The Turkish Journal of Pediatrics 2023; 65: 973-979
https://doi.org/10.24953/turkjped.2023.227

Original Article

Chest pain in children with familial Mediterranean fever

Emine Nur Sunar Yayla[1], Pelin Esmeray Şenol[1], Deniz Gezgin Yıldırım[1], Oğuz Söylemezoğlu[1]

[1]*Division of Pediatric Rheumatology, Department of Pediatrics, Faculty of Medicine, Gazi University, Ankara, Türkiye.*

ABSTRACT

Background. Familial Mediterranean fever (FMF) is the most common and autosomal recessive inherited autoinflammatory disease. The most common signs and symptoms are fever, abdominal pain, chest pain, and arthritis. The aim of this study was to describe the clinical, laboratory and genetic differences between pediatric FMF patients with and without chest pain.

Methods. Between January 2006 and January 2022, 1134 patients with FMF were analyzed retrospectively. Patients were divided into two groups including those with and without recurrent chest pain. These groups were compared in demographic, clinical, treatment, and *MEFV* gene analyses.

Results. A hundred and sixty-two (14.3%) patients had recurrent chest pain. In patients with recurrent chest pain, the age of onset of symptoms was younger (p=0.003), and the family history of FMF was higher (p=0.002). Patients with chest pain had a higher annual attack frequency (p<0.001), a longer attack duration (p<0.001), and higher Pras disease activity scores (p<0.001). The colchicine dose used in the treatment was higher in FMF patients with chest pain (p=0.005), and anti-IL-1treatment was higher (p<0.001). M694V homozygous mutation was found more frequently (p=0.001), whereas M694V/V726A mutation was found less frequently in patients with recurrent chest pain (p=0.017).

Conclusions. Patients with recurrent chest pain seem to have early onset symptoms, often are more likely to have family history, and have a higher disease severity. In addition, the presence of homozygous M694V mutation is more common in patients with chest pain.

Key words: chest pain, familial Mediterranean fever, pleurisy, pyrin.

Familial Mediterranean fever (FMF) is the most common and autosomal recessive inherited autoinflammatory disease, characterized by fever and serositis episodes.[1,2] The disease is common in Turks, Armenians, Arabs, and Jews living in the eastern Mediterranean.[3] The estimated prevalence of FMF in Turkey is 1/1000, and the carrier rate is 1:5.[4,5] It is caused by a Mediterranean FeVer (*MEFV*) gene mutation which is on the arm of the 16th chromosome and encodes a protein called pyrin. The mutated pyrin protein causes hyperinflammation.[6] The most common mutations are M694V, M680I, V726A and M694I mutations, located on the 10th exon of the *MEFV* gene. These mutations are responsible for 85% of cases.[7-9] Some studies have investigated the effects of genetic mutations on clinical outcomes.[10] Clinical signs and symptoms usually manifest in the first decade of life and therefore patients are usually diagnosed in childhood.[4] Inflammatory attacks are often self-limiting within 1-3 days. Typically acute phase reactants rise in attack and return to normal at the end of the attack.[1] The most common signs and symptoms are fever, abdominal pain, chest pain, and arthritis/ arthralgia.[11] Pleuritic chest pain is the third most common symptom after abdominal pain and arthritis. Chest pain is often unilateral and aggravated by inspiration. Chest pain usually ends in 1 to 4 days. The patients may benefit from analgesics and non-steroidal

✉ Emine Nur Sunar Yayla
enursunar@hotmail.com

Received 8th Apr 2023, revised 12th Aug 2023, 17th Sep 2023, accepted 9th Nov 2023

anti-inflammatory drugs. Etiology of chest pain in FMF patients is usually pleurisy. However, physical examination and X-ray are usually normal. Transient minimal pleural effusion can be detected in very few patients. The underlying cause may rarely be pericarditis.[12]

The aim of this study was to describe the clinical, laboratory and genetic differences between pediatric FMF patients with and without chest pain.

Material and Methods

Between January 2006 and January 2022, 1134 patients with FMF who applied to the outpatient clinic of Gazi University Faculty of Medicine, Department of Pediatric Rheumatology, were analyzed retrospectively. All patients were younger than 18 years at diagnosis and were selected according to Turkish pediatric FMF criteria.[13] Gender, age of symptom onset and diagnosis, family history of FMF, number of attacks and duration of attacks in the last year with data obtained at the time of diagnosis, and Pras severity score obtained at the last visit.[14] The presence of family history was defined as having an FMF diagnosis in 1st, 2nd, or 3rd-degree relatives. The colchicine dose at their last visit was recorded. Patients with colchicine intolerance or inadequate treatment response are switched to interleukin (IL)-1 antagonist treatment in our clinic. The patients' data using IL-1 antagonists were recorded from the file records. Presence of fever, peritonitis, chest pain, arthralgia, arthritis, erysipelas-like rash, and amyloidosis were recorded. *MEFV* gene analysis results of 1131 patients were available. No mutation was detected in 61 of them. The term "patients without *MEFV* gene mutation" was used for these patients. *MEFV* gene was derived from blood samples in EDTA tubes at the Nephrology and Tissue Laboratory at the Gazi University Medical Faculty. The polymerase chain reaction workup, which was revealed with the pyrosequence DNA analysis system, demonstrated the 2-3-5-10 exons of the *MEFV* gene. Patients were divided into two groups as those with and without recurrent chest pain. These groups were compared in demographic, clinical findings, treatment, and *MEFV* gene analyses. The present study was approved by the local ethics committee of the Gazi University (Decision no: E-77082166-604.01.02-332908 dated 05.04.2022).

Statistical analysis

Data were analyzed with SPSS version 21 software (SPSS, Chicago, USA). Categorical data were expressed by frequency and percentage. Quantitative data were not normally distributed, and the median was presented as an interquartile range. The Mann-Whitney U test was used to compare the quantitative data of patients with and without chest pain. Chi-square or Fisher's exact tests were used for categorical data comparisons. *P* values less than 0.05 were accepted as statistically significant.

Results

One thousand one hundred thirty-four patients with FMF were included in the study. The demographic and clinical characteristics of the patients are presented in Table I. A hundred and sixty-two (14.3%) patients had recurrent chest pain. In patients with recurrent chest pain, the age of onset of symptoms was younger ($p=0.003$), and the family history of FMF was higher ($p=0.002$). Patients with chest pain had a higher annual attack frequency ($p<0.001$), a longer attack duration ($p<0.001$), and higher Pras disease activity scores ($p<0.001$) (Table I). Other clinical findings of patients with and without chest pain were similar. The colchicine dose used in the treatment was higher in FMF patients with chest pain ($p=0.005$), and Anti-IL-1 treatment was higher ($p<0.001$) (Table I). In the patients with chest pain, 92 of the patients (56.8%) had posteroanterior (PA) chest x-ray, and 27 of the patients (16.7%) had electrocardiography (ECG) and echocardiography (ECO). Pleural effusion was detected in 2.2% (2/92) and pericarditis in 3.7% (1/27) was detected.

Table I. Comparison of demographic and clinical characteristics of patients with and without chest pain.

	All patients N=1134	FMF patients with chest pain N=162	FMF patients without chest pain N=972	p
Gender†				0.827
female	593 (52.3)	86 (53.1)	507 (52.2)	
male	541 (47.7)	76 (46.9)	465 (47.8)	
Age of symptom onset, year‡	6 [6]	4 [5]	6 [6]	**0.003**
Age of diagnosis, year‡	7 [7]	6 [6]	7 [6]	0.122
Family history†	579 (51.1)	101 (62.3)	478 (49.2)	**0.002**
Attack count, (Last 6 months before FMF diagnosis)‡	2 [3]	2 [4]	2 [2]	**<0.001**
Attack duration, days‡	2 [1]	3 [2]	2 [1]	**<0.001**
Pras score‡	6 [2]	6 [3]	5 [3]	**<0.001**
Clinical features†				
Abdominal pain	946 (83.4)	131 (80.9)	815 (83.8)	0.344
Fever	873 (77)	120 (74.1)	753 (77.5)	0.342
Arthralgia	644 (56.8)	94 (58)	550 (56.6)	0.732
Arthritis	186 (16.4)	30 (18.5)	156 (16)	0.432
Erysipelas-like lesion	92 (8.1)	18 (11.1)	74 (7.6)	0.131
Amyloidosis	9 (8)	3 (1.9)	6 (0.6)	0.125
Medication				
Colchicine dose, mg/day‡	1 [0]	1 [0.5]	1 [0]	**0.005**
Anti–IL–1 therapy usage†	27 (2.4)	12 (7.4)	15 (1.5)	**<0.001**

† Data are given as numbers and percentages.
‡ Data were given as median (interquartile range).
FMF: Familial Mediterranean fever.

MEFV gene mutation analyzes of 1131 patients were performed. The data of 3 patients were missing. M694V homozygous mutation was found more frequently (p=0.001), whereas M694V/V726A mutation was found less frequently in patients with recurrent chest pain (p=0.017) (Table II).

Demographic, clinical findings, and genetic characteristics of 14 patients with only recurrent chest pain and FMF family history, without fever, peritonitis, and arthritis, are presented in Table III.

Discussion

Recurrent chest pain is observed in approximately 20% of FMF patients and is among the most common clinical findings following abdominal pain and arthritis.[15,16] This study demonstrated that 14% of patients had recurrent chest pain. Patients with chest pain had a younger age at diagnosis. Our previous study evaluated the impact of age at diagnosis in clinical findings; we showed that chest pain complaints were more common in children diagnosed under 2 years of age.[17] Also, in another study by Tanatar et al.[18], chest pain was more common in patients aged three years and older. However, other studies have not shown a relationship between the age of symptom onset and the presence of chest pain.[19,20]

We showed that family history is more common in patients with recurrent chest pain. To the best of our knowledge, there is no detailed study on clinical findings of patients with a family history. However, in a study evaluating the effects of

Table II. Comparison of *MEFV* gene analyzes of patients with and without chest pain.

	All patients* N=1131	FMF patients with chest pain N=161	FMF patients without chest pain N=970	p
M694V/-	321 (28.4)	38 (23.6)	283 (29.2)	0.146
M694V/M694V	218 (19.3)	47 (29.2)	171 (17.6)	**0.001**
M680I/-	82 (7.3)	9 (5.6)	73 (7.5)	0.380
E148Q/-	80 (7.1)	13 (8.1)	67 (6.9)	0.593
M694V/V726A	68 (6)	3 (1.9)	65 (6.7)	**0.017**
M694V/M680I	57 (5)	12 (7.5)	45 (4.6)	0.131
M694V/E148Q	41 (3.6)	10 (6.2)	31 (3.2)	0.058
V726A/-	32 (2.8)	6 (3.7)	26 (2.7)	0.441
M680I/M680I	30 (2.7)	4 (2.5)	26 (2.7)	>0.999
Other mutations**	141(12.5)	12(7.5)	129(13.3)	-
Patients without *MEFV* mutation	61 (5.4)	7 (4.3)	54 (5.6)	0.526

**MEFV* gene analysis data of 3 patients could not be reached
** Other *MEFV* mutation analyzes are mutations that occur less than 20 in total. Among other mutations, there was no statistically significant difference between the two groups. Other *MEFV* mutations; F479L/-, E148Q/E148Q, M694V/R202Q, M680I/R761H, M680I/P369S, M694I/M694I, R202Q/-, A744S/-, M694V/M694I, V726A/V726A, M694V/K695R, M694V/A744S, M694V/P369S, V726A/F479L, R761H/-, K695R/-, E148Q/L110P, E148Q/A744S, E148Q/R202Q, P369S/R408Q, E167D/-, A202G/-, E148Q/P369S, V726A/E148Q, M680I/V726A, M680I/E148Q, M694V/R761H.
FMF: Familial Mediterranean fever.

Table III. Patients with only chest pain complaint.

	Age of diagnosis, year	Sex	*MEFV* gene mutation	Attack count at one year before the diagnosis of FMF	Total attack count before the diagnosis of FMF	Coexistent diseases	Amyloidosis	Anti–IL–1 therapy usage
Patient 1	6	Female	E148Q/-	0	5	IgAV	Absent	Absent
Patient 2	5	Female	M694V/-	2	6	-	Absent	Absent
Patient 3	17	Male	M694V/E148Q	6	6	-	Absent	Absent
Patient 4	15	Male	M694V/-	12	12	-	Absent	Absent
Patient 5	6	Female	M694V/M694V	2	4	-	Absent	Absent
Patient 6	8	Female	M694V/E148Q	2	3	-	Absent	Absent
Patient 7	14	Female	E148Q/-	0	6	-	Absent	Absent
Patient 8	5	Female	M694V/M694V	6	7	-	Absent	Absent
Patient 9	5	Female	M694V/-	2	4	-	Absent	Absent
Patient 10	4	Male	M694V/M694V	4	6	-	Absent	Absent
Patient 11	9	Female	M694V/E148Q	3	3	-	Absent	Absent
Patient 12	15	Male	E148Q/-	2	5	-	Absent	Absent
Patient 13	4	Male	M694V/M694V	2	5	-	Absent	Absent
Patient 14	7	Male	M694V/-	2	4	-	Absent	Absent

FMF: Familial Mediterranean fever, IgAV: Immunoglobulin A vasculitis.

MEFV gene mutations on clinical findings, it was reported that the frequency of chest pain might be less in those with a family history.[21] In addition, it has been reported that family history is more frequently positive in patients with FMF complicated by amyloidosis.[22]

It is known that chest pain is more common in adult and pediatric FMF patients with persistent inflammation.[23,24] Although several studies describe an increased incidence of chest pain in adult FMF patients with amyloidosis, some studies claim vice versa.[22,25] In the current study, we found the frequency of amyloidosis to be similar in both groups. However, Pras scores were higher in patients with chest pain. In our study, the increased frequency of family history, number of attacks, longer duration of attacks, and higher disease severity scores in patients with chest pain suggest that the disease progresses more severely in these patients. For this reason, the need for an IL-1 antagonist was probably more significant in the patients with chest pain.

Many studies have been conducted to assess the effect of *MEFV* gene mutations on clinical findings. In a study based on real-life data from Turkey, chest pain was significantly more common in FMF patients with M694V/M680I, M680I/M680I, M694V/R761H, and M680I/E148Q mutations.[15] Kilic et al.[26] reported an increased frequency of chest pain in patients with M694V homozygous and E148Q heterozygous mutations. There may also be ethnicity differences in the effect of *MEFV* mutations on chest pain. Jewish children with the M694V homozygous mutation have been reported to have more pulmonary symptoms than Arab children.[27] In the presented study, we detected M694V homozygous (29%), M694V heterozygous (24%), E148Q heterozygous (8%), and M694V/M680I (7.5%) compounds heterozygous mutations as the most common mutations in patients with chest pain (Table II). When we compare the groups with and without chest pain, we found that the presence of M694V homozygous mutation is more common, and presence of M694V/V726A compound heterozygous mutation is less common in the group with chest pain (Table II). In a previous study, it was reported that symptoms such as fever and chest pain were less common in patients with the V726A mutation.[28] In the light of this information, it can be said that the V726A mutation may be associated with milder symptoms. However, more comprehensive data are needed for definitive conclusions.

Our study has limitations, such as its single-center retrospective design and lack of detailed pulmonary and cardiac imaging of patients with chest pain. Despite this, the study has its strengths in that it has revealed the characteristics of patients with recurrent chest pain based on data of a relatively large number of patients despite being drawn from a single center.

As a result, patients with recurrent chest pain seem to have early onset symptoms, more often have family history, and have a higher disease severity. In addition, the presence of homozygous M694V mutation is more common in patients with chest pain.

Ethical approval

The present study was approved by the local ethics committee of the Gazi University (Decision no: E-77082166-604.01.02-332908 dated 05.04.2022).

Author contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ENSY, PŞD, DGY and OS. The first draft of the manuscript was written by ENSY and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. J Inflamm Res 2016; 9: 13-20. https://doi.org/10.2147/JIR.S91352
2. Barut K, Sahin S, Adrovic A, et al. Familial Mediterranean fever in childhood: a single-center experience. Rheumatol Int 2018; 38: 67-74. https://doi.org/10.1007/s00296-017-3796-0
3. Ben-Chetrit E, Levy M. Familial mediterranean fever. Lancet 1998; 351: 659-664. https://doi.org/10.1016/S0140-6736(97)09408-7
4. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine 2005; 84: 1-11. https://doi.org/10.1097/01.md.0000152370.84628.0c
5. Soylemezoglu O, Kandur Y, Gonen S, et al. Familial Mediterranean fever gene mutation frequencies in a sample Turkish population. Clin Exp Rheumatol 2016; 34: 97-100.
6. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997; 17: 25-31. https://doi.org/10.1038/ng0997-25
7. International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 1997; 90: 797-807. https://doi.org/10.1016/s0092-8674(00)80539-5
8. Yalçinkaya F, Cakar N, Misirlioğlu M, et al. Genotype-phenotype correlation in a large group of Turkish patients with familial mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatology (Oxford) 2000; 39: 67-72. https://doi.org/10.1093/rheumatology/39.1.67
9. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet 2001; 9: 473-483. https://doi.org/10.1038/sj.ejhg.5200658
10. Papadopoulos VP, Giaglis S, Mitroulis I, Ritis K. The population genetics of familial mediterranean fever: a meta-analysis study. Ann Hum Genet 2008; 72: 752-761. https://doi.org/10.1111/j.1469-1809.2008.00471.x
11. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-1885. https://doi.org/10.1002/art.1780401023
12. Livneh A, Langevitz P, Pras M. Pulmonary associations in familial Mediterranean fever. Curr Opin Pulm Med 1999; 5: 326-331. https://doi.org/10.1097/00063198-199909000-00011
13. Yalçinkaya F, Ozen S, Ozçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009; 48: 395-398. https://doi.org/10.1093/rheumatology/ken509
14. Pras E, Livneh A, Balow JE, et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet 1998; 75: 216-219. https://doi.org/10.1002/(sici)1096-8628(19980113)75:2<216::aid-ajmg20>3.0.co;2-r
15. Öztürk K, Coşkuner T, Baglan E, et al. Real-Life data from the largest pediatric familial Mediterranean fever cohort. Front Pediatr 2022; 9: 805919. https://doi.org/10.3389/fped.2021.805919
16. Demir F, Bolac GL, Merter T, et al. The musculoskeletal system manifestations in children with familial Mediterranean fever. North Clin Istanb 2020; 7: 438-442. https://doi.org/10.14744/nci.2020.96636
17. Gezgin Yildirim D, Gönen S, Fidan K, Söylemezoğlu O. Does age at onset affect the clinical presentation of Familial Mediterranean Fever in children? J Clin Rheumatol 2022; 28: e125-e128. https://doi.org/10.1097/RHU.0000000000001637
18. Tanatar A, Karadağ ŞG, Çakan M, Sönmez HE, Ayaz NA. Age of onset as an influencing factor for disease severity in children with familial Mediterranean fever. Mod Rheumatol 2021; 31: 219-222. https://doi.org/10.1080/14397595.2020.1719594
19. Padeh S, Livneh A, Pras E, et al. Familial Mediterranean Fever in the first two years of life: a unique phenotype of disease in evolution. J Pediatr 2010; 156: 985-989. https://doi.org/10.1016/j.jpeds.2009.12.010
20. Yalcinkaya F, Özçakar Z, Tanyıldız M. Paediatric rheumatology Familial Mediterranean fever in small children in Turkey. Clin Exp Rheumatol 2011; 29: S87-S90.
21. Sönmezgöz E, Özer S, Gül A, et al. Clinical and demographic evaluation according to MEFV genes in patients with Familial Mediterranean Fever. Biochem Genet 2019; 57: 289-300. https://doi.org/10.1007/s10528-018-9889-y

22. Cefle A, Kamali S, Sayarlioglu M, et al. A comparison of clinical findings of familial Mediterranean fever patients with and without amyloidosis. Rheumatol Int 2005; 25: 442-446. https://doi.org/10.1007/s00296-004-0471-z

23. Gezgin Yıldırım D, Esmeray Senol P, Söylemezoğlu O. Predictors of persistent inflammation in children with familial Mediterranean fever. Mod Rheumatol 2022; 32: 803-807. https://doi.org/10.1093/mr/roab054

24. Babaoglu H, Armagan B, Bodakci E, et al. Predictors of persistent inflammation in familial Mediterranean fever and association with damage. Rheumatology (Oxford) 2021; 60: 333-339. https://doi.org/10.1093/rheumatology/keaa378

25. Kasifoglu T, Bilge SY, Sari I, et al. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology (Oxford) 2014; 53: 741-745. https://doi.org/10.1093/rheumatology/ket400

26. Kilic A, Varkal MA, Durmus MS, et al. Relationship between clinical findings and genetic mutations in patients with familial Mediterranean fever. Pediatr Rheumatol Online J 2015; 13: 59. https://doi.org/10.1186/s12969-015-0057-1

27. Brik R, Gershoni-Baruch R, Shinawi M, Barak L, Bentur L. Pulmonary manifestations and function tests in children genetically diagnosed with FMF. Pediatr Pulmonol 2003; 35: 452-455. https://doi.org/10.1002/ppul.10270

28. Cekin N, Akyurek ME, Pinarbasi E, Ozen F. MEFV mutations and their relation to major clinical symptoms of Familial Mediterranean Fever. Gene 2017; 626: 9-13. https://doi.org/10.1016/j.gene.2017.05.013