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ORIGINAL ARTICLE

The expanded spectrum of arthritis in children with familial Mediterranean fever

Pinar Ozge Avar-Aydın[1] · Zeynep Birsin Ozcakar[1] · Fatma Aydın[1] · Hatice Dilara Karakas[1] · Nilgun Cakar[1] · Fatos Yalcınkaya[1]

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Abstract

Introduction Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease that can present with various forms of arthritis. This retrospective study aims to evaluate the characteristics of patients with arthritis in a large pediatric cohort of FMF patients.

Methods The demographic and clinical data were extracted from electronic medical records. Patients with arthritis were grouped as arthritis of FMF and arthritis of FMF-associated diseases.

Results A total of 541 patients were followed with a diagnosis of FMF in the last 5 years. Acute arthritis of FMF (*n*: 138) was the most common cause. It showed a recurrent course in the majority with a longer duration than other attack symptoms. Significantly higher frequencies of biallelic exon 10 and M694V mutations, erysipelas-like erythema, and protracted febrile myalgia were detected in these patients, particularly in those older than 2 years of age. Sacroiliitis of FMF was the second most common cause (*n*: 19). Patients with acute arthritis and sacroiliitis of FMF needed higher doses of colchicine. One patient with neonatal-onset FMF and M694V homozygosity was diagnosed with protracted arthritis. Arthritides of FMF-associated diseases including IgA vasculitis (*n*: 10), juvenile idiopathic arthritis (*n*: 9), chronic nonbacterial osteomyelitis (*n*: 5), and inflammatory bowel disease (*n*: 2) were detected in 26 patients.

Conclusions Arthritis is an important clinical finding of FMF mostly associated with M694V mutations. The frequency of protracted arthritis is declined, whereas sacroiliitis of FMF and arthritis of associated diseases expand the spectrum of arthritis. This study represents the changing face and current perspectives of arthritis in FMF.

Key Points
- *Arthritis is an important clinical finding of familial Mediterranean fever (FMF) that can present in various forms*
- *Arthritis is most likely associated with M694V mutations*
- *The frequency of protracted arthritis is declined whereas sacroiliitis of FMF and arthritis of associated diseases expand the spectrum of arthritis in FMF*

Keywords Arthritis · Familial Mediterranean fever · FMF-associated diseases · Sacroiliitis

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease. Although it is reported from all around the world, it mainly affects certain ethnic groups including Turks, Jews, Arabs, and Armenians. Typical febrile FMF attacks include signs of peritonitis, pleuritis, or acute synovitis that last for 0.5–3 days [1].

Arthritis is one of the frequent and important manifestations of FMF. During acute attacks, a transient monoarthritis affecting mostly large joints of lower extremities is seen in about 50% of children with FMF. Acute arthritis during disease attacks can be the presenting or rarely, the only major clinical feature of FMF. Despite recurrences, there is generally no permanent damage [2]. In a small portion of patients, protracted arthritis may develop, mostly in hips or knees and immunosuppressive therapies, synovectomy, or

✉ Fatos Yalcınkaya
fatos.yalcinkaya@medicine.ankara.edu.tr

[1] Department of Pediatric Rheumatology, Ankara University Faculty of Medicine, Ankara, Turkey

joint replacement surgeries are usually needed [3]. Besides acute arthritis and protracted arthritis, sacroiliitis of FMF is increasingly reported among articular manifestations of FMF [4].

Familial Mediterranean fever is associated with a variety of diseases showing increased frequencies compared to the general population. Vasculitis, juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD) are the most common associated diseases and arthritis can be seen as a manifestation of these diseases [5]. Arthritides seen in FMF-associated diseases expand the spectrum of arthritis seen in patients with FMF and differential diagnosis of arthritis might be difficult.

This study aims to evaluate the demographic, clinical, and genetic characteristics of patients with arthritis in a large pediatric cohort of FMF patients. Treatments used for arthritis were reviewed. Furthermore, the differences between patients with and without acute arthritis were examined.

Patients and methods

Study population

Patients with a diagnosis of FMF and a follow-up for at least 6 months were included in this retrospective study. The study period was established from October 2016 to October 2021. The diagnosis of FMF was based on Turkish pediatric criteria [6]. Additionally, patients with recurrent or persistent arthritis suspected of FMF and found to have biallelic exon 10 mutations of the MEFV gene were diagnosed with FMF after the exclusion of other reasons. Sacroiliitis related to FMF was defined by the presence of inflammatory back pain and typical radiological findings of sacroiliitis on magnetic resonance imaging (MRI) with negative human leukocyte antigen-B27 (HLA-B27) antigen. The International League of Associations for Rheumatology (ILAR) criteria for the classification of JIA and the international criteria for the diagnosis of vasculitis were used in the clinical setting [7, 8]. The diagnosis of chronic nonbacterial osteomyelitis (CNO) was based on clinical symptoms and imaging features after the exclusion of CNO-mimicking diseases [9]. The study protocol was approved by the Human Research Ethics Committee of Ankara University Faculty of Medicine (#i10-643–21).

Study procedures

The demographic and clinical data were extracted from electronic medical records. Laboratory data included serum acute phase reactants (APRs; C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), complete blood cell counts, and serum biochemistry. Patients with symptom onset before 2 years of age were defined as early-onset FMF. Exon 10 mutations of the MEFV gene studied by direct sequencing of the PCR-amplified fragments and exon 2 mutations by PCR-restricted fragment polymorphism protocol including at least six mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, and p.E148Q) were recorded. Patients with arthritis were grouped as arthritis of FMF and arthritis of FMF-associated diseases.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics 21.0.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). Descriptive statistics were used for continuous variables with a normal distribution (mean ± standard deviation (minimum–maximum)) and categorical variables (frequency (*n*) and percentage (%)). Statistical normalization techniques were applied to variables with the nonnormal distribution. One-way ANOVA was used for parametric data with homogeneity of variance test, and Kruskal–Wallis test for non-parametric data. The statistical significance level was $p \leq 0.05$.

Results

Study population

A total of 541 patients were followed with a diagnosis of FMF in the last 5 years. The mean follow-up after the diagnosis was 6.38 ± 4.12 years (0.50–19.58). The demographic and clinical characteristics of the study population are shown in Table 1.

Arthritis of FMF included acute arthritis, sacroiliitis, and protracted arthritis whereas arthritides of IgA vasculitis (IgAV)/Henoch-Schönlein purpura, IBD, JIA, and CNO were identified as arthritis of FMF-associated diseases. None of the patients was found to have a diagnosis of infectious arthritis, reactive arthritis, or amyloid arthropathy in the study population.

Patients with arthritis of FMF

Acute arthritis seen during attacks was the most common cause of arthritis of FMF and constituted 79.3% of the causes. The majority of the patients with acute arthritis had monoarthritis (83.3%) and ankle (81%) was the most common site. During the attacks with arthritis, mean CRP and ESR levels were 93.14 ± 58.66 mg/L and 38.52 ± 22.72 mm/h, respectively. Acute arthritis was one of the initial manifestations of FMF in 94 (17.4%) patients. A recurrent course was observed in 116 (84.1%) patients with acute arthritis. Patients with disease onset

Table 1 The characteristics of the study population

	$n=541$ (%) or mean ± SD
Female gender	284 (52.5)
Age at onset of FMF, years	3.69 ± 3.63
Age at diagnosis of FMF, years	6.90 ± 4.14
Patients with early-onset FMF	242 (44.7)
Patients with neonatal-onset FMF	13 (2.4)
Arthritis of FMF	
Acute arthritis	138 (25.5)
Sacroiliitis	19 (3.5)
Protracted arthritis	1 (0.2)
Other manifestations of FMF	
Fever	501 (92.6)
Abdominal pain	475 (87.8)
Chest pain	133 (24.6)
Erysipelas-like erythema	46 (8.5)
Protracted febrile myalgia	11 (2.0)
Renal amyloidosis	5 (0.9)
MEFV gene mutations*	
Biallelic exon 10 mutations	310 (57.3)
M694V/M694V	162 (29.9)
M694V/M680I	56 (10.4)
M694V/V726A	39 (7.2)
At least one M694V mutation	392 (72.5)
Heterozygous mutations	
M694V/-	100 (18.5)
E148Q/-	35 (6.5)
Familial consanguinity	132 (24.4)
Familial history	
Familial Mediterranean fever	354 (65.4)
Renal amyloidosis	38 (7.0)
Treatment for FMF	
Colchicine	541 (100.0)
IL-1 blockers	32 (5.9)

FMF familial Mediterranean fever, *IL-1* interleukin-1, *MEFV* Mediterranean FeVer, *SD* standard deviation

*MEFV mutations detected in > 5% of the study population are presented

after 2 years of age had significantly more frequent acute arthritis attacks compared to the patients with early-onset FMF (28.2% vs. 18.1%, $p=0.009$). In five patients, recurrent acute arthritis was the only clinical diagnostic criteria of FMF who were diagnosed with FMF after the detection of biallelic exon 10 mutations of the MEFV gene. Febrile acute attacks lasted for 2.85 ± 0.70 days (1.00–5.00) whereas the mean duration of acute arthritis was found 5.20 ± 3.00 days (1.00–10.00). In addition to recurrent acute arthritis, ten patients developed other causes of arthritis during follow-up. The comparison of 128 patients who had only acute arthritis and the patients without arthritis is shown in Table 2.

Familial Mediterranean fever-related sacroiliitis was the second most common cause of arthritis in FMF detected in 10.9% of the causes. The clinical and laboratory characteristics of FMF patients with sacroiliitis are presented in Table 3. Although the mean age at the diagnosis of sacroiliitis was 11.64 ± 4.27 (2.92–17.42), three patients had the diagnosis of sacroiliitis before the age of 5. Clinical features of FMF and mutations in the MEFV gene were found similar between patients with sacroiliitis and without arthritis. All patients with sacroiliitis had at least one M694V mutation except three patients carrying heterozygous E148Q mutation. The patients with sacroiliitis used higher doses of colchicine at the latest visits when compared to the patients without arthritis (1.07 ± 0.28 vs. 0.92 ± 0.20 mg/m^2/d, $p=0.004$). None of the patients with E148Q mutations needed biologics.

One patient with neonatal onset of FMF and M694V homozygosity was diagnosed with protracted arthritis in the knee at the age of 14. Corticosteroids and IL-1 blockers were used for treatment in addition to colchicine.

Patients with arthritis of associated diseases

Arthritis of FMF-associated diseases was detected in 26 patients. The characteristics of the patients with arthritis of associated diseases are shown in Table 4.

Among 14 patients with IgAV, ten of them presented with arthritis in addition to other findings of IgAV. Eight patients were diagnosed with FMF after recurrent or severe courses of IgAV and found to carry at least one M694V mutation. All patients received non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis.

Juvenile idiopathic arthritis was diagnosed in nine patients. The subtypes of JIA were as follows: enthesitis-related arthritis (ERA, *n*: 5), oligoarthritis (*n*: 3), and RF-negative polyarthritis (*n*: 1). None of them had uveitis. Two patients had anti-nuclear antibody (ANA) positivity. Four of the patients with ERA had sacroiliitis and HLA-B27 positivity. All patients with JIA received NSAIDs and disease-modifying anti-rheumatic drugs (DMARDs) while three of them used tumor necrosis factor-alpha (TNF-α) blockers. Intraarticular corticosteroids were used in four patients.

Chronic nonbacterial osteomyelitis was the cause of arthritis in five patients; four had biallelic exon 10 mutations and one had heterozygous M694V mutation of the MEFV gene. Two of them carrying biallelic exon 10 mutations received the diagnosis of FMF after the onset of CNO and benefitted from colchicine to control the disease. All had a persistent multifocal course of CNO. Four patients with CNO had sacroiliitis with bone edema of the pelvis as a component of CNO. The mean CRP and ESR levels were 52.42 ± 42.39 mg/L and 24.60 ± 18.43 mm/h, respectively. All patients with CNO received NSAIDs. Biphosphonates

Table 2 The comparison of the patients with and without acute arthritis of FMF

	Patients with acute arthritis (*n*: 128)*	Patients without arthritis (*n*: 382)	*p*-value[#]
Female gender	82 (64.1)	189 (49.5)	*0.004*
Age at onset of FMF, years	4.24 ± 3.74	3.50 ± 3.55	*0.047*
Age at diagnosis of FMF, years	7.60 ± 4.18	6.54 ± 4.03	*0.011*
Symptoms of FMF			
Fever	114 (89.1)	361 (94.5)	*0.035*
Abdominal pain	107 (83.6)	347 (90.8)	*0.023*
Chest pain	39 (30.5)	88 (23.0)	0.093
Erysipelas-like erythema	36 (28.1)	9 (2.4)	*< 0.001*
Protracted febrile myalgia	6 (4.7)	5 (1.3)	*0.023*
Renal amyloidosis	0	5 (1.3)	0.194
MEFV gene			
Biallelic exon 10 mutations	98 (76.6)	190 (49.7)	*< 0.001*
M694V/M694V	67 (52.3)	81 (21.2)	*< 0.001*
At least one M694V mutation	108 (84.4)	259 (67.8)	*< 0.001*
Colchicine dosage at the latest visit, mg/m^2/d	1.01 ± 0.22	0.92 ± 0.20	*< 0.001*
Patients treated with IL-1 blockers	13 (10.2)	14 (3.7)	*0.005*

n (%) or mean ± SD; [#]the statistical significance level was accepted $p \leq 0.05$.

FMF familial Mediterranean fever, *IL* interleukin, *IL-1* interleukin-1, *MEFV* Mediterranean FeVer, *SD* standard deviation

*Patients who developed other causes of arthritis were excluded from group analyses

Table 3 The characteristics of the patients with sacroiliitis of FMF

	n = 19 (%) or mean ± SD
Female gender	9 (47.4)
Age at onset of FMF, years	3.38 ± 2.82
Age at diagnosis of FMF, years	8.41 ± 4.47
Age at diagnosis of sacroiliitis, years	11.64 ± 4.27
MEFV gene	
Biallelic exon 10 mutations	13 (68.4)
M694V/M694V	7 (36.8)
At least one M694V mutation	16 (84.2)
Laboratory tests at diagnosis of sacroiliitis	
C-reactive protein, mg/L	13.24 ± 16.49
Erythrocyte sedimentation rate, mm/h	24.56 ± 19.29
ANA positivity	1 (5.3)
HLA-B27 positivity	0
Treatment for sacroiliitis	
NSAIDs	19 (100)
DMARDs	10 (52.6)
TNF-α blockers	4 (21.1)

ANA anti-nuclear antibody, *DMARDs* disease-modifying anti-rheumatic drugs, *FMF* familial Mediterranean fever, *HLA-B27* human leukocyte antigen-B27, *MEFV* MEditerranean FeVer, *NSAIDs* non-steroidal anti-ınflammatory drugs, *SD* standard deviation, *TNF-α* tumor necrosis factor-alpha

were used in two patients and TNF-α blockers in four patients.

Inflammatory bowel disease was diagnosed in 11 patients and IBD-related peripheral monoarthritis was the cause of arthritis in two patients. Arthritis lasted for 3 weeks with a

Table 4 The characteristics of the patients with arthritis of FMF-associated diseases

	n = 26 (%) or mean ± SD
Female gender	10 (38.5)
Age at onset of FMF, years	5.63 ± 5.22
Age at diagnosis of FMF, years	9.05 ± 4.79
Age at diagnosis of associated disease, years	9.46 ± 4.95
FMF-associated diseases with arthritis	
IgA vasculitis	10 (38.5)
Juvenile idiopathic arthritis	9 (34.6)
Chronic nonbacterial osteomyelitis	5 (19.2)
Inflammatory bowel disease	2 (7.7)
MEFV gene	
Biallelic exon 10 mutations	14 (53.8)
M694V/M694V	8 (30.8)
At least one M694V mutation	19 (73.1)
Colchicine dosage at the latest visit, mg/m^2/d	0.99 ± 0.23
Specific treatment for arthritis	
NSAIDs	26 (100)
DMARDs	9 (34.6)
TNF-α blockers	7 (26.9)
Intraarticular corticosteroids	4 (15.4)
Biphosphonates	2 (7.7)

n (%) or mean ± SD

DMARDs disease-modifying anti-rheumatic drugs, *FMF* familial Mediterranean fever, *MEFV* MEditerranean FeVer, *NSAIDs* non-steroidal anti-ınflammatory drugs, *SD* standard deviation, *TNF-α* tumor necrosis factor-alpha

flare of IBD and resolved after the initiation of immunosuppressive therapy together with NSAIDs in both patients.

Discussion

In this study, the etiology of arthritis was evaluated in a large pediatric cohort of FMF patients. Acute arthritis continued to be an important clinical finding of FMF. While sacroiliitis was diagnosed with increasing frequencies, the rates of protracted arthritis seemed to decrease. The spectrum of arthritis was expanded with strikingly enlarged profile of FMF-associated diseases.

Self-limiting acute monoarthritis of lower extremities is a prevalent articular manifestation of FMF reported in about 50% of the patients [10, 11]. In our cohort, acute arthritis of FMF was detected in 25% of the patients. This rate was slightly lower than previously reported frequencies from Turkey [12, 13] while it was comparable to the previous report from our clinic published 20 years ago [3]. Pediatric FMF patients originating from Europe or Eastern Mediterranean countries but living in Europe had less frequent arthritis attacks (16.7% and 7.0%, respectively) while arthritis was reported up to 70% in non-Ashkenazi Jews [14, 15]. Patients presenting with acute arthritis demonstrated several differences from the patients without arthritis. The ages at the disease onset and the diagnosis of FMF were significantly higher in patients with acute arthritis. The frequency of acute arthritis increased to 30% for patients with disease onset older than 2 years of age. Additionally, these patients displayed fever and abdominal pain less frequently compared to the patients without arthritis whereas significantly higher frequencies of erysipelas-like erythema (ELE) and protracted febrile myalgia were detected in patients with acute arthritis. Similar to these findings, a large study in children with FMF reported that fever and peritonitis were significantly more common in patients with early-onset FMF whereas patients with disease onset after the age of 3 presented with arthritis and ELE more frequently [16]. As compatable with several studies, patients experiencing acute arthritis had a higher frequency of the highly penetrant biallelic exon 10 and M694V mutations of the MEFV gene [2, 17, 18]. Moreover, these patients needed higher doses of colchicine and IL-1 blockers more commonly, delineating that the patients presenting with acute arthritis have a more severe disease course.

A study from our clinic reported 124 children with arthritis of FMF in 2002, 10% of them developed protracted arthritis and only one patient had sacroiliitis. Interestingly, all those patients with protracted arthritis were diagnosed with FMF and treated with colchicine after this serious manifestation. In the current study, only one patient was found to have protracted arthritis. This suggests that, although relatively young age of the study population might be a reason for this low frequency of protracted arthritis, together with increasing awareness of FMF, early diagnosis and treatment of the disease prevent the development of this serious articular presentation. On the other hand, sacroiliitis related to FMF was thought to be a rare phenomenon in early reports, particularly in the pediatric population. Inflammatory back pain, radiographic sacroiliitis without vertebral involvement, and negative HLA-B27 antigen are the main characteristic features of sacroiliitis of FMF. In this report, sacroiliitis constituted > 10% of the causes of FMF arthritis, and interestingly, three patients with sacroiliitis were diagnosed before 5 years of age, displaying another important difference from other causes of spondyloarthropathies. The majority of these patients had at least one M694V mutation similar to other patients in the cohort. Moreover, patients with sacroiliitis needed higher doses of colchicine and more than half of them needed additional therapeutics such as DMARDs and TNF-α blockers whereas none of the patients with sacroiliitis carrying E148Q mutations needed biologic agents. These findings suggest a more severe disease phenotype in patients with sacroiliitis, specifically in these carrying M694V mutations.

Familial Mediterranean fever-associated diseases include a wide spectrum of inflammatory disorders that cause different patterns of arthritis. Almost 75% of the patients with arthritis of associated diseases carried at least one M694V mutation and more than half of them had biallelic exon 10 mutations. More than 70% of the patients with IgAV presented with arthritis. Similar to this finding, the frequency of arthritis was reported higher in patients with IgAV carrying MEFV mutations compared to other IgAV patients in previous studies [19, 20]. Besides, acute peripheral arthritis related to activated IBD was rarely encountered in our study. The association of JIA with FMF was increasingly reported in recent years [5]. Nine patients were found to have JIA in the current study. In contrast to the previous studies reporting the distribution of JIA categories in Turkish population, the most common subtype was ERA and most of them presented with sacroiliitis [21, 22]. Recently, CNO has been reported as an associated disease of FMF that may also cause arthritis in FMF patients [23]. Five FMF patients with concomitant CNO were found. All had a persistent multifocal course of CNO and the majority received biologics. All mutations seen in these patients were exon 10 mutations that were homozygous or compound heterozygous in 80% of them. Although APRs are expected normal or modestly elevated in CNO, patients with FMF and CNO were found to have high APRs at the diagnosis of CNO [24]. These findings indicate a severe disease phenotype of CNO ongoing with increased inflammation in patients carrying MEFV mutations. Moreover, sacroiliitis was found in 80% of the patients with FMF and CNO. Although sacroiliac joint

involvement is not common in CNO, the presence of MEFV mutations was found to increase the risk of sacroiliitis with an odds ratio of 2.4 [23, 25]. These results show a modifying effect of FMF on associated diseases and the development of arthritis.

The major limitation of the study was its retrospective design. Despite it, our study is one of the largest to assess the etiology of arthritis, the clinical and laboratory features of patients with arthritis over time in a large pediatric cohort of FMF patients.

In conclusion, arthritis is an important clinical finding of FMF that can present in various forms but is most likely associated with M694V mutations. The increased awareness of FMF, timely diagnosis, and treatment decline the frequencies of severe disease manifestations such as protracted arthritis. On the other hand, a better understanding of the disease results in an expansion of the arthritis spectrum, for instance, the emergence of sacroiliitis as a component of FMF. Moreover, growing knowledge of disease associations leads to an increase in the recognition of a wide variety of different forms of arthritis. Unexplained recurrent or persistent arthritis may deserve a genetic screening of the MEFV gene, particularly in the regions where FMF is prevalent. This study represents the changing face and current perspectives of arthritis seen in pediatric FMF patients by the explosive growth of the knowledge in the field of genetics and the pathophysiology of FMF.

Declarations

Ethics approval The study was approved by the Human Research Ethics Committee of Ankara University Faculty of Medicine (#i10-643–21).

Consent to participate Informed consent was obtained from participants and\or parents.

Consent for publication Patients signed informed consent regarding publishing their data.

Disclosures None.

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