequent in the febrile group, the difference was not significant. Five patients in group 1 were resistant to colchicine and biologic therapy was started due to their recurrent musculoskeletal complaints. In the literature, features of musculoskeletal involvement were evaluated in a limited number of studies, Eshed et al. et al. displayed the association between exertional leg pain and severity of FMF in adults, they reported that patients with exertional leg pain had more frequent joint attacks, fever attacks and pleuritis attacks [29]. In our study group, exercise-induced leg pain occurred more frequently with accompanying musculoskeletal system findings in group 1. However, FMF severity was not evaluated in the entire cohort, and we acknowledge this as a limitation of our research, but the presence of colchicine resistance in group1 can be considered to indicate the undeniable importance of persistent inflammation in patients even without fever during attacks. The retrospective design is another limitation of this study, and parents may not accurately remember every attack. However, taking a detailed history of attacks and examining the patients regularly by the same pediatric rheumatology teams may reduce the bias to some extent while collecting data.

CONCLUSIONS

In conclusion, it is important to raise awareness of the various presentations of FMF in populations with higher disease prevalence. Regardless of the knowledge that fever is the most common feature in FMF, we found that 7% of our patients had afebrile attacks with predominant musculoskeletal symptoms and were diagnosed earlier than patients with febrile attacks, probably due to early referral to pediatric rheumatology clinics. Therefore, we wish to emphasize that pediatric rheumatologists should not miss the opportunity to diagnose FMF in patients with recurrent musculoskeletal symptoms, even in the absence of fever.

Declarations

Authors’ contributions:

SDA, GKK and NAA designed the form of the study. SDA, FGD, GKK, VG, and NAA prepared the initial draft of the article. AT, ÖA, ŞÇ, KU, TC, ŞGK, and BS revised it critically for important intellectual content. All authors contributed to data collection, analysis and interpretation of data, providing comments to the draft article and final approval of the article.
Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval (number:816470) was obtained from Istanbul University, Faculty of Medicine.

Consent to participate

Because of the retrospective nature of the study, obtaining written informed consent from the patients was not required.

Consent for publication

Not applicable.

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Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest and source of funding

None of the authors received financial support and there are no potential conflicts of interest and no source of funding for this work.

References


Supplementary Files

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- Supplementarytable.docx