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Original Article

Sacroiliitis associated with familial Mediterranean fever in childhood: a case series and review of literature

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ABSTRACT

Background and objectives. Familial Mediterranean fever (FMF) is an autosomal-recessive auto-inflammatory disorder characterized by recurrent episodes of fever with serositis. Sacroiliitis associated with FMF is very rare, especially in children. We aimed to describe the demographic, clinical, laboratory features, and treatment responses of pediatric patients with FMF -related sacroiliitis.

Methods. The study consisted of seven pediatric patients younger than 16 years, diagnosed with sacroiliitis associated with FMF between 2010 and 2017. Medical records of patients were retrospectively evaluated. Sacroiliitis was diagnosed based on magnetic resonance imaging. We also reviewed previous studies of FMF related sacroiliitis.

Results. Five of the seven patients (male:female ratio of 5:2) had a *M694V* (homozygous) mutation, one patient had a *M694V* (heterozygous) mutation, and one patient had a *V726A* (heterozygous) mutation. All patients were *HLA-B27* negative. One of the cases achieved remission with colchicine plus non-steroidal anti-inflammatory drug treatment, and one patient's symptoms were managed by the addition of sulfasalazine. Four patients responded to etanercept treatment, and one patient's symptoms were suppressed with canakinumab.

Conclusion. Sacroiliitis can be seen in pediatric FMF patients suffering with inflammatory back pain. This manifestation generally occurs in FMF patients who have *M694V* mutation. Etanercept could likely show a beneficial effect in patients who are resistant to disease modifying anti-rheumatic drugs and non-steroidal anti-inflammatory drugs. In addition, canakinumab treatment should be considered as a successful alternative therapy in this rare group of patients.

Key words: childhood, familial Mediterranean fever, sacroiliitis, treatment.

Familial Mediterranean fever (FMF) is an autosomal-recessive autoinflammatory disorder characterized by recurrent episodes of fever with serositis. Untreated patients may develop AA type amyloidosis which results in renal impairment and associated morbidity and mortality.[1] In terms of the ethnicity spectrum, FMF is found in Armenian, Turkish, Jewish and Arabic people in Mediterranean regions.[2] Mediterranean fever gene (*MEFV*) mutation located on chromosome 16p13.3, encodes a 781–amino acid length protein denoted as pyrin or marenostrin, leads to the hyperactivity of inflammasome which in turn increases IL-1β, and causes severe inflammation.[3]

Monoarthritis of the large joints of the lower extremities with a self-limiting course is one of the most common features of the musculoskeletal involvement in FMF.[4] In addition to peripheral arthritis, some FMF patients with chronic arthritis fulfil the diagnostic criteria of spondyloarthritis (SPA) such as the presence of

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sacroiliitis, enthesitis, inflammatory back pain; although they are *HLA-B27* negative.[5] Lehman et al.[6] described the first case report of *HLA-B27* negative FMF-related sacroiliitis in 1978.

Sacroiliitis associated with FMF is very rare, especially in children. In this study, we aimed to describe the demographic, clinical, laboratory features, and treatment responses of pediatric patients with FMF-related sacroiliitis.

Material and Methods

The retrospective study consisted of seven pediatric patients younger than 16 years, diagnosed with sacroiliitis associated with FMF between 2010-2017 in our department. All the patients were evaluated clinically according to Tel Hashomer criteria.[2] The diagnosis of FMF was confirmed genetically using a panel of common *MEFV* mutations; *A744S, F479L, I720M, K695R, M680I, M694I, M694V, P369S, R761H* and *V726A*. *MEFV* gene was evaluated using direct sequencing of the Polymerase Chain Reaction (PCR) amplified fragments. *HLAB27* antigen was performed by flow cytometry method. Clinical findings, direct radiography and magnetic resonance imaging (MRI) technique were used to confirm sacroiliitis. The patients were followed up at 3-months intervals. At follow-ups, the patients underwent a physical examination, and systemic arthritic activity was evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores.[7] Acute phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were also monitored.

Patients' characteristics, such as age, sex, age at onset of FMF, age at onset of sacroiliitis, treatments (disease modifying anti-rheumatic drugs [DMARDs] and biologics) disease duration, MRI of sacroiliitis, existence of peripheral arthritis, BASDAI scores and acute phases (at onset and last visit), were recorded.

Clinical-radiological-laboratory responses were evaluated according to the response of therapies: resolution of all sacroiliitis symptoms with decreasing acute phases was accepted as a complete response, while reduced of sacroiliitis symptoms without full recovery was a partial response.

We also reviewed previous studies of patients with FMF, complicated by sacroiliitis. A search of PubMed for studies from inception to April 2017 was conducted using 'familial Mediterranean fever' and 'sacroiliitis' as keywords. Studies that discussed the treatment of FMF- related sacroiliitis were included. Studies of *HLA-B27* positive spondyloarthropaties (SPAs) and coexistence of FMF with SPAs were excluded.

The study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from all individual participants included in the study. All of the analyses were entered as variables into a database and analysed using SPSS, version 23. Descriptive statistics were evaluated.

Results

Among 392 pediatric FMF patients, 7 out of them (1.7%) had sacroiliitis associated with FMF. Demographic, clinical and laboratory features of patients are described in Table I. Two of the seven patients were females (28%). One patient had *V726A* (heterozygous), five patients had a M694V (homozygous) mutation and one patient had a *M694V* (heterozygous) mutation. All the patients were *HLA-B27* negative, rheumatoid factor negative and anti-nuclear antibodies negative. There was no amyloidosis. All patients had restricted movement in Schober's test and suffered from inflammatory back pain in the physical examination, supporting a diagnosis of sacroiliitis. Direct radiography and MRI findings were positive for sacroiliitis. FMF was diagnosed at a median of 5 (2-9) years, and sacroiliitis detected at median of 8 (7-15) years. The median duration between FMF diagnosis and development of sacroiliitis was 5 (0-12) years.

All the patients received treatment with colchicine and naproxen, a non-steroidal anti-

Table I. Patients characteristics, treatment features and response indicators.

Cases	1	2	3	4	5	**6**	**7**
Age (years)	14	9	14	16	11	9	16
Gender	male	male	male	female	male	male	female
FMF onset age(years)	5	6	3	9	2	8	3
Sacroiliitis onset age (years)	7	8	13	15	7	8	15
Peripheral arthritis/enthesitis	-	knee	ankle	ankle	ankle		
FMF diagnosis to sacroiliitis (months)	24	24	120	72	60	0	144
Sacroiliitis (unilateral/bilateral)	Bilateral	Unilateral	Bilateral	Bilateral	Bilateral	Unilateral	Bilateral
NSAIDs	+	+	+	+	+	+	+
SSZ	+	+	+	+	+	-	+
MTX	-	+	-	-	+	-	+
Anti-IL1	+	-	-	-	-	-	-
Anti-TNF	-	+	-	+	+	-	+
MEFV mutation	*V726A* (heterozygous)	*M694V* (homozygous)	*M694V* (heterozygous)	*M694V* (homozygous)	*M694V* (homozygous)	*M694V* (homozygous)	*M694V* (homozygous)
DMARDs duration (months)	40	17	12	12	30	-	12
Biologic duration (months)	44	16	-	1	30	-	1
BASDAI onset of sacroiliitis	4.9	3.7	2.9	2.7	3	3.2	5.5
BASDAI last visit	1.9	1.1	1.3	1.5	1	1.1	4.4
ESR onset sacroiliitis	42	37	12	33	48	36	39
ESR last visit	5	8	11	14	20	10	29
CRP onset sacroiliitis	36	20.1	1.5	15.2	18.3	17.5	22
CRP last visit	3	4.4	1	3	2.3	2	8

FMF: familial Mediterranean fever, BASDAI: bath ankylosing spondylitis disease activity index, NSAIDs: non-steroidal anti-inflammatory drugs, DMARDs: disease modifying anti-rheumatic drugs, MEFV: Mediterranean fever, SSZ: sulfasalazine, MTX: methotrexate, ESR: erythrocyte sedimentation rate (0-20 mm/h), CRP: C-reactive protein (0-5 mg/L).

inflammatory drug (NSAID). The colchicine dose was gradually increased to a maximum dose of 2 mg/day, followed by treatment NSAIDs and DMARDs, such as sulfasalazine (SSZ) and methotrexate (MTX). One patient whose clinical course included resistant fever attacks was managed with anti-IL-1 therapy. Four patients were treated with etanercept (ETC) after failure of NSAID and DMARD therapy. The clinical status of all patients treated with anti-TNF improved within 1 month of treatment commencement. The clinical course of only one patient was managed using colchicine and NSAIDs. Six patients received DMARD therapy. At the 12-month follow-up, only one patient, (i.e. the patient with the M694V [heterozygous] mutation) showed a therapeutic response to DMARDs.

The duration of DMARD treatment ranged from 12 to 40 months, whereas the duration of biological treatment varied from 1 to 44 months. Four (57.1%) patients had peripheral arthritis and enthesitis, including knee and/or ankle arthritis. The median BASDAI score at treatment onset was 3.2 (2.7-5.5) and the median score at the final follow-up was 1.3 (1.0- 4.4).

Acute phase reactants decreased by medical therapies. At the onset of sacroiliitis, the median ESR rate was 37 (12-48) mm/h and the median CRP was 18,3 (1.5-36) mg/L. At the last visit, the median ESR rate had decreased to 11 (5-29) mm/h, and the median CRP had decreased to 3 (1-8) mg/L.

Discussion

HLA-B27 negative FMF-related sacroiliitis is a rare disorder, with limited studies on the topic in a subgroup of pediatric patients. According to the literature, almost all reports of FMF-related sacroiliitis comprise adult patient series. Thus, the present pediatric case series is important.

Distinguishing FMF-related sacroiliitis from FMF coexisting with SPA is difficult, as there are no standardized definitions. Sönmez et al.[8] described that FMF patients with sacroiliitis had higher acute phases, less common *HLA-B27* positivity, enthesitis and vertebral involvement than in patients with SPA. Additionally, they showed that M694V mutation was the most common *MEFV* mutation among FMF patients with sacroiliitis. In the present series, all patients had restricted Schober test and increased acute phase reactants. There were no *HLA-B27* positivity. 6 of 7 patients (86%) had M694V mutation. 4 out of 7 patients (57%) had peripheral arthritis and enthesitis. Additionally, we did not reveal any vertebral involvement in our cases.

In a study of 157 adult FMF patients, Akar et al.[9] reported that only 15 (7.5%) patients had *HLA-B27* negative SPAs. They also found that the *M694V* mutation was common in this group. Their study suggested that factors other than *HLA-B27* played a role in the coexistence of FMF and SPA.

The primary treatment for FMF is colchicine, which effectively suppresses the frequency of attacks and prevents the development of amyloidosis.[10] Colchicine is well tolerated by pediatric patients.[11] In recent years, biological agents have been used as an alternative treatment for colchicine-resistant patients. Anti-IL 1 treatment, including anakinra and canakinumab, suppresses inflammation caused by IL-1 activation.[12] Anti Tumour Necrosis Factor (TNF) treatment, such as ETC, infliximab or adalimumab, is also effective in controlling FMF attacks in patients with chronic arthritis or sacroiliitis.[13]

We prepared a mini literature review regarding to sacroiliitis accompanied with FMF in Table II and III. Lehman et al.[6] described the first case report of *HLA-B27* negative FMF-related sacroiliitis in 1978, noting that the patient showed a partial response to treatment with colchicine and a NSAID. Majeed et al.[4] reported the use of colchicine plus NSAID therapy in the treatment of a 14-year-old patient with FMF-related sacroiliitis and achieved a partial response. Langevitz et al.[14] reported a large study of 3000 FMF patients. The primary

Table II. Literature review of demographic data to HLA-B27 negative FMF related sacroiliitis.

Author	Number of patients	Age at dx	MEFV mutation
Lehman et al.[6]	2	10	NA
Majeed et al.[4]	1	14	NA
Langevitz et al.[14]	11	25-51	NA
Eifan et al.[23]	1	11	M694V/M694V
Demirag et al.[15]	1	22	M694V/M694V
Borman et al.[16]	2	18-29	M694V/M694V
Erten et al.[17]	3	33-48	M694V/M694V, M694V/M680I
Bilgen et al.[18]	8	25-42	M694V/M694V, M694V/M680I, E148Q/E148Q
Erten et al.[24]	1	18	M694V/M694V
Sahin et al.[21]	1	45	A744S/E148Q
Estublier et al.[19]	1	39	M694I/M694I
Varan et al.[20]	1	39	V726A/ -
Ugan et al.[22]	1	22	M694V/M694V

FMF: familial Mediterranean fever, NA: not avialable.

Table III. Literature review of treatment approach to HLA-B27 negative FMF related sacroiliitis.

Author	Anti TNF	Anti IL-1	Agents prior biologics	Median follow-up time	Clinical effects
Lehman et al.[6]	-	-	Colchicine, NSAID	NA	PR
Majeed et al.[4]	-	-	Colchicine, NSAID	10 months	PR
Langevitz et al.[14]	-	-	Colchicine, NSAID, SSZ, MTX	NA	PR, PD
Eifan et al.[23]	-	-	Colchicine, NSAID	24 months	CR
Demirag et al.[15]	-	-	Colchicine, NSAID, Gold (im)	8 months	PR
Borman et al.[16]	-	-	Colchicine, NSAID, SSZ	NA	PR
Erten et al.[17]	-	-	Colchicine, SSZ	NA	CR
Bilgen et al.[18]	INF, ADA, ETC	-	Colchicine, NSAID, SSZ, MTX	NA	PR, CR
Erten et al.[24]	INF, ETC	-	Colchicine	NA	CR
Sahin et al.[21]	ETC	-	NSAID, pred, SSZ, LFN, MTX, HCQ	96 months	PR
Estublier et al.[19]	ADA, ETC	ANA	Colchicine, NSAID, SSZ, Pred	144 months	CR
Varan et al.[20]	ADA, ETC	ANA	Colchicine, NSAID, SSZ	51 months	PR
Ugan et al.[22]	-	-	Colchicine, NSAID, SSZ, Pred	1 month	CR

FMF: familial Mediterranean fever, NA: not avialable, INF: infliximab, ADA: adalimumab, ETC: etanercept, ANA: anakinra, NSAID: non-steroidal anti-inflammatory drug, Pred: prednisolon, SSZ: sulfasalazine, MTX: methotrexate, LFN: leflunomide, AZA: azatiopurin, PR: partial response, PD: progressive disease, CR: complete response.

objective of their study was to determine the association between FMF and seronegative SPA, coexisting with FMF and ankylosing spondylitis (AS) or FMF-related sacroiliitis. They detected *HLA-B27* negative sacroiliitis in only 11 (0.4%) patients, nine of whom were males. All patients had inflammatory back pain. Six patients had enthesitis, and seven patients suffered from heel pain. Peripheral arthritis was monoarticular in five patients and oligoarticular in the other patients. Treatment consisted of MTX, SSZ, NSAIDs and colchicine. The outcome was favorable in eight patients, but disease progression occurred in three patients. In addition, they emphasized that in these patients who had FMF-related sacroiliitis, none of them had any radiologic vertebral changes. Demirag et al.[15] reported a partial response of a

22-year-old patient who had sacroiliitis related to FMF, to intramuscular gold therapy. Borman et al.[16] and Erten et al.[17] presented adult cases that showed favorable responses to colchicine plus SSZ. Bilgen et al.[18] examined the response of colchicine-resistant adult patients with FMF-associated sacroiliitis to anti-TNF therapy. In their study, eight patients had a M694V mutation (homozygous) and compound heterozygous *M680I/M694V* mutation. One patient had a *E148Q* (homozygous) mutation. The duration and frequency of attacks decreased in two patients, and a complete response was obtained in five patients.[18] In recent years also anti IL-1 treatments have been used effectively in this small group of patients. Estublier et al.[19] and Varan et al.[20] reported two adult cases of FMF-related sacroiliitis resistant to anti TNF therapy. Both patients showed favorable responses to anakinra treatment, demonstrating that this drug may be useful in the treatment of FMF-related sacroiliitis.

As noted above, *HLA-B27* negative FMF-related sacroiliitis cases treated with anti-TNF or anti-IL-1 therapy are very rare. There are no reports of canakinumab treatment of pediatric and adult patients in FMF related sacroiliitis. Herein, we described seven cases of FMF-related sacroiliitis, five with a *M694V* (homozygous) mutation and one with a heterozygous mutation of the same gene. Four of 7 patients improved with etanercept therapy. The patient who had *V726A* (heterozygous) mutation, was successfully controlled with canakinumab.

In conclusion, we suggested that in FMF patients who are suffering from inflammatory back pain with increased acute phases in laboratory work-up, should be investigated for sacroiliitis with MRI. This manifestation generally occurs in FMF patients who have *M694V* mutation. Firstly, NSAIDs and DMARDs could be prefer for the treatment of sacroiliitis. When there is insufficient response to these therapies, biological agents (anti TNF and anti IL-1) could be useful in this rare group patients.

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