Comparison of patients with familial Mediterranean fever accompanied with sacroiliitis and patients with juvenile spondyloarthropathy

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Received on March 15, 2017; accepted in revised form on July 11, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 108): S124-S127.

Key words: familial Mediterranean fever, sacroiliitis, juvenile spondyloarthropathy

Competing interests: none declared.

ABSTRACT

Objective. *Familial Mediterranean fever (FMF) is the most common autoinflammatory disease manifesting with self-limited recurrent febrile attacks and polyserositis. Acute recurrent monoarthritis is the most common form of musculoskeletal involvement in FMF; however, up to 5% of FMF patients may develop chronic joint diseases including sacroiliitis. It is difficult to distinguish whether sacroiliitis is a musculoskeletal finding of FMF or whether this is the coexistence of two diseases, FMF and SpA. In this study, we aimed to evaluate FMF patients with sacroiliitis, and compare their features with juvenile spondyloarthropathy (SpA) patients, all of whom had sacroiliitis.*

Methods. *15 paediatric FMF patients with sacroiliitis and 30 patients with juvenile SpA followed between 2014-2016 at the Department of Paediatric Rheumatology at Hacettepe University, Ankara, were included in the study.*

Results. *The median (min-max) age at diagnosis of sacroiliitis was 11 (7-15) for FMF+sacroiliitis, and 11.5 (7-16) years for juvenile SpA patients. All patients suffered from hip pain and morning stiffness. Only two FMF+sacroiliitis patients had enthesitis, while nearly half of juvenile SpA patients (46.7%) had enthesitis. Four FMF patients suffered from lower back pain, although none of them had spinal involvement. On the other hand, approximately one third of juvenile SpA patients had spinal involvement. The median white blood cell count, erythrocyte sedimentation rate, and C reactive protein values in FMF+sacroiliitis patients were higher ($10.1x10^3/mm^3$ vs. $7.8x10^3/mm^3$, p=0.002; 41 vs. 28 mm/h, p<0.001; 4.6 vs. 1.3 mg/dl, p<0.001; respectively) than juvenile SpA patients. HLA B27 positivity was more common in juvenile SpA than FMF+sacroiliitis patients (86.6% vs. 26.7%, respectively, p=0.001). The most common MEFV* (MEditerranean FeVer) *mutation was M694V in FMF patients. All juvenile SpA patients but one were negative for MEFV mutations. One juvenile SpA patient was heterozygous for E148Q.*

Conclusion. *We demonstrated that paediatric patients with FMF+sacroiliitis showed different characteristics (higher inflammatory markers, less frequent spinal and enthesitis involvement and HLA-B27 positivity) from patients with juvenile SpA. Whether FMF is a triggering factor for SpA or sacroiliitis is a feature of FMF, is still a matter of debate.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease, caused by mutations in the *Mediterranean FeVer (MEFV)* gene located on chromosome 16p13.3 (1, 2). It is characterised by self-limited recurrent febrile attacks and polyserositis accompanied with elevated acute phase reactants. Joint involvement is one of the most common symptoms during the disease course and about 75% of patients complain from arthritis during the FMF attacks (3, 4). Acute recurrent monoarthritis is the most common form of musculoskeletal involvement in FMF, while about 5% of FMF patients may develop chronic arthritis, mostly in hips or knees (5). Chronic arthritis is one of the chronic sequelae of FMF which may reflect the severe course of the disease and this restricts the quality of life which takes an important place in the contemporary practice (6, 7). The increased frequency of sacroiliitis has been reported among

FMF patients (8, 9). Patients with FMF and sacroiliitis usually present with unilateral or bilateral sacroiliitis, recurrent enthesitis, and inflammatory back or neck pain (10). Sacroiliac involvement in FMF may resemble juvenile spondyloarthropathy (SpA).

Juvenile SpA is a group of seronegative arthritis which is characterised by enthesitis, asymmetrical oligoarthritis of lower extremities, axial involvement and HLA B27 positivity and starts prior to age 16 years (11). The nomenclature and classification of SpA have changed during the years. European Spondyloarthropathy Study Group criteria was the most widely accepted criteria for classification (12); however, it was shown that it had some limitations in children (11). Finally, Petty *et al*. established a new classification criteria set for childhood chronic arthritis which is called International League of Associations of League Associations for Rheumatology (ILAR) criteria and introduced a new subtype which is called enthesitis related arthritis (ERA) (13). ERA is a subtype of juvenile idiopathic arthritis (JIA) which accounts for approximately 20% of JIA patients in Turkey (14). According to ILAR classification, patients are classified as having ERA, if she/he has arthritis and enthesitis or arthritis or enthesitis and at least two of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain; presence of human leukocyte antigen-B27 (HLA-B27); onset of arthritis in a boy older than 6 years; acute anterior uveitis; or first-degree relative with HLA-B27-associated disease (13). SpA is defined as inflammation of entheses and joints of the lumbosacral spine (13). ERA has a strong association with the HLA-B27. However in patients with FMF and sacroiliitis, the presence of HLA-B27 or spine involvement is unusual (10).

In this study we aimed to evaluate the FMF patients with sacroiliitis, and compare these patients with juvenile SpA patients.

Patients and methods

We retrospectively reviewed the medical files of children (aged 0-18 years) seen at our hospital between January 2014 and January 2017 who were diagnosed with FMF and sacroiliitis or juvenile SpA.

Patients are diagnosed with FMF according to the Turkish criteria (15). Patients are classified as having juvenile SpA according to the ILAR classification criteria (13).

Demographic data, clinical manifestations, laboratory findings (white blood cell [WBC] count, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], HLA-B27), and treatment were documented. The acute phase reactants at attack-free period but during active sacroiliitis were evaluated in FMF patients. For SpA patients, the acute phase reactants during active sacroiliitis were included, as well. The following parameters were also questioned in these patients: 1) inflammatory back pain lasting more than three months, 2) morning stiffness, 3) enthesitis, 4) Schober's test, 5) Patrick-Faber test and tenderness on pressure of the pelvis to evaluate the presence of sacroiliitis, 6) uveitis, and 7) familial history of HLA-B27-associated disease or FMF. Patients with psoriasis and inflammatory bowel disease were excluded.

All patients underwent magnetic resonance imaging (MRI) of sacroiliac joint and cervical, thoracic, and lumbosacral spine. MRI was performed with 1.5 tesla (T). Active sacroiliitis was determined in MRI according to the Assessment in Spondyloarthritis International Society (ASAS) criteria (16).

MEFV gene variant analysis was performed in patients by Sanger sequencing and 12 variants (E148Q, P369S, F479I, M680I (G-C), M680I (G-A), I692del, M694V, M694I, K695R, V726A, A744S, R761H) were tested in the *MEFV* gene.

The study protocol was approved by the local Ethics Committee of Hacettepe University. A general consent approving anonymous data use for academic purpose was obtained from all children and/or their parents when the patients admitted to the hospital.

Statistical analyses

Statistical analyses were performed using the SPSS software v. 21. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed.

Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. The Mann-Whitney U-test was used to compare the non-normally distributed variables between two groups. A *p*-value of less than 0.05 was considered to show a statistically significant result.

Results

The study group consisted of 15 patients with FMF and sacroiliitis, and 30 juvenile SpA patients. The characteristics of these patients and comparison between these two groups are presented in Table I.

The median (minimum-maximum) age at FMF-related symptom onset and FMF diagnosis were 5 (1-14.5) and 5 (2-15) years, respectively. Among 15 FMF patients, all had fever, 46.7% had abdominal pain, 26.7% had arthritis, and 13.4% had chest pain during FMF attacks. The median (minimum-maximum) attack number per year and the duration of fever attacks before colchicine initiation were 6 (4-10) and 2 (2-4) days, respectively. In physical examination, all FMF patients had tenderness in sacroiliac joint area, and Patrick-Faber test positivity; however, the Schober test was normal (>6) in these patients. None of the patients had family history for neither FMF nor sacroiliitis. Of FMF patients, 7 (46.6%) were M694V/M694V, 3 (20%) M694V/E148Q, 2 (13.4%) M694V/M680I, 2 (13.4%) M694V/-. 1 (6.7%) was M694V/V726A.

The WBC count, ESR and CRP levels were found to be higher in patients with FMF+sacroiliitis than juvenile SpA patients (p=0.002, p<0.001, and p<0.001, respectively). Spinal involvement and enthesitis were significantly more frequent in juvenile SpA than FMF+sacroiliitis patients (p=0.008 and p=0.02, respectively). HLA-B27 positivity was more frequent in juvenile SpA patients (p=0.001). All juvenile SpA patients but one were negative for

Table I. Comparison of patients with familial Mediterranean fever (FMF) accompanied with sacroiliitis and patients with juvenile spondyloarthropathy (SpA).

	Patients with FMF[a] and sacroiliitis (n=15)	Juvenile SpA[a] patients (n=30)	*p*-value
Female/male (n)	5/10	2/28	0.032
Age, years, median (min-max)	13 (8-18)	15 (10-18)	0.075
Age at diagnosis of sacroiliitis, years, median (min-max)	11 (7-15)	11.5 (7-16)	0.96
Family history of SpA	0 (0)	2 (6.6)	0.54
Musculoskeletal symptoms			
Arthralgia, n (%)	13 (86.7)	24 (80)	0.69
Arthritis, n (%)	4 (26.7)	15 (50)	0.13
Hip pain, n (%)	15 (100)	30 (100)	-
Lower back pain, n (%)	4 (26.7)	17 (56.7)	0.05
Morning stiffness, n (%)	15 (100)	28 (93.3)	0.54
Spinal involvement, n (%)	0 (0)	11 (36.7)	0.008
Enthesitis, n (%)	2 (13.4)	14 (46.7)	0.02
Sacroiliitis, n (%)	15 (100)	30 (100)	-
Unilateral sacroiliitis, n (%)	5 (33.3)	12 (40)	
Bilateral sacroiliitis, n (%)	10 (66.7)	18 (60)	
Laboratory findings			
WBC[a] count, x10^3/mm^3, median (min-max)	10.1 (6.4-18)	7.8 (4.6-11.4)	0.002
ESR[a], mm/h, median (min-max)	41 (23-78)	28 (3-38)	<0.001
CRP[a], mg/dl, median (min-max)	4.6 (1.05-11.4)	1.3 (0.17-4.6)	<0.001
HLA-B27[a] positivity, n (%)	4 (26.7)	26 (86.6)	0.001
Treatment			
Methotrexate, n (%)	9 (60)	19 (63.3)	0.71
Sulphosalazine, n (%)	9 (60)	20 (66.6)	0.55
Etanercept, n (%)	10 (66.6)	18 (60)	0.54
NSAIDs, n (%)	15 (100)	25 (83.3)	0.15

[a]CRP: C-reactive protein; SpA: spondyloarthropathy; ESR: erythrocyte sedimentation rate; FMF: familial Mediterranean fever; HLA-B27: human leukocyte antigen- B27; NSAIDs: non-steroidal anti-inflammatory drugs; WBC: white blood cell.

MEFV mutations. One juvenile SpA patient was heterozygous for E148Q. FMF+sacroiliitis patients received non-steroidal anti-inflammatory drugs (NSAIDs) more frequently than juvenile SpA patients (100% *vs*. 83.3%), however this difference was not statistically significant.

Discussion

Patients with sacroiliac involvement in FMF may present with inflammatory back or hip pain, and they often lack HLA-B27 and spine involvement. The increased frequency of sacroiliitis has been reported in Turkish and Jewish adult FMF patients (8, 17). However, there are only few case reports of FMF and sacroiliitis in childhood. To our knowledge, the present study is the first to evaluate paediatric patients with FMF and sacroiliitis.

We here demonstrated that the inflammatory markers were higher; and spinal involvement, enthesitis, and HLA-B27 positivity were less frequent in paediatric FMF+sacroiliitis than juvenile SpA patients.

Whether sacroiliitis in FMF is a musculoskeletal finding of FMF itself or a separate disease, SpA is still a matter of debate. Langevitz *et al*. (10) evaluated 3000 adult patients who were diagnosed with FMF, and found the prevalence of sacroiliitis as 0.4% among these patients without the presence of HLA-B27 and rheumatoid factor. In this study, three patients had bamboo spine, bilateral sacroiliitis, and HLA-B27 positivity fulfilling the criteria for SpA. The authors claimed that the presence of HLA-B27 may be associated with the more severe phenotype of FMF-related sacroiliitis. Kasifoglu *et al*. (17) found the frequency of sacroiliitis as 7% in Turkish adult FMF patients with musculoskeletal complaints. In this study, HLA-B27 was positive in almost half of the FMF patients with sacroiliitis while only 6.3% of FMF patients without sacroiliitis had HLA-B27 antigen. In addition, the patients who were HLA-B27 positive had more severe and chronic course of arthritis. The authors suggested that the increased frequency of sacroiliitis in Turkish patients might be related with environmental and genetic factors, as well as HLA-B27 positivity (17). In the same lines, Cefle *et al*. (8) also reported high frequency of sacroiliitis (10.5%) among Turkish FMF patients, but did not mention the status of HLA-B27 antigen. In the presented study, we found that 26.7% of FMF+sacroiliitis patients were HLA-B27 positive; however, this ratio was significantly lower than the ratio in juvenile SpA patients (86.6%). Spinal involvement is not common in patients with FMF and sacroiliitis (10, 17). Similar to, previous studies none of our FMF patients had spinal involvement. However, we will follow these patients for spinal involvement since the presence of sacroiliitis may be a risk factor for spinal involvement in the long term follow-up.

Akar *et al*. (18) reported an increased prevalence of SpA in the first degree relatives of FMF patients. Furthermore, patient and family history for other inflammatory diseases such as vasculitis and psoriasis has been reported previously (19, 20). However, none of our FMF+sacroiliitis patients had a positive family history for SpA.

It is well known that M694V mutation is related with a more severe phenotype (3, 21). The positive correlation between M694V mutation and recurrent arthritis was also reported (22). Furthermore, chronic destructive arthritis was found to be associated with a higher risk of secondary amyloidosis which is the most severe complication of FMF (8, 23). Kasifoglu *et al*. previously showed an increased frequency of M694V mutations among FMF patients with sacroiliitis (17). In our study, all of our patients had M694V mutation in at least one allele and approximately half of our patients (46.6%) were homozygous for M694V. On the other hand we had previously reported a high frequency of *MEFV* mutations in ERA patients and had suggested that in HLA-B27 negative patients, *MEFV* mutations can be associated with the disease in the part of

the world where FMF is frequent (24). Thus *MEFV* mutations do seem to be associated with this form of arthropathy however the classification is still a matter of debate.

There is no consensus about the treatment of patients with FMF and sacroiliitis. Effectiveness of disease-modifying anti-rheumatic drugs (DMARDs) and anti-tumour necrosis factor (anti-TNF) agents in FMF patients with chronic musculoskeletal involvement have been reported in previous studies (25-27). Recently Bilgen *et al*. (28) have shown that anti-TNF treatment was effective to control the disease activity in adult patients with FMF and sacroiliitis. All of our patients received NSAIDs, colchicine, and at least one DMARD. Ten patients who were resistant to these therapies received etanercept and improved after anti-TNF treatment.

Conclusion

The limitations of our study were its retrospective characteristic and small number of patients.

In conclusion, it is difficult to distinguish whether sacroiliitis is a musculoskeletal finding of FMF or this is the coexistence of two diseases; FMF and SpA. However, we demonstrated that patients with FMF+sacroiliitis showed different characteristics (higher inflammatory markers, less frequent spinal and enthesis involvement and HLA-B27 positivity) from patients with juvenile SpA. We may suggest that these group of patients should be evaluated differently than juvenile SpA patients; however, the therapy options remain the same. Further multicentre studies with more patients and prospective follow-up may help us to understand the whole spectrum in these patients.

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