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Characteristics of Siblings with Familial Mediterranean Fever: A Single-Center Experience

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What is already known on this topic?

- *Siblings with the same genetic mutation and living in the same environment may have different disease phenotypes.*

What this study adds on this topic?

- *To the authors' knowledge, this study has the largest number of siblings with FMF.*
- *Patients having a sibling previously diagnosed with FMF have less delay in diagnosis compared to their sibling.*

ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a hereditary, autoinflammatory disease. The characteristics of siblings with FMF have not been described in large cohorts up to now. This study aimed to examine the features of siblings with FMF.

Materials and Methods: This was a retrospective, cross-sectional study. Patients were divided into 2 groups according to the time of diagnosis (group I, the child diagnosed first in the family, and group II, the sibling diagnosed later).

Results: A total of 143 siblings (65 families) with FMF were included in the study. Seventy-two percent of the patients had the same genetic mutation as their siblings. Despite having the same genetic mutation, 59% of the patients had different attack symptoms from their siblings. In 56% of the patients, the Pras disease severity score and in 45% of the patients, the response to colchicine treatment differed from their siblings with the same mutation. Fever and abdominal pain were statistically significantly more frequent in group I than in group II ($P = .032$). The age of disease onset in group I was statistically lower than in group II ($P = .031$). Genetic mutations, attack symptoms, and colchicine response were the same in twin pairs. The age of disease onset and age at diagnosis were also the same in half of the twin pairs.

Conclusion: Parents of children diagnosed with FMF should be informed of all the symptoms of FMF disease and that siblings may present with different clinical findings.

Keywords: Familial Mediterranean fever*MEFV*, sibling, twin

INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by a gain-of-function mutation in the *Mediterranean FeVer (MEFV)* gene, which is located on the short arm of chromosome 16.[1] It is common in Mediterranean societies, including Turks, Armenians, Jews, and Arabs.[2] Patients typically present with recurrent episodes of fever, abdominal pain, chest pain, and joint pain, which typically resolve spontaneously within 1-3 days.[3]

MEFV gene mutations and clinical symptoms of patients vary between ethnic groups.[4] Studies have reported that the most commonly identified mutations in Turkey are *M694V*, *M694I*, *M680I*, and *V726A*.[5,6] Despite autosomal recessive inheritance, a single pathogenic variant is found in about 30% of patients.[3] In 90% of patients, the first symptoms of the disease appear before the age of 20.[7] The disease phenotype with heterozygous mutations in the *MEFV* gene suggests that environmental factors and epigenetic mechanisms also play a role in the pathogenesis.[8]

Patients show heterogeneity in attack symptoms, disease severity, age of disease onset, response to colchicine, and risk of amyloidosis. The reasons for these differences remain

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unclear. It has been demonstrated in clinical studies that patients with homozygous exon 10 mutations, particularly those with the *M694V* and *M680I* variants, frequently present with a severe phenotype.[2,9] Interestingly, different phenotypes can be seen in patients with the same *MEFV* mutation.[10,11] The genotype-phenotype relationship has been studied extensively.[12,13] However, there is still no consensus. Despite the growing understanding of phenotype–genotype correlations, there is still limited information about the course of the disease in siblings.

Ozturk et al[5] reported that 55.2% of the patients had a family history of FMF. Another study from Türkiye found a family history of 46.1% in patients with FMF.[12] Despite such a high rate of family history, studies provide limited information about the disease status of the parents, second or third-degree relatives, or siblings. Family history information has not yet been studied in detail.

The primary aim of this study is to examine the features of siblings with FMF and to determine whether the characteristics of the siblings are similar or different. The secondary aim is to compare the characteristics of siblings who were first diagnosed with the characteristics of siblings who were diagnosed later.

MATERIALS AND METHODS

Study Design and Population

This was a single-center, retrospective, cross-sectional study. It included siblings of patients who were followed up with a diagnosis of FMF at the pediatric rheumatology clinic of a tertiary children's hospital between January 2017 and June 2023. Patients were diagnosed with FMF according to the Ankara criteria.[14] Patients with at least 1 year of follow-up at the clinic were included in the study. Patients with homozygous exon 10 mutations detected by familial screening but without FMF-related symptoms were excluded from the study.

Siblings were divided into 2 groups according to the order of diagnosis in the family (group I, the first child diagnosed with FMF in the family; group II, the child who already had a sibling diagnosed with FMF and was diagnosed later than the sibling), and clinical characteristics were compared. Colchicine resistance was defined as ≥1 attack per month and/or persistence of subclinical inflammation in compliant patients receiving the maximum tolerated dose for 6 months.[15] A decrease in the number of attacks with colchicine treatment was defined as a partial response.[15] Pras disease severity score was used to assess the severity of the disease.[16]

Siblings were considered to have the same attack frequency if they had the same number of attacks in a year. If 1 sibling had abdominal pain and fever, and the other had chest pain and fever, these siblings were considered to have attacks with different symptoms. If the siblings' attacks ended in the same time period, these siblings were considered to have the same attack duration. In families with more than 2 siblings, if at least 1 sibling had different features, even if the other siblings had the same features, all siblings in that family were considered to have different features.

Data Collection

The demographic and clinical characteristics of the patients were recorded from electronic medical files. Siblings were compared in terms of age at disease onset and diagnosis, delay in diagnosis, attack frequency and duration, attack symptoms, *MEFV* mutations, response to treatment, and disease severity.

Ethics Committee Approval

The study was approved by Ankara Etlik City Hospital's ethics committee (approval number: AESH-EK1-2023-542, date: 13.09.2023). Since it was a retrospective study, written patient consent was not required.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analyses in this study. Categorical variables were summarized using frequencies and percentages. Visual (histogram, probability plots) and analytical (Kolmogorov–Smirnov) methods were used to test for normal distribution, and it was found that all continuous variables were not normally distributed. Continuous variables were summarized using medians (25-75th percentiles). The Chi-square test was used to compare categorical variables. The Mann–Whitney U test was used to detect differences between 2 independent groups for continuous variables. Statistical significance was defined as $P < .05$. At the end of the study, a post hoc power analysis was performed. The post hoc power analysis was conducted using Cohen's $d = 0.5$ effect size and $\alpha = 0.05$, in accordance with a 2-tailed hypothesis. The power of the research was calculated as 0.84.

RESULTS

Characteristics of Patients

This study included 143 siblings diagnosed with FMF from 65 families (4 siblings from 2 families, 3 siblings from 9 families, and 2 siblings from 54 families) identified among 1050 FMF patients. The demographic and clinical characteristics of the patients are given in Table 1. The patients' follow-up period was 6 (4-8) years.

Characteristic of Siblings

The same mutation was found in 103 (72%) siblings (4 siblings in 1 family, 3 siblings in 5 families, 2 siblings in 42 families) from 48 (73%) families. Forty (28%) of the patients in the cohort had a different genetic mutation from their siblings. Siblings with the same genetic mutation were compared. Forty-two (41%) of them (in 21 families) had attack symptoms similar to their siblings. Despite having the same genetic mutation, 59% of the siblings (in 27 families) had different attack symptoms. Responses to colchicine treatment in siblings with the same mutation were examined. The response to colchicine treatment was similar among 79 (55%) patients (37 families) and their siblings. In 57 (56%) patients with the same mutation, the Pras

score was different from that of their siblings. Attack durations and frequency per year before colchicine treatment were compared with those of siblings with the same mutation. The attack frequencies were similar in 30 (29%) patients (14 families), and the attack durations were similar in 30 (29%) patients (15 families) and their siblings. (Figure 1).

Table 1. The Demographic and Clinical Characteristics of Siblings with Familial Mediterranean Fever

	Whole Group n = 143 (%)
Age (median) (years) (25-75th percentile)⁺	16 (12-18)
Sex, female, n (%)*	91 (63.6)
Age at disease onset (years) (median) (25-75th percentile)⁺	3 (1.6-6)
Age at diagnosis (years) (median) (25-75th percentile)⁺	6 (3.5-8)
Delay in diagnosis (months) (median) (25-75th percentile)⁺	18 (6-36)
Parental consanguinity, n (%)*	55 (38.5)
Attack frequency before colchicine (years) (median) (25-75th percentile)⁺	6 (6-12)
Attack duration before colchicine (days) (median) (25-75th percentile)⁺	2 (2-3)
Clinical findings*	n (%)
Fever	134 (93.7)
Abdominal pain	134 (93.7)
Arthralgia	40 (28)
Arthritis	24 (16.8)
Chest pain	23 (16.1)
Erysipelas-like erythema	16 (11.2)
Myalgia	14 (9.8)
Leg pain with exercise	14 (9.8)
Prolonged febrile myalgia	3 (2.1)
Amyloidosis	1 (0.7)
MEFV mutations*	n (%)
M694V/M694V	75 (52.4)
M694V/-	22 (15.4)
M694V/M680I	18 (12.6)
M680I/ V726A	8 (5.6)
M694V/V726A	6 (4.2)
M694V/E148Q	5 (3.5)
M680I/M680I	3 (2.1)
M680I/K695R	2 (1.4)
V726A/A744S	2 (1.4)
M680I/E148Q	1 (0.7)
M694V/I259V	1 (0.7)
Colchicine response*	n (%)
Complete response	125 (87.4)
Partial response	8 (5.6)
Colchicine resistant	10 (7.0)
Biological therapy*	n (%) 15 (10.5)
Pras disease severity score*	n (%)
Mild	41 (28.7)
Moderate	84 (58.7)
Severe	18 (12.6)

*Data was given as numbers and percentages.
⁺Continuous variables were summarized with medians (25-75th percentile).
MEFV, Mediterranean fever gene.

Siblings were divided into groups according to the order of diagnosis. The first diagnosed child in the family was considered group I, and the other child patients in the family were considered group II. Fever and abdominal pain were statistically significantly higher in group I than in group II (P = .032 and P = .032, respectively). The age of disease onset was statistically earlier in group I than in group II (P = .031). There was no statistically significant difference in age at diagnosis between the 2 groups. Group II showed a statistically significant shorter delay in diagnosis (P = .002). Patients having a sibling previously diagnosed with FMF have less delay in diagnosis compared to their sibling. In addition, the analysis showed no statistically significant difference between the children with a first diagnosis and the others in terms of attack symptoms (except fever and abdominal pain), attack frequency and duration, response to treatment, and disease severity scores (Table 2).

Characteristics of Twins

The study included 4 pairs of twins with FMF. No information was obtained in the patient records on whether the twins were monozygotic or dizygotic. The twin pairs were of the same sex. Genetic mutations were the same in the twins. Unlike the others, only one of the twins was heterozygous for the *M694V* mutation. Attack frequency and Pras score differed between twin pairs. Half of the twin pairs had the same age of disease onset and age at diagnosis. The attack symptoms were the same in all twin pairs. All twin pairs had a complete response to colchicine (Table 3).

DISCUSSION

In this study, 143 siblings with FMF were evaluated. To the best of the knowledge, the present study is the largest cohort of siblings with FMF in the literature. This study showed that approximately 50% of patients with the same genetic mutation as their siblings exhibited differences in attack duration, frequency, and symptoms.

There are studies examining rheumatic diseases and FMF in other family members of patients with FMF. A recent study has shown that there is a significantly higher incidence of rheumatic diseases in the families of children with FMF.[17] Barut et al[18] found that about 50% of patients diagnosed with FMF had a family history. Most studies define family history as a diagnosis of FMF disease in a family member (parents, siblings, second or third-degree relatives). However, few studies have specifically investigated FMF in siblings or twins[19,20] Studies have shown that siblings with FMF may have different mutations and clinical presentations.[21,22] Özçakar et al[23] found that siblings with FMF had different clinical findings and disease severity. One of the most important findings of the study, which confirms the literature, is that although 72% of the patients had the same genetic mutation as their siblings, only 29% of patients had attack symptoms similar to those of their siblings. The findings of the study indicate that there may be differences in the clinical manifestations observed among siblings, even when they are exposed to the same genetic mutation and environmental factors. The role of environmental factors in the pathogenesis of FMF has been demonstrated. Nevertheless, the fact that there are different clinical findings in family members with the same mutation and similar environmental factors indicates that many mysteries in the pathogenesis of FMF still need to be clarified.

In this study, the delay in diagnosis was found to be longer in group I than in group II. The prevalence of fever and abdominal pain symptoms was higher in group I than in group II. It is well documented that the most common symptoms observed

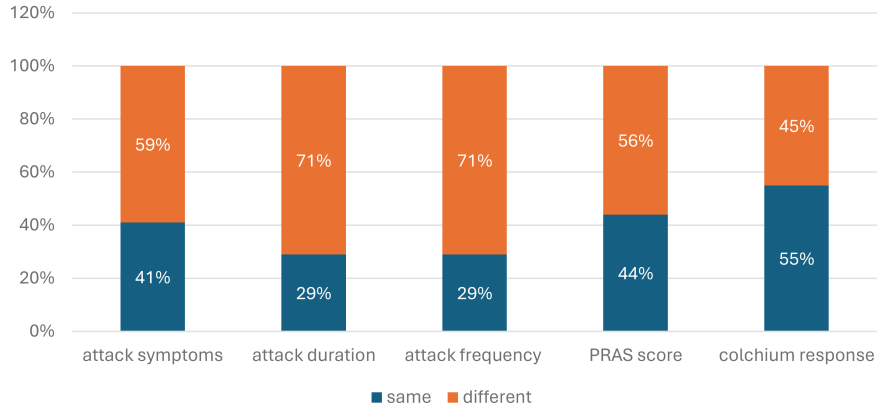

Figure 1. The similarities and differences in clinical features of siblings with the same MEFV mutations. MEFV, Mediterranean fever.

in patients with FMF are fever and abdominal pain.[5] It is possible that patients initially diagnosed within the family may have exhibited these symptoms. In other siblings, even in the absence of fever and abdominal pain, there may be an increased awareness of FMF disease within families and among physicians due to the presence of a family history. This hypothesis also lends support to the shorter delay in diagnosis observed in group II.

The existing literature contains only a limited number of studies on twins with FMF.[24,25] In 1992, Shohat et al[24] reported 10 monozygotic and 11 dizygotic twins. While all monozygotic patients had FMF symptoms, 7 of 11 dizygotic twins did not have any symptoms.[24] The age of disease onset was different in half of the monozygotic twins, and clinical findings were different in 40%, similar to those of dizygotic twins.[24] In contrast, in this study, the attack symptoms were the same in twin pairs, but

Table 2. Comparison of the First Children to be Diagnosed in the Families and the Other Patients

	Group I n = 65 (45.5%)	**Group II n = 78 (54.5%)**	***P***
Age at last visit (median) (years) (25-75th percentile)⁺	18 (15-19)	14 (11-17)	**< .001**
Sex, female, n (%)*	42 (64.6)	49 (62.8)	.825
Age at disease onset (years) (median) (25-75th percentile)⁺	2 (1.3-4.5)	3.6 (2-6)	**.031**
Age at diagnosis (years) (median) (25-75th percentile)⁺	5 (3.8-8)	6 (3.1-9)	.508
Delay in diagnosis (months) (median) (25-75th percentile)⁺	24 (12-45)	12 (6-30)	**.013**
Attack frequency before colchicine (years) (median) (25-75th percentile)⁺	12 (9-18)	12 (6-12)	.203
Attack duration before colchicine (days) (median) (25-75th percentile)⁺	2 (2-3)	2 (1.8-3)	.094
Clinical findings*	n (%)	n (%)	
Fever	64 (98)	70 (89)	**.032**
Abdominal pain	64 (98)	70 (89)	**.032**
Arthralgia	15 (23)	25 (32)	.234
Arthritis	9 (14)	15 (19)	.391
Chest pain	13 (20)	10 (13)	.245
Erysipelas-like erythema	5 (7.6)	11 (14)	.226
Myalgia	7 (10.7)	7 (8.9)	.719
Leg pain with exercise	5 (7.6)	9 (11.5)	.441
Prolonged febrile myalgia	2 (3.1)	1 (1.2)	.456
Amyloidosis	1 (1.5)	0 (0)	.272
Colchicine response#	n (%)	n (%)	
Complete response	53 (81.5)	72 (92.3)	.071
Partial response	4 (6.2)	4 (5.1)	
Resistant	8 (12.3)	2 (2.6)	
Biological therapy*	8 (12.3)	7 (8.9)	.519
Pras disease severity score*	n (%)	n (%)	
Mild	15 (23)	26 (33.4)	.366
Moderate	42 (64.6)	42 (53.8)	
Severe	8 (12.4)	10 (12.8)	

*Chi-square test was used for statistical analysis.
#Fisher–Freeman–Halton exact test was used for statistical analysis.
⁺The Mann–Whitney U test was used for statistical analysis.
Statistically significant *P* values are highlighted in bold.
Group I, the first child diagnosed with familial Mediterranean fever in the family Group II, the child who already had a sibling diagnosed with familial Mediterranean fever

Table 3. Summary of Clinical Characteristics in Twin Pairs with Familial Mediterranean Fever

Twin Pairs	Sex	*MEFV* Mutation	Age at Disease Onset (years)	Age at Diagnosis (years)	Delay in Diagnosi (months)	Attack Frequency per Year before Colchicine (years)	Attack Duration before Colchicine (days)	Attack Symptoms	Colchine Response	Pras Disease Severity Score*
1A	M	*M694V/M694V*	4	4.5	6	12	2	Fever, abdominal pain,	Complete response	1
1B	M	*M694V/-*	6	7	12	1	2	Fever, abdominal pain,	Complete response	2
2A	F	*M694V/M694V*	1.6	3.1	18	12	2	Fever, abdominal pain,	Complete response	1
2B	F	*M694V/M694V*	2.7	2.9	2	12	2	Fever, abdominal pain,	Complete response	1
3A	M	*M694V/M694V*	9	12	36	12	2	Fever, abdominal pain,chest pain	Complete response	2
3B	M	*M694V/M694V*	9	12	36	3	2	Fever, abdominal pain, chest pain	Complete response	1
4A	F	*M694V/M694V*	2	7	60	48	2	Fever, abdominal pain,	Complete response	2
4B	F	*M694V/M694V*	2	7	60	48	3	Fever, abdominal pain,	Complete response	1

*Pras disease severity score 1, mild; 2, moderate; 3, severe.
MEFV, Mediterranean fever.

the age of disease onset and age of diagnosis were different in half of the twin pairs, as reported in the literature.

The study revealed that the *M694V* mutation was present in 89% of the siblings in a homozygous or heterozygous state. Öztürk et al[5] reported a frequency of 55% for the *M694V* allelic mutation. Batu et al[6] reported that approximately 3-quarters of patients in a large cohort exhibited the *M694V* homozygous or heterozygous mutation. The high rate of the *M694V* mutation in siblings may be related to the fact that *M694V* is the most common mutation in the country. It has also been shown that there are individuals with 2 pathogenic mutations in the *MEFV* gene but without symptoms of FMF.[26] In the authors' clinical practice, patients without symptoms are not tested for the *MEFV* mutation, even if they have a family member with FMF. The present study included siblings who presented with symptoms and were diagnosed with FMF. It is currently unclear whether asymptomatic siblings are carriers of the mutation.

Strengths and Limitations

The most significant limitation of the study is that it is a single-center, retrospective design. As the study was cross-sectional and retrospective in nature, the long-term follow-up results for siblings may have been less comprehensive. This article evaluated pediatric patients diagnosed with FMF and their siblings from the patients' medical records. Unfortunately, this article ignored late-onset FMF patients, even though it is known that 90% of FMF patients are diagnosed before the age of 20. Another limitation is that the patients' environmental factors, nutritional status, and stress factors should have been thoroughly questioned. Despite these limitations, the current study is the study with the largest number of siblings with FMF and also includes information on twins with FMF. Therefore, it is believed that the study can contribute to the literature.

CONCLUSION

It is notable that clinical features and disease severity may differ even when siblings with FMF have the same genetic mutations. It is important for parents to be informed about the different clinical presentations of FMF, as siblings may have different symptoms. Siblings with the same genetic mutations and living in the same environment have different disease phenotypes, which suggests that the pathogenesis of FMF disease is quite complex. Elucidating the pathogenesis of FMF disease is very important for the management of the disease and the development of personalized medicine. Prospective studies of siblings, especially twins with FMF, would be useful.

Availability of Data and Materials: The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara Etlik City Hospital (approval numbero: AESH-EK1-2023-542, date: 13.09.2023).

Informed Consent: Since this was a retrospective study, written consent was not obtained from the patients.

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