

# Familial Mediterranean Fever in Children Presenting with Attacks of Fever Alone

SHAI PADEH, AVI LIVNEH, ELON PRAS, YAEL SHINAR, MERAV LIDAR, OLGA FELD, and YACKOV BERKUN

**ABSTRACT. Objective.** Familial Mediterranean fever (FMF) is an inherited disease characterized by attacks of febrile polyserositis. In children, attacks of fever alone, or with headache and malaise, may precede other forms of attacks. Our objective was clinical and genetic characterization of FMF and its development in pediatric patients who first presented with attacks of fever alone.

**Methods.** Clinical characterization and MEFV genotype of all FMF patients < 16 years of age at disease onset and first presenting with attacks of fever alone were analyzed and compared for age, sex, and disease duration with matched FMF patients presenting with serositis at the onset of the disease.

**Results.** There were 814 patients with FMF in our registry. Fifty patients formed the study group and 234 patients the control group. In the study group, the first (febrile) attacks appeared at a younger age than in the control group ( $1.7 \pm 1.6$  yrs vs  $5.0 \pm 4.1$  yrs, respectively;  $p < 0.0001$ ), diagnosis was made earlier ( $4.2 \pm 2.7$  yrs vs  $6.7 \pm 4.1$  yrs;  $p < 0.0001$ ), despite a trend for a longer delay in diagnosis. In the study group, attacks were shorter ( $1.6 \pm 0.8$  days vs  $2.1 \pm 1.0$  days;  $p = 0.023$ ) and homozygosity to the *M694V* mutation was more prevalent (46% vs 31%;  $p = 0.03$ ). Attack rate, colchicine dose, and the MEFV mutation carrier rates were comparable between the groups. In 40/50 (80%) of the patients with fever alone, serositis had developed over a course of  $2.9 \pm 2.2$  years after disease onset.

**Conclusion.** FMF in young children may begin with attacks of fever alone, but it progresses to typical FMF disease over the next  $2.9 \pm 2.2$  years. Our study demonstrates that clinical heterogeneity at presentation is more likely to indicate a feature of a disease in development, rather than to mark distinct phenotypes of FMF. (J Rheumatol First Release March 1 2010; doi:10.3899/jrheum.090687)

## Key Indexing Terms:

FAMILIAL MEDITERRANEAN FEVER CHILDREN PHENOTYPE MUTATIONS MEFV

Familial Mediterranean fever (FMF, MIM249100) is an autosomal recessive disease, mainly affecting Jews, Armenians, Turks, Arabs, and other ethnic groups living around the Mediterranean Basin<sup>1-3</sup>. The FMF gene (MEFV) was identified by positional cloning<sup>4,5</sup>, and its product, pyrin/marenostrin<sup>6,7</sup>, appears to play a pivotal role in the regulation of inflammation<sup>8</sup>. To date, more than 50 MEFV mutations, mostly missense substitutions, have been associated with FMF<sup>9</sup>. Nevertheless, the diagnosis of FMF is still determined clinically<sup>10</sup>, since 2 mutations are found in only 38%–72% of patients with FMF<sup>11-13</sup>, and no other laboratory finding has been proven pathognomonic<sup>14</sup>.

Painful febrile episodes, manifested in most cases as peritonitis, pleuritis, or acute synovitis, are the hallmark of

the disease. In children, however, attacks of fever alone, or with headache and general malaise, can be the only manifestation of the disease, occurring years before the other forms of attack appear<sup>15</sup>. A minority of these patients may not experience serositis attacks throughout their entire childhood<sup>16</sup>.

In order to better recognize the characteristics of this subgroup of patients with FMF, and perhaps to prompt early diagnosis and initiation of colchicine prophylaxis, we reviewed all cases in our practice presenting with attacks of fever alone; we used the computer database collected in our ongoing prospective study, with the aim of defining the FMF phenotype and genotype in pediatric patients.

## MATERIALS AND METHODS

**Patients.** The pediatric section of the Israeli National Center for FMF at the Safra Children's Hospital, Sheba Medical Center, serves as a referral center for the diagnosis and treatment of children suspected of having FMF. In January 2000, we established a database for all pediatric patients referred to the center, and initiated an ongoing prospective study to define the FMF phenotype and genotype in patients presenting at age < 16 years. Clinical manifestations and demographic data, family history, basal laboratory test results, and genetic analysis of MEFV mutations were obtained initially and over the course of the disease. Followup visits were scheduled at 6–12 month intervals, in which response to therapy and changes in the basic data were recorded for each patient. The registry contained a total of 814 FMF patients out of 2000 referrals by mid-2008.

From the Department of Pediatrics, Edmond and Lily Safra Children's Hospital, Department of Medicine F, and Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel.

S. Padeh, MD; Y. Berkun, MD, Department of Pediatrics A, Edmond and Lily Safra Children's Hospital; E. Pras, MD, Genetic Institute; Y. Shinar, PhD; A. Livneh, MD; M. Lidar, MD; O. Feld, MD, Department of Medicine F and Heller Institute of Medical Research, Sheba Medical Center, and Sackler School of Medicine, Tel-Aviv University.

Address correspondence to Dr. S. Padeh, Department of Pediatrics A, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel. E-mail: Shaypade@sheba.health.gov.il  
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A total of 112 patients were referred to our center during this period for investigation of recurrent episodes of fever, unaccompanied by serositis or pharyngitis. Of these, 50 patients were diagnosed and treated for FMF. In a further 50 patients, the diagnosis of FMF was rejected for the reasons shown in Table 1, because they had not fulfilled the criteria for diagnosis of FMF or their diagnosis remained questionable at termination of the study. Twelve children were lost to followup.

The study group comprised all 50 FMF patients (26 males, sex ratio 1.1:1) aged 16 years old or younger, who had attacks of fever alone at presentation, and were diagnosed and followed in our center between January 2000 (initiation of the study) and July 2008 (conclusion of the study). Diagnosis of FMF was established clinically in all children, based on a set of published criteria formulated for the diagnosis of FMF, with a sensitivity and specificity of > 95%<sup>10</sup>. These criteria require the presence of recurrent typical attacks with at least one of the following forms: peritonitis, pleuritis, monoarthritis, or fever alone (major criteria). A combination of minor criteria (less typical attacks, leg pain on exertion, and responsiveness to colchicine) and supportive criteria (e.g., family history of FMF and 9 other criteria) may also lead to the diagnosis of FMF in case major criteria are not met.

This group was compared to a control group of 234 FMF patients (132 males, sex ratio 1.3:1), diagnosed based on the above criteria, who had typical attacks of FMF from disease onset and were matched to the study group patients based on a similar disease duration. Disease duration of around 7.3 years from date of diagnosis, comparable to that of the study group, was considered imperative for the study, since in our experience childhood FMF may change clinically over the course of the disease. Patients' data from the 2 groups were analyzed, focusing on demographics, laboratory tests, family history, disease manifestations, disease course, and response to therapy. The ethical committee of our institute approved the study protocol.

**Genetic analysis.** Mutation analysis was performed for the 3 most common FMF mutations found in the Israeli FMF population: *M694V*, *V726A*, and *E148Q*, using a commercial kit (Gamidigen, Rehovot, Israel) or polymerase chain reaction amplification and restriction enzyme analysis, as described<sup>17</sup>. The *M680I* and the *M694I* mutations were additionally studied only in non-Jewish patients (less than 2% of our patient population), using a similar technology.

**Statistical analysis.** Results are given as a mean ± standard deviation or proportions as appropriate. Differences between the groups in discrete variables were evaluated by chi-square or Fisher's exact test as needed. Comparisons of continuous variables were by unpaired Student t test or Wilcoxon 2-sample test, as required. All p values are 2-sided. P values < 0.05 are considered significant.

## RESULTS

Of the 814 children fulfilling the criteria for FMF, in 50 (6.2%), the first FMF manifestation was an attack of fever alone, unaccompanied by serositis or erysipelas-like erythema. Demographic and disease characteristics of patients and

controls are shown in Table 2. Of note, the mean age at onset differs significantly between the 2 groups ( $p < 0.0001$ ). Not surprisingly, the younger age at onset, scanty manifestations, and shorter duration of attacks in the study group led to a longer delay in diagnosis in patients of the study group than in the control group, by a mean of 0.8 years ( $p = 0.3$ ). Only the median delay (0.9 yrs) was statistically significant (2.0 and 1.1 yrs in the study and control group, respectively;  $p = 0.007$ , Wilcoxon 2-sample test). Nevertheless, despite the longer delay in diagnosis, the age at diagnosis remained significantly younger in the study group (Table 2).

Of the 50 patients with attacks of fever alone, in 40 patients (80%) additional forms of attacks developed, including abdominal, joint, chest, skin, and acute scrotum attacks, variably appearing over the course of the disease, in proportions shown in Table 3. The rate of the different FMF attack sites was comparable to that observed in patients presenting with serositis from the onset of disease (Table 3). Interestingly, the patients of the study group developed serositis at an age similar to the age of presentation with the same manifestations in patients with serositis from the onset of disease (the control group). Abdominal attacks developed about 3 years after the onset of fevers in the study group, as compared to immediately at disease onset in the control group ( $p = 0.0001$ ). Similar delays in appearance of arthritis, chest pain, and erysipelas-like erythema from the onset of disease were observed in both groups (Table 3).

Table 2. Demographic and disease characteristics in patients and controls.

Characteristic	Patients with Attacks of Fever Alone, n = 50	Patients with Serositis at Disease Onset, n = 234	p
Male/female	26/24	132/102	NS
Age at disease onset, yrs	1.7 ± 1.6	5.0 ± 4.1	0.0001
Age at first visit to the clinic, yrs	4.1 ± 2.7	6.5 ± 4.1	0.0001
Age at diagnosis, yrs	4.2 ± 2.7	6.7 ± 4.2	0.0001
Delay in diagnosis, yrs	2.5 ± 2.0	1.7 ± 5.7	NS
Family history	38 (76%)	97 (41%)	0.0001
Sephardic Jewish extraction	47 (94%)	193 (82%)	NS
Attacks per month	2.0 ± 1.3	1.9 ± 1.6	NS
Days of fever	1.6 ± 0.8	2.1 ± 1.5	0.02

NS: not statistically significant.

Table 1. Patients with recurrent episodes of fever not included in the study: reasons for exclusion.

Factor	N (%)*	Age at Disease Onset, yrs	Age at Last Followup Visit, yrs	Duration of Followup, yrs
Recurrent infections	28 (56)	2.0 ± 2.6	4.1 ± 3.7	2.1 ± 4.5
Long episodes (> 5 days)	14 (28)	3.7 ± 5.1	5.9 ± 5.5	2.2 ± 7.5
Attacks stopped	14 (28)	2.2 ± 2.7	5.3 ± 2.7	3.1 ± 3.8
No elevation of acute phase	13 (26)	3.1 ± 4.7	5.6 ± 4.6	2.4 ± 6.6
Failure of colchicine trial	7 (14)	1.8 ± 1.3	6.0 ± 1.8	4.2 ± 2.6
Total	50 (100)	2.5 ± 3.3	5.6 ± 4.5	3.1 ± 5.6

\* Some patients had more than one indication for rejecting a diagnosis of FMF.

Table 3. Additional forms of attack and other manifestations in 40 patients in comparison to controls.

Manifestations	N (%)	Patients, n = 40		Controls, n = 243		
		Age at Appearance of Manifestation, yrs	Lag After Onset, yrs	N (%)	Age at Appearance of Manifestation, yrs	Lag After Onset, yrs
Abdominal pain	40 (100)	4.7 ± 3.2	2.9 ± 1.3	188 (80.3)	4.5 ± 3.6	0.1 ± 1.4*
Arthritis	21 (53)	5.9 ± 3.7	4.3 ± 4.0	114 (48.7)	6.7 ± 4.9	2.2 ± 4.1
Chest pain	13 (33)	4.4 ± 2.9	3.0 ± 1.8	28 (29.0)	9.4 ± 4.8	4.4 ± 5.2
Erysipelas-like erythema	7 (18)	6.0 ± 1.5	4.4 ± 0.3	39 (16.7)	6.0 ± 4.5	3.5 ± 4.9
Acute scrotum	4 (10)	5.3 ± 2.5	4.4 ± 2.3	15 (6.2)	9.9 ± 4.4	6.5 ± 3.6
Vasculitis	3 (7.5)	5.7 ± 2.2	3.1 ± 3.2	4 (1.6)	9.2 ± 5.4	4.2 ± 4.8
Appendectomy	4 (10)	7.7 ± 4.0	6.2 ± 3.3	15 (4.5)	12.6 ± 3.9**	7.2 ± 5.7

\* Differences between the 2 groups were statistically insignificant in all variables except for the shorter lag time after onset of abdominal pain (p = 0.0001) and older age at time of appendectomy (p = 0.04) in the control group.

In 10 patients (20%) with attacks of fever alone, no additional manifestations were reported at the study conclusion. A comparison of their characteristics to those of patients who developed a second form of FMF attacks over the course of the disease is summarized in Table 4. The only differences found in the 10 patients were that a lower colchicine dose was needed to prevent the attacks, and there was a shorter period of followup, partly explaining the clinical discrepancy between the groups. These patients entered the study much later and were younger at the conclusion of the study (Table 4).

Mutation analysis of the MEFV gene was available for 35 patients (70%) and 129 controls (51%). There was a higher prevalence of homozygosity for M694V mutation in patients in general, particularly in those who later developed serositis, compared to the control group (p = 0.03). The distribution of all other MEFV mutations and the number of patients with 2 mutations were comparable between the groups (Table 5). The E148Q mutation, which forms an allele with a controversial effect on the expression of FMF, was present in only 5% of the alleles of the patients and the control group and therefore had no role in our findings.

At conclusion of the study, all 50 patients reported a

favorable (complete or partial) response to colchicine prophylaxis. The colchicine dose used to control the attacks was 1.3 ± 0.4 mg/day in patients with attacks of fever alone, which was comparable to the dose used by patients with polyserositis, 1.3 ± 0.4 mg/day. Colchicine was well tolerated by all patients, with mild transient diarrhea as the only reported side effect found in 8% of patients in both groups. Colchicine was not discontinued in any patient, and none had amyloidosis or nephropathy related to FMF.

## DISCUSSION

Compared to FMF patients with serositis, patients who first presented with attacks of fever alone were found to begin their disease at a younger age, had attacks of shorter duration, were more commonly homozygous to the M694V mutation, and had a higher prevalence of FMF in their family. Most of these patients will develop serositis over time, at an age similar to that of FMF patients presenting with serositis from the very onset. As expected, the delay in diagnosis of FMF in the patients of our study group was longer (about 10 months), which at this age is clinically important, but it was found to be statistically significant only by analysis of the differences in medians of the delays.

Table 4. Phenotypic characterization of patients developing a second form of attack.

Characteristic	Patients with Second Form of Attack, n = 40	Patients Continuing with Fever Alone, n = 10	p
Male/female	20/20	4/6	NS
Age at onset, yrs	1.8 ± 1.7	1.0 ± 0.7	NS
Age at diagnosis, yrs	4.5 ± 2.9	3.0 ± 1.4	NS
Delay in diagnosis, yrs	2.7 ± 3.3	2.0 ± 1.6	NS
Age at study conclusion, yrs	15.7 ± 5.4	8.6 ± 3.4	0.0003
Family history of FMF	30 (75%)	8 (80%)	NS
Sephardic Jewish extraction	38 (95%)	9 (90%)	NS
Attacks per month	2.9 ± 1.3	2.4 ± 1.3	NS
Days of fever	1.7 ± 0.8	1.6 ± 0.6	NS
Colchicine dose, mg/day	1.2 ± 0.4	0.9 ± 0.2	0.026

NS: not statistically significant.

Table 5. Distribution of MEFV mutations by groups.

Genotypes	Patients with Fever Alone, n = 50, n (%)	Patients with Fever Alone, Never Having Serositis, n = 10, n (%)	Patients with Fever Alone, Who Developed Serositis Later, n = 40, n (%)	All Other FMF Patients, n = 234, n (%)
Tested	35 (70)	10 (100)	25 (62)	129 (51)
2 mutations*	23 (66)	6 (60)	17 (68)	76 (58)
<i>M694V/M694V</i> **	16 (46)**	4 (40)	12 (48)**	41 (31)**
<i>M694V/0</i> ***	11 (31)	4 (40)	7 (28)	36 (28)
<i>M694V/V726A</i>	0	0	0	19 (14.7)
<i>M694V/E148Q</i>	3 (8.6)	0	3 (12)	9 (7.0)
<i>V726A/V726A</i>	1 (2.9)	0	1 (4)	3 (2.3)
<i>V726A/E148Q</i>	1 (2.9)	1 (10)	0	3 (2.3)
<i>V726A/M694V</i>	0	0	0	2 (1.6)
<i>E148Q/E148Q</i>	1 (2.9)	1 (10)	0	0
No mutations	1 (3)	0	1 (4)	9 (7)

\* 2 MEFV mutations: homozygous or compound heterozygotes. \*\* p = 0.03, comparing patients of study group to controls. All other differences between groups did not reach statistical significance. \*\*\* 0 denotes unknown mutation.

In young children, the diagnosis of FMF is often difficult, resulting in considerable delay in the initiation of prophylactic colchicine treatment. The longest delay in diagnosis of FMF in our cohort was observed in patients  $\leq 2$  years of age at disease onset<sup>15</sup>. As febrile illnesses in children in the first years of life are commonly attributed to intercurrent infections, we expected a much longer delay, not a borderline delay, in the diagnosis of FMF in patients first presenting with attacks of fever alone. To explain the discrepancy between the expected and actual delay, it could be argued that many FMF patients first presenting with serositis may have had previous FMF attacks of fever alone, which were overlooked or were interpreted as common pediatric infections, making the true population of patients with attacks of fever alone larger and the true delay to diagnosis in patients with attacks of fever alone much longer. This possibility is supported by the fact that serositis developed in patients presenting with fever alone at an age comparable to FMF patients of the other group (Table 3). Alternatively, a shorter than expected delay in diagnosis is explained by the possibility that in the absence of serositis the diagnosis of FMF was considered by attentive pediatricians due to a suspicious family history (76%) and appropriate ethnicity (94%).

Of the 50 patients with attacks of fever alone, 10 patients did not develop additional FMF manifestations at the conclusion of the study. This cohort was clinically and genetically comparable to the group of 40 patients who eventually developed serositis. However, these patients were enrolled later in the study, and were significantly younger at study conclusion. They also had a significantly shorter followup period than the 40 patients who later developed serositis (Table 4). It is therefore possible that they will develop more symptoms later in the course of their disease, possibly after a longer delay than the  $2.9 \pm 2.2$  years in the 40-patient group.

The diagnosis of FMF was based on the set of criteria established in 1997<sup>18</sup>, as this was the only statistically reliable set of criteria available at the initiation of our study. Contrary to the recent experience of Yalçinkaya, *et al*<sup>19</sup>, claiming lower than expected specificity for children with FMF, the Tel Hashomer criteria seem to perform in our hands with sensitivity and specificity similar to the published figures (Padeh, *et al*, unpublished observation).

Previous reports suggest homozygosity for the *M694V* mutation correlates with a more severe disease<sup>11,12,15,20</sup>. We have nevertheless found that patients with attacks of fever alone (allegedly with a milder form of FMF) have a higher prevalence of homozygosity for the *M694V* mutation. This finding may simply result from a selection bias, since genetic analysis forms the basis of endorsement in cases of diagnostic uncertainty. Alternatively, one may speculate that the higher level of evidence of the genetic background in patients with attacks of fever alone is a true finding that simply predicts a more aggressive disease in the future, illuminating the genetic aspect of the concept of a disease in evolution, which we attribute to childhood FMF.

We refrained from assessment of disease severity using published scores, as none of these are validated or seem to be appropriate for FMF in patients of this age group. The Tel-Hashomer severity scores by Pras, *et al*<sup>21</sup> and Mor, *et al*<sup>22</sup> were not designed for pediatric patients with FMF. These scores are based on variables such as age at disease onset and the number of sites involved that are not applicable in our setting. The pediatric severity score recently suggested by Ozen, *et al*<sup>23</sup> is also inappropriate for our patients for the same reasons, and also because their colchicine treatment policy differs greatly from ours.

Our series is much larger and more comprehensive than (yet in many aspects comparable to) that of Majeed, *et al*<sup>24</sup>, who reported 8 patients with recurrent episodic fever, with-



out serositis, as a presenting feature of FMF in their series of 309 FMF patients (3.2% vs 6.2% in our series). The disease onset in their patients was at age 2.5 years, in contrast to 1.8 years in our series. Five of their 8 patients developed serositis, between 1.5 and 3 years after onset of fevers, similar to the 1.2–4.4 years in our patients.

The limitation of our study is inherent in the episodic nature of FMF, namely, that many data relating to the clinical manifestations of FMF are obtained indirectly and are based on reports from patients and parents, such as the family history, the rate and characteristics of attacks, and response to therapy, which may lead to recall bias. The genetic analysis for MEFV genes was available for only 70% of the patients due to expenses borne by patients. Although we tested for only 5 MEFV mutations, these are the most common mutations found in the Israeli FMF population, relevant to > 95% of our FMF patient cohort<sup>25</sup>. Finally, our study may have ethnic bias, as only 2% of our study cohort was of non-Jewish origin. The strengths of the study lie in the large patient cohort, the setting in a single large national center for pediatric FMF in a children's hospital, the 8-year followup duration, and the use of an ongoing prospective protocol, with in-clinic continuous computerized data collection.

In summary, in 6.2% of our pediatric patients with FMF, the first disease manifestation was attacks of fever alone, with a delay of 3 to 6 years from disease onset before additional FMF symptoms, and a delay in diagnosis and initiation of colchicine treatment of 2.5 years, comparable to FMF patients presenting with recurrent serositis. We believe that this set of FMF patients manifest a disease in evolution rather than a different FMF phenotype, reflected clinically by a progressive course and genetically a more severe mutation setup. Rheumatologists and pediatricians who practice in a population with a high prevalence of FMF should be aware of the different clinical presentation of FMF in this age group, namely a tangible rate of attacks of fever alone.

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