North Clin Istanb 2020;7(5):438–442
doi: 10.14744/nci.2020.96636

Original Article PEDIATRICS

The musculoskeletal system manifestations in children with familial Mediterranean fever

Ferhat Demir,[1] Gizem Leyla Bolac,[2] Tuba Merter,[2] Sezin Canbek,[3] Ozlem Akgun Dogan,[3] Yasemin Kendir Demirkol,[3] Jale Yildiz,[3] Hamdi Levent Doganay,[3] Betul Sozeri[1]

[1]Department of Pediatric Rheumatology, University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey
[2]Department of Pediatrics, University of Health Sciences, Umraniye Training and Research Hospital Istanbul, Turkey
[3]Genomic Laboratory (GLAB), University of Health Sciences, Umraniye Training and Research Hospital, Istanbul, Turkey

ABSTRACT

OBJECTIVE: Familial Mediterranean fever (FMF) is a monogenic inherited periodic fever syndrome presenting with episodes of self-limiting fever and inflammation of serosal membranes. Besides the findings in the diagnostic criteria, musculoskeletal findings can also be seen in FMF patients attacks. In this study, we aim to reveal the frequency and genotype association of musculoskeletal manifestations in children with FMF.

METHODS: The patients diagnosed with FMF between January 1, 2017 and June 1, 2019, and followed for at least six months in our pediatric rheumatology clinic were included in this study. Musculoskeletal manifestations of patients were enrolled. The patients were grouped according to the "Mediterranean Fever" (MEFV) gene variants. Musculoskeletal manifestations of the patients were compared between the groups.

RESULTS: The study group included 634 children with FMF (336 female and 298 male, F/M: 1.13/1). The clinical manifestations of patients in the attack period were as follows: 99% of the patients had a fever, 87.3% had abdominal pain, 20.7% had chest pain, 11.3% had vomiting, 10.7% had erysipelas like erythema, and 9.3% had a headache. The musculoskeletal symptoms were accompanied by 58.6% (n=372) of the patients during the attack period. The most common musculoskeletal manifestation was found as arthralgia (32.6%, n=206). Also, the other musculoskeletal manifestations were as follows during attacks: arthritis in 23.7% (n=150), myalgia in 20.5% (n=130), exertional leg pain in 6.5% (n=41), and protracted febrile myalgia in 1% (n=7) of the patients. It was observed that the musculoskeletal manifestations were significantly higher in patients with homozygous M694V variants in exon-10 (p=0.017). The musculoskeletal manifestations were more common in the attack periods of patients carrying the M694V variant in at least one allele (p=0.019).

CONCLUSION: We found that the musculoskeletal manifestations were accompanied in more than half of patients with FMF. M694V variant was found as a risk factor for emerging musculoskeletal manifestations.

Keywords: Familial Mediterranean fever; MEFV; musculoskeletal.

Cite this article as: *Demir F, Bolac GL, Merter T, Canbek S, Akgun Dogan O, Kendir Demirkol Y, et al. The musculoskeletal system manifestations in children with familial Mediterranean fever. North Clin Istanb 2020;7(5):438–442.*

Familial Mediterranean fever (FMF) is the most common cause of monogenic inherited periodic fever syndrome in children. Patients are present with episodes of self-limiting fever and inflammation of serosal membranes [1, 2]. The attacks that emerge with arthritis were defined as one of the major diagnostic criteria besides the involvement of serosal membranes in the Ankara pediatric FMF criteria reported in 2009 and the Eurofever/PRINTO FMF classification criteria reported in 2019 [3, 4]. Arthritis findings last longer than usual attacks for

Received: May 06, 2020 *Accepted:* June 12, 2020 *Online:* September 04, 2020

Correspondence: Ferhat DEMIR, MD. Saglik Bilimleri Universitesi Umraniye Egitim ve Arastirma Hastanesi, Cocuk Romatoloji Klinigi, Istanbul, Turkey.
Tel: +90 544 551 21 22 e-mail: drferhat@outlook.com

up to 7–10 days, and there have no permanent sequelae in most cases. Besides the findings in the diagnostic criteria, non-specific musculoskeletal findings, such as myalgia, arthralgia, transient synovitis, and more rare manifestations like protracted febrile myalgia, can also be seen in FMF patients' attacks [5]. Also, HLA-B27 negative sacroiliitis is a permanent musculoskeletal comorbid condition that can be seen in a significant part of FMF patients [6].

The research related to the genotype linkage of musculoskeletal involvement in patients with FMF is limited. Protracted febrile myalgia as attack manifestation is more common in patients with homozygous mutations in the 10th exon of the Mediterranean Fever (MEFV) gene [7]. In the present study, we aim to reveal the frequency and genotype association of musculoskeletal manifestations in children diagnosed with FMF.

MATERIALS AND METHODS

This was a retrospective study conducted at the University of Health Sciences, Umraniye Training and Research Hospital, Department of Pediatric Rheumatology. The protocol of this study was approved by the local ethics committee (Approval No/Date: B.10.1.TKH.4.34.H.GP.0.01/233/18.12.2019). The patients diagnosed with FMF in our pediatric rheumatology clinic between January 1, 2017 and June 1, 2019, were included in this study. All patients were evaluated during attacks by two pediatric rheumatology specialists (BS or FD). The diagnosis of FMF was based on the pediatric FMF (Ankara) criteria [3]. The patients with the clinical suspicion of FMF underwent MEFV panel genetic screening in which four most common mutations in our country (M694V, M680I, V726A and E148Q) were included, at our Genomic Laboratory after clinical diagnosis [8]. Whole MEFV gene analysis was performed in patients with negative panel analysis. The patients included in this study with a diagnosis of FMF were consisted of genetically established children. The patients with a follow-up period of less than six months or had another chronic illness were excluded from this study.

Demographic, clinical, laboratory and genetic data of patients were collected. The musculoskeletal manifestations (arthritis, arthralgia, myalgia, exercise-induced myalgia-arthralgia, exertional leg pain, protracted febrile myalgia, reflex sympathetic dystrophy and sacroiliitis) of the patients in attacks and healthy period were also enrolled. The patients were grouped according to the MEFV variants. Musculoskeletal manifestations of the patients were compared between the groups.

Statistical Analysis

Statistical package for the social sciences (SPSS) (version 23.0, SPSS-Inc., Chicago, IL, USA) was used for statistical analysis. Categorical data were presented as numbers and percentages. Numerical data with asymmetrical distribution are presented as the median with data range (minimum to maximum). The normality of the distribution of numerical variables was assessed by the Shapiro-Wilk test. Mann-Whitney U test was used to compare the numerical variables that were not normally distributed between the patient groups. The χ^2-test was used to compare categorical variables between groups. A p-value <0.05 was considered statistically significant.

RESULTS

The study group included 634 children with FMF (336 female and 298 male, F/M: 1.13/1). The median diagnosis age and follow-up duration of patients were found 72 (min–max: 8–211) and 17.5 (min–max: 6–36) months, respectively. While 32% of patients had consanguinity between their parents, 62% had at least one patient diagnosed with the autoinflammatory disease in their relatives. Also, 145 (23%) patients had an autoimmune disease in their relatives. The clinical manifestations of patients in the attack period were as follows: 99% of the patients had a fever, 87.3% had abdominal pain, 20.7% had chest pain, 11.3% had vomiting, 10.7% had erysipelas like erythema, and 9.3% had a headache. The musculoskeletal symptoms were accompanied by 58.6% (n=372) of the patients during the attack period. The most common musculoskeletal manifestation was found as arthralgia (32.6%, n=206). Also, the other musculoskeletal manifestations were found as follows during attacks; arthritis in 23.7% (n=150), myalgia in 20.5% (n=130), exertional leg pain in 6.5% (n=41), and protracted febrile myalgia in 1% (n=7) of the patients. Besides, the findings showed that 14% (n=89) of the patients developed myalgia or arthralgia triggered by prolonged walking or standing during healthy periods. The sacroiliitis as chronic comorbidity of FMF was found in 26 (4%) patients. The reflex sympathetic dystrophy also emerged in 0.3% (n=2) of the patients. The demographic and clinical characteristics of the study group are presented in Table 1.

An exon-10 variant was found in at least one allele of 92% of the patients. In 8% of patients, variants were found in other exons. 33.3% of the patients (n=211) had homozygous or compound heterozygous variants in the 10th exon. One hundred sixty-four patients (26%) had M694V homozygous variant. While 230 patients (36.3%) had

Table 1. The demographic and clinical characteristics of the study group

Characteristics	Patients (%)
Gender	
Female	53
Male	47
Age of diagnosis (month)*	72 (8–211)
Follow-up duration (month)*	17.5 (6–36)
The consanguinity between parents	32
Autoimmune diseases in relatives	23
Autoinflammatory diseases in relatives	62
The clinical manifestations of patients in attack period	
Fever	99
Abdominal pain	87.3
Chest pain	20.7
Erysipelas-like erythema	10.7
Vomiting	11.3
Headache	9.3
The musculoskeletal symptoms of patients in attack periods	
Arthralgia	32.6
Arthritis	23.7
Myalgia	20.5
Exertional leg pain	6.5
Protracted febrile myalgia	1
The musculoskeletal symptoms of patients between attack periods	
Myalgia or arthralgia triggered by prolonged walking or standing	14
Sacroiliitis	4
The reflex sympathetic dystrophy	0.3
Genetic screening (MEFV gene) results	
The all homozygous or compound heterozygous variants in the 10th exon	33.3
M694V homozygous	26
The all heterozygous variants in the 10th exon	58.6
M694V heterozygous	36.3
The M694V variant in at least one allele	72
The variants in other exons	8.2

*: Median (minimum–maximum).

M694V heterozygous mutation, 141 patients (22.3%) had other variants as heterozygous in exon-10. There were 457 patients carrying the M694V variant in at least one allele. When we evaluated the patients with and without musculoskeletal manifestations with the genotypic results, it was observed that the presence of a homozygous, a combined heterozygous or any heterozygous variant in the exon-10 which not included M694V, did not cause a statistically significant increase for musculoskeletal manifestations. Also, the presence of the M694V variant in one allele was not significantly correlate with the presence of musculoskeletal symptoms in attacks (p=0.49), while it was found that the musculoskeletal symptoms are more common in the attack periods of patients carrying the M694V homozygous variant (p=0.017) or M694V variant in at least one allele (p=0.019) (Table 2). It was also shown that all patients with protracted febrile myalgia had an exon-10 variant in at least one allele.

DISCUSSION

FMF is the most common monogenic inherited autoinflammatory disease in our country [9, 10]. In addition to the serosal inflammation, the musculoskeletal system can also be affected during attacks. In this study, we presented the musculoskeletal manifestations and their genotype relationship in Turkish pediatric FMF patients.

There are a limited number of studies in the literature evaluated musculoskeletal manifestations in pediatric FMF patients. Arthralgia and arthritis are the most common reported musculoskeletal manifestations of FMF [5, 11]. Especially, recurrent and self-limiting arthritis attacks should suggest FMF. It may be triggered by minor trauma or prolonged efforts, such as walking or standing. The researchers have shown that arthritis usually lasts longer than usual attacks, often affects large joints and improves without permanent sequelae [12, 13]. It has also been shown that up to 5% of patients developed chronic arthritis, in whom the hip and knee joints were particularly affected [14]. Brik et al. [5] showed that musculoskeletal findings are common in FMF attacks in pediatric patients and their frequency varies racially. They found that the arthritis was seen in FMF attacks in 71% of Jewish children and 40% of Arab children. In a study, including pediatric patients from Turkey, 18% of the FMF patients present arthritis in the attack period, while 2.2% of all patients had persistent arthritis [15]. In our study, the FMF attack was observed in 23.7% of our patients as monoarthritis. We found similar results with other pediatric research from our country. Besides, arthritis is found less common in Turkish patients compared with the Arab and Jewish cohorts. Different from the other studies, although some arthritis attacks lasting weeks, we did not have any patient developed persistent arthritis in our cohort. We also found the arthralgia as

Table 2. The comparison of the patient groups according to genotypic results

The patients MEFV variants	The patients with MSCs manifestations (n)	The patients without MSCs manifestations (n)	p
The homozygous or compound heterozygous variants that not included M694V in the 10th exon	26	21	0.42
M694V homozygous	113	51	**0.017**
The heterozygous variants except for M694V in the 10th exon	75	66	0.57
M694V heterozygous	134	96	0.49
The M694V variant in at least one allele	281	176	**0.019**
The variants in other exons	29	23	0.52

MEFV: Mediterranean fever; MSCs: Musculoskeletal system.

the most common musculoskeletal manifestation during attacks (in 32.6% of patients).

Myalgia is a musculoskeletal system manifestation that can be seen in up to half of the patients with FMF during the attack periods [16, 17]. It may accompany fever and serositis attacks without other musculoskeletal complaints. Besides, it can be seen as an isolated attack by displaying different patterns. It can emerge as a form of spontaneous or exercise-induced myalgia. Also, protracted febrile myalgia is a longer, more severe and often steroid-responsive attack pattern. Majeed et al. [17] determined that 25% of the pediatric 264 FMF patients had myalgia in the attack period. The most common pattern in their studies was found to exercise-induced myalgia. Kunt et al. [15] also found the frequency of myalgia in attacks of Turkish FMF pediatric patients as 7.6%. In another study included 59 Sephardic Jewish pediatric patients, the protracted febrile myalgia attack incidence was found as high as 10% [5]. It was determined that 20.5% of our patients had myalgia during the attack period. Also, 6.5% of our FMF patients had exertional leg pain, and 1% had protracted febrile myalgia as an attack manifestation. Although the incidence of protracted febrile myalgia is relatively low compared to literature, the frequency of myalgia was consistent with the other cohorts. We found reflex sympathetic dystrophy in two of our patients. These children did not have elevated inflammatory markers during these periods and they were not considered as in attack period. Additionally, it was determined that 14% (n=89) of the patients developed myalgia or arthralgia triggered by prolonged walking or standing during healthy periods. When we evaluated these patients in myalgia period, these complaints were not considered as an FMF attack because they were improved by rest in a short time and were not accompanied by an acute phase reactant elevation. In this regard, two different myalgia patterns can be confused. It may evaluate as myalgia attack or as ordinary myalgia (not attack) triggered by exercise. A comprehensive evaluation of the patient during this period can help differentiate it is an attack or not.

The frequency of sacroiliitis was found to be 2.6% in patients with FMF in a recently published study [18]. Sacroiliitis, as a comorbid condition that can be seen in together with FMF, was found in our 26 (4%) patient with FMF. We found similar results with the frequency of sacroiliitis in Turkish research [18, 19]. None of our patients were diagnosed with juvenile spondyloarthritis or juvenile idiopathic arthritis. In another recent study, it has been determined that the clinical characteristics of spondylitis-related sacroiliitis and FMF-related sacroiliac show differences [20]. It has been reported that patients with juvenile spondylitis exhibit higher acute phase response, and HLA-B27 positivity. Similarly, HLA-B27 positivity frequency was found low, and acute phase responses were within the normal range between attack periods in our FMF patients with sacroiliitis.

The manifestations of FMF may be associated with variant differences in the MEFV gene. In studies evaluated the relationship between musculoskeletal symptoms and genotype, it has been shown that arthritis and arthralgia are more common in patients with a homozygous M694V variant [21–23]. In a pediatric FMF study conducted in our country, it was found that the frequency of arthralgia and exertional leg pain increased in M694V heterozygous patients [15]. Similarly, in studies, including adult patients, M694V mutation carriage has been reported to be effective in the development of musculoskeletal complaints [24]. We observed in our study that the

presence of homozygous or combined heterozygous variants in the exon-10 that did not include M694V did not cause a risk for musculoskeletal manifestations, while we found that the musculoskeletal symptoms are more common in patients carrying the M694V homozygous variant or M694V variant in at least one allele. Different from the previous studies, the presence of only the M694V heterozygous variant did not cause an increase in musculoskeletal symptoms. Our study results suggested that especially the homozygous and compound heterozygous mutations carrying the M694V variant in at least one allele may be associated with musculoskeletal manifestations.

Conclusion

The findings showed that the musculoskeletal manifestations were seen as an attack symptom in more than half of FMF patients. Also, homozygous and compound heterozygous MEFV mutations, including the M694V variant, were found as a risk factor for emerging musculoskeletal manifestations. In children with unexplained and recurrent musculoskeletal symptoms, especially in ethnicities with the high frequency of FMF, analysis of the MEFV gene can help reveal the underlying cause.

Acknowledgements: We are grateful to all participating children and their families.

Ethics Committee Approval: The protocol of this study was approved by the local ethics committee (date: 18.12.2019, number: B.10.1.TKH.4.34.H.GP.0.01/233).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – FD, BS; Design – FD, BS; Supervision – FD, BS; Fundings – HLD, BS; Materials – FD, GLB, TM, SC, OAD, YKD, JL, HLD, BS; Data collection and/or processing – FD, GLB, TM, SC, OAD, YKD, JL, HLD, BS; Analysis and/or interpretation – FD, SC, OAD, YKD, JL, HLD, BS; Literature review – FD, BS; Writing – FD, BS; Critical review – FD, HLD, BS.

REFERENCES

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967;43:227–53.
2. Livneh A, Langevitz P. Diagnostic and treatment concerns in familial Mediterranean fever. Baillieres Best Pract Res Clin Rheumatol 2000;14:477–98. [CrossRef]
3. Yalçinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009;48:395–8. [CrossRef]
4. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al; Eurofever Registry and the Paediatric Rheumatology International Trials Organisation (PRINTO). Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019;78:1025–32. [CrossRef]
5. Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R. The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. Arthritis Rheum 2001;44:1416–9.
6. Akkoc N, Gul A. Familial Mediterranean fever and seronegative arthritis. Curr Rheumatol Rep 2011;13:388–94. [CrossRef]
7. Sidi G, Shinar Y, Livneh A, Langevitz P, Pras M, Pras E. Protracted febrile myalgia of familial Mediterranean fever. Mutation analysis and clinical correlations. Scand J Rheumatol 2000;29:174–6. [CrossRef]
8. Doganay L, Ozdil K, Memisoglu K, Katrinli S, Karakoc E, Nikerel E, et al. Integrating personalized genomics into Turkish healthcare system: A cancer-oriented pilot activity of Istanbul Northern Anatolian Public Hospitals with GLAB. North Clin Istanb 2017;4:1–3. [CrossRef]
9. Sag E, Bilginer Y, Ozen S. Autoinflammatory Diseases with Periodic Fevers. Curr Rheumatol Rep 2017;19:41. [CrossRef]
10. Tanatar A, Sönmez HE, Karadağ ŞG, Çakmak F, Çakan M, Demir F, et al. Performance of Tel-Hashomer, Livneh, pediatric and new Eurofever/PRINTO classification criteria for familial Mediterranean fever in a referral center. Rheumatol Int 2020;40:21–7. [CrossRef]
11. Jarjour RA, Dodaki R. Arthritis patterns in familial Mediterranean fever patients and association with M694V mutation. Mol Biol Rep 2011;38:2033–6. [CrossRef]
12. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet 1998;351:659–64. [CrossRef]
13. Garcia-Gonzalez A, Weisman MH. The arthritis of familial Mediterranean fever. Semin Arthritis Rheum 1992;22:139–50. [CrossRef]
14. Livneh A, Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, et al. The changing face of familial Mediterranean fever. Semin Arthritis Rheum 1996;26:612–27. [CrossRef]
15. Kunt SŞ, Aydın F, Çakar N, Özdel S, Yalçınkaya F, Özçakar ZB. The effect of genotype on musculoskeletal complaints in patients with familial Mediterranean fever. Postgraduate Medicine 2020;132. [CrossRef]
16. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al; Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005;84:1–11. [CrossRef]
17. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM. The clinical patterns of myalgia in children with familial Mediterranean fever. Semin Arthritis Rheum 2000;30:138–43. [CrossRef]
18. Aydin F, Özçakar ZB, Çakar N, Çelikel E, Uncu N, Çelikel Acar B, et al. Sacroiliitis in Children With Familial Mediterranean Fever. J Clin Rheumatol 2019;25:69–73. [CrossRef]
19. Özçakar ZB, Çakar N, Uncu N, Çelikel BA, Yalçinkaya F. Familial Mediterranean fever-associated diseases in children. QJM 2017;110:287–90.
20. Sönmez HE, Batu ED, Demir S, Bilginer Y, Özen S. Comparison of patients with familial Mediterranean fever accompanied with sacroiliitis and patients with juvenile spondyloarthropathy. Clin Exp Rheumatol 2017;35 Suppl 108:124–7.
21. Padeh S, Shinar Y, Pras E, Zemer D, Langevitz P, Pras M, et al. Clinical and diagnostic value of genetic testing in 216 Israeli children with Familial Mediterranean fever. J Rheumatol 2003;30:185–90.
22. Olgun A, Akman S, Kurt I, Tuzun A, Kutluay T. MEFV mutations in familial Mediterranean fever: association of M694V homozygosity with arthritis. Rheumatol Int 2005;25:255–9. [CrossRef]
23. Güncan S, Bilge NŞ, Cansu DÜ, Kaşifoğlu T, Korkmaz C. The role of MEFV mutations in the concurrent disorders observed in patients with familial Mediterranean fever. Eur J Rheumatol 2016;3:118–21. [CrossRef]
24. Zhong L, Song H, Wang W, Li J, Ma M. MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: A meta-analysis. PLoS One 2017;12:e0182967. [CrossRef]