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Spondyloarthritis in familial Mediterranean fever: a cohort study

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Abstract

Familial Mediterranean fever (FMF) and spondyloarthritis (SpA) may show several common signs. This study aimed to evaluate the frequency of SpA and its manifestations in FMF, the impact of SpA on FMF, and the associations of non-episodic findings (heel enthesitis, protracted arthritis, and sacroiliitis) with the FMF features. Demographic, clinical, imaging, and genetic data were retrieved from medical records of the patients with adult FMF. To identify patients who met the classification criteria for SpA, data including rheumatologic inquiry were recorded. Patients with SpA and those who did not meet the criteria were compared in terms of FMF features. Regression analyses were performed to determine the factors that were most associated with sacroiliitis, enthesitis, and protracted arthritis. Of the 283 patients with FMF, 74 (26.1%) met the SpA criteria (64 axial, 10 peripheral); and 65 (22.9%) patients had sacroiliitis, 27 (9.5%) protracted arthritis, and 61 (21.6%) heel enthesitis. Patients with SpA were older and had more FMF severity, and heel pain rate than those without; however, genetic features, CRP, resistance to colchicine, and heel enthesitis did not differ. A meaningful number of patients without SpA had also displayed heel enthesitis, protracted arthritis, inflammatory back pain, heel pain, family history of SpA, and elevated CRP. Age was found to be the main predictor of heel enthesitis and protracted arthritis was linked with FMF severity. A significant number of patients with FMF meet the peripheral SpA classification criteria as well as axial SpA. SpA and its shared manifestations with FMF may have an impact on FMF.

Keywords Familial Mediterranean fever · Arthritis · Sacroiliitis · Enthesopathy · Spondylarthropathies

Introduction

Familial Mediterranean fever (FMF), the most common hereditary autoinflammatory disease, is characterized by attacks of peritonitis, pleuritis, or acute synovitis [1, 2]. Patients with FMF are associated with an increased prevalence of various diseases compared to the general population. The most common associated diseases include spondyloarthropathies (SpA), psoriasis, vasculitis, Behçet's disease, juvenile idiopathic arthritis, and inflammatory bowel disease (IBD) [3, 4]. Among them, the co-occurrence of SpA and FMF has been studied multiple times [3, 5–13]. In addition to the clinical relationships, there are also studies advocating the potential genetic relationships for this association [14, 15]. However, those studies mostly assessed axial SpA (axSpA), and little is known regarding peripheral SpA (pSpA) in FMF. Protracted arthritis, sacroiliitis, and enthesitis, which are also seen in patients with FMF, may expand the spectrum of pSpA, making differential diagnosis and treatment difficult [5, 8, 9].

The prevalence of SpA in patients with FMF is highly variable [5, 9, 14–16]. This might be due to the differences in the methods of SpA definitions or missing data on the manifestations. The skewed distribution of this data, especially the lopsided focus on sacroiliitis and the bias in the inclusion criteria used in these studies, still causes variations even in the association between FMF and SpA prevalence. On the other hand, the assessment of spondyloarthritis international society (ASAS) has developed the classification criteria for axSpA and pSpA based on the predominance of axial or peripheral involvement [17, 18]. However, most manifestations in the ASAS criteria do not have enough FMF data in the literature. This is important in clinical practice because

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of a possible impact of SpA presence on some complications of FMF such as amyloidosis.

Besides sacroiliitis/axSpA, enthesitis is increasingly reported in association with FMF [6, 7, 9, 16, 19]. On the other hand, there are only a few studies on chronic arthritis in adult FMF [5, 11, 20–22]. Arthritis is one of the most common symptoms of FMF and SpA [2]. Joint involvement of FMF is generally in the lower extremities as a short-term, self-limiting, non-deforming mono-oligoarthritis. A small percentage of patients with FMF may develop protracted arthritis, mostly in the hips or knees, and generally require immunosuppressive therapies, synovectomy, or joint replacement surgery [10, 14, 22]. Protracted arthritis is somewhat similar to the SpA group of diseases in terms of disease pattern and joint preference [14]. Apart from these, data pointing to an overall SpA assessment and examining its impact on FMF are limited. As a result, there is a need to assess the overall SpA-related manifestations in FMF.

From another perspective, it is still unknown why about 30% of patients with FMF have persistent subclinical inflammation during attack-free periods and why some patients suffer from chronic fatigue or persistent findings like protracted arthritis [23, 24]. They may occur due to predisposing effects of disrupted immune pathways. It should be identified whether these chronic inflammatory conditions are part of FMF itself or incurred by the co-occurrence of FMF and SpA due to genetic mechanisms.

This study aims to determine the frequencies of SpA (axial and peripheral) and all of its manifestations observed in an adult FMF cohort. It investigated the relations of FMF features with SpA, sacroiliitis, protracted arthritis, and established heel enthesitis in order to assess the impact of SpA on FMF. To this end, demographic, clinical, and genetic characteristics, laboratory results, and therapies of the patients with FMF were assessed. Finally, FMF features that were most associated with the main manifestations (enthesitis, sacroiliitis, and protracted arthritis) were discovered.

Methods

Patients

This retrospective study included adult patients (> 18 years of age) diagnosed with FMF based on the Tel Hashomer criteria [25]. The study covered the data between January 2015 and July 2020. Patients with unclear FMF diagnosis (e.g., those yet expected to respond to colchicine) or genetic carriers with atypical symptoms without an established diagnosis were excluded from the study. Pregnant patients and those with infection, malignancies, and psychosis at the time of investigation were also excluded. All patients who met the specified criteria were indiscriminately enrolled for the study. The study was approved by the institutional clinical ethics committee of Marmara University (the approval date and number were 04.12.2020 and 09.2020.1255, respectively) and conducted in accordance with the Helsinki Declaration.

Data collection

Patient data, including age, gender, duration of the disease, number of attacks in the last 3 months, characteristics of the attacks that have occurred in recent years, MEFV mutations, the presence of known amyloidosis, medications, and colchicine resistance [2] were recorded. Disease severity of FMF was calculated based on the international severity score for FMF (ISSF) and Pras disease severity scoring (PrasS) [26, 27].

In this cohort, all patients underwent an exhaustive rheumatological questioning in their first visits even if they had been diagnosed in childhood. This rheumatological questioning includes a standard list of questions [28]: arthralgia, arthritis, psoriasis, family history of SpA, inflammatory back pain (IBP), heel pain, urinary symptoms, bowel disease, uveitis, oral and genital mucocutaneous lesions, fever, abdominal pain, fetal loss or thrombosis, photosensitivity, rash, Raynaud, weakness, and dry eyes and mouth. For example, "heel pain" is one of items on the first-visit-questioning list, and patients were only asked, "Do you suffer from heel pain?". When the patient says yes, a detailed questioning starts to understand the type and location of the pain. The patients were asked for their past or current medications and family history for rheumatic diseases. Clinical interviews and examinations in this cohort were performed by experienced rheumatologists who had undergone training by the same supervisor (MTD, professor).

Patients were asked for back pain, then if present, the type of pain was identified according to the following ASAS definition: insidious onset, morning stiffness, improvement with exercise, improvement with rest, alternating buttock pain, pain at night with improvement upon getting out of bed [17]. All patients with IBP underwent the sacroiliac joint X-ray examination. If a patient was diagnosed with established AS by X-ray and other clinical findings, then he/she did not undergone further imaging. If not, magnetic resonance imaging (MRI) for sacroiliitis was applied. Remaining patients with IBP and other patients with a clinical suspicion of SpA (i.e., combination of protracted arthritis, enthesitis, uveitis, elevated inter-attack CRP, family history of SpA, or combination of these with mechanical/undefined low back pain) underwent sacroiliac MRI.

SpA-related parameters from these inquiries/findings were thus recorded, including IBP, heel pain, arthritis and protracted arthritis (long-standing arthritis in which effusion lasts longer than a month [29]), arthralgia, uveitis, IBD,

psoriasis, dactylitis, infection history, family history, *HLA-B27* positivity if available, sacroiliitis on X-ray and MRI, heel enthesitis on X-ray, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) during inter-attack intervals, and response to nonsteroidal anti-inflammatory drugs (NSAID).

All imaging and laboratory data were confirmed again by the same experienced physician (SAK) using picture archiving communication system and the hospital's automated system, respectively.

SpA classification

ASAS criteria were used for SpA classifications [17, 18]. IBP [30], sacroiliitis in X-ray and/or MRI findings [31], and *HLA-B27* positivity were used as the entry criteria for axSpA, whereas protracted arthritis, dactylitis, and enthesitis were used as the entry criteria for pSpA. Confirmed data were recorded, i.e., the presence of sacroiliitis based on imaging and according to the ASAS definition; IBP, arthritis, and dactylitis based on the anamnesis of the patient; protracted arthritis based on physical examination findings; and enthesitis based on imaging or physical examination findings. Patients with chronic reactive arthritis were included, but patients with acute reactive arthritis with a prior history of infection were excluded because of the conditions listed in the exclusion criteria. The diagnosis of psoriatic arthritis (PsA) was also confirmed according to the classification criteria for psoriatic arthritis (CASPAR) [32].

Statistical analysis

Descriptives: In the descriptive statistical analysis, normally distributed data were evaluated using mean with standard deviation, data with a skewed distribution were evaluated using median with quartiles (IQR; 25%–75%), and dichotomous data were evaluated using percentage (%) distributions. Distributions of continuous variables for normality were assessed by Kolmogorov–Smirnov test and histogram graphs. The rate of each parameter included in the diagnostic criteria for SpA and observed in all patients with FMF was given as percentages (%).

Comparisons: Patients who met the diagnostic criteria for SpA (axial and/or peripheral) (SpA +) and those who did not meet the criteria (SpA −) were identified and compared in terms of FMF characteristics. The FMF characteristics of patients with heel enthesitis as per X-ray findings and all other patients who were theoretically considered as not having heel enthesitis were compared. In addition, patients with and without sacroiliitis and patients with and without protracted arthritis were compared in terms of FMF characteristics. These pairwise comparisons were performed using Student's *t* test for normally distributed continuous variables, Mann–Whitney *U* test for non-normal distributions, and Kruskal–Wallis test for dichotomal comparisons.

Best associations: univariate and multivariate (Enter method) logistic regression analyses were performed to determine the FMF features that were most associated with the main manifestations (enthesitis, sacroiliitis, and protracted arthritis). Models of the multivariate analysis included the parameters that were found to be significant in univariate analysis. Analyses were conducted using IBM SPSS statistics 21.0. Statistical significance was set at $p < 0.05$. None of the parameters that were drawn from the cohort for analysis had > 10% of missing data.

Results

Characteristics of patients with FMF

The study included 283 patients with FMF (73.9% female) with a median disease duration of 9 years (IQR, 4–20). Demographic, clinical, genetic, laboratory, imaging, and therapeutic data of the patients are presented in Table 1.

Frequency of SpA and its manifestations in the cohort

Of the total, 94 (33.2%) patients had previous IBP and 44 (15.5%) had it at the time of the investigation. A hundred patients (35.3%) had arthritis; of which, 27 (9.5%) had protracted arthritis. The other manifestations of SpA were given in Fig. 1.

Regarding the imaging criteria, 65 (22.9%) patients were found to have sacroiliitis. Of these, 14 (4.9%) patients were diagnosed with obvious sacroiliitis by X-ray according to the modified New York criteria. Of the 94 patients with IBP, the remaining 80 patients underwent sacroiliac MRI as well as other 40 patients without IBP and with a clinical SpA suspicion (i.e., protracted arthritis, enthesitis, uveitis, elevated inter-attack CRP, family history of SpA, and a combination of these with or without mechanical/undefined low back pain). In total, 120 patients had undergone sacroiliac MRI; of which, 37 (13.1%) had bilaterally sacroiliitis and 14 (4.9%) had unilaterally sacroiliitis. Additionally, 109 patients had heel X-rays and 61 (21.6%) of the total had heel enthesitis on X-ray.

Finally, A total of 74 (26.1%) patients met the diagnostic criteria for SpA. Of these, 64 (22.6%) were classified as having axSpA and 10 (3.5%) were classified as having pSpA (remaining 1 patient with sacroiliitis did not meet any ASAS criteria). Four patients from the pSpA group met the criteria for PSA based on the CASPAR, whereas two patients had IBD-associated SpA.

Table 1 Demographic, clinical, and MEFV[a] characteristics of the study population

	n = 283 (%), mean (SD), or median (25–75%)
Age, years	37 (28–46)
Diagnosis duration, years	9 (4–20)
MEFV Exon 10 mutations	
M694V	113 (39.9%)
V726A	27 (9.5%)
M680I	26 (9.2%)
R761H	2 (7%)
M694I	1 (0.4%)
K695R	1 (0.4%)
MEFV Exon 2 mutations	
R202Q	72 (25.4%)
E148Q	35 (12.4%)
E167D	3 (1.1%)
L110P	2 (0.7%)
D102D	1 (0.4%)
761-764dup	1 (0.4%)
MEFV Exon 3 mutations	
P369S	12 (4.2%)
R408Q	6 (2.1%)
S339F	1 (0.4%)
MEFV Exon 5 mutation, F479L	3 (1.1%)
MEFV Exon 9 mutation, I591T	1 (0.4%)
Amyloidosis, *n*	10 (3.5%)
Dominant attack sign of the last years	
Peritonitis	215 (76%)
Fever	25 (8.8%)
Arthritis	25 (8.8%)
Pleuritis/pericarditis	12 (4.2%)
Other	3 (1.1%)
FMF treatment	
Colchicine	263 (92.9%)
Anakinra	6 (2.1%)
Canakinumab	12 (4.2%)
None	11 (3.9%)
Colchicine dose, mg	1.5 (1–2)
Colchicine resistance	54 (19.1%)
Number of attacks (last 3 months)	0.5 (0–2)
CRP, mg/L (intervals)	3.14 (1.5–6)
Pras score	4 (3–6)
ISSF score	1 (0–2)
History of arthritis	100 (35.3%)
Ankle	41 (14.5%)
Knee	29 (10.2%)
Hand joints	15 (5.3%)
Wrist	4 (1.4%)
Root joint	3 (1%)

MEFV Mediterranean Fever, *FMF* familial Mediterranean fever, *ISSF* International severity score for FMF, *SD* standard deviation

[a]Homozygous or heterozygous mutation

Comparison of SpA + and SpA − patients in terms of FMF characteristics

Table 2 presents a comparison of SpA + and SpA − patients with FMF. The mean ages of the SpA + and SpA − groups were 40.22 (SD 12.10) and 36.94 (SD 12.28), respectively, and the difference was significant (p: 0.045). There was no difference in terms of the other demographics analyzed, MEFV mutations, and the inter-attacks laboratory parameters (ESR and CRP). While the optimal colchicine dose the patients were using, colchicine resistance rates and the amyloidosis rates did not differ between the groups, patients with SpA + had a higher ISSF score with a p value of 0.038. The heel pain rate was higher in the SpA + group than in SpA − (0.025), but the heel enthesitis on X-ray did not differ.

Relations between heel enthesitis and FMF characteristics

In the pairwise comparisons between the patients with and without established heel enthesitis, patients with heel enthesitis (Table 3) were older than those without ($p < 0.001$). The other clinical, MEFV mutations, laboratory, and activity parameters of FMF did not differ between the groups, except disease severity evaluated with the PrasS. PrasS were significantly lower in the patients with heel enthesitis compared to those without [3 (2–5) vs 4 (3–6) $p = 0.017$, respectively].

Univariate analysis discovered the age and PrasS relations with established heel enthesitis (Table 3), then age remained to be the only determinant of established heel enthesitis in the multivariate analysis [ß 1.03 (95%Cl 1.01–1.06), $p = 0.001$].

Relations between sacroiliitis and FMF characteristics

Pairwise comparisons between 65 patients with sacroiliitis and 218 patients who were presumed not to have sacroiliitis revealed no difference in overall FMF characteristics, including demographics, disease duration, MEFV mutations, inter-attack CRP and ESR, amyloidosis and arthritis rates, optimal colchicine dose patients were using, colchicine resistance, and disease activity and severity parameters as presented in Table 4 ($p > 0.05$ for all). Univariate analysis were also insignificant with the p values of > 0.05.

Relations between protracted arthritis and FMF characteristics

Six patients had suspicious/missing data in the history of protracted arthritis, so they were not included in the analysis. The median CRP levels were significantly higher in

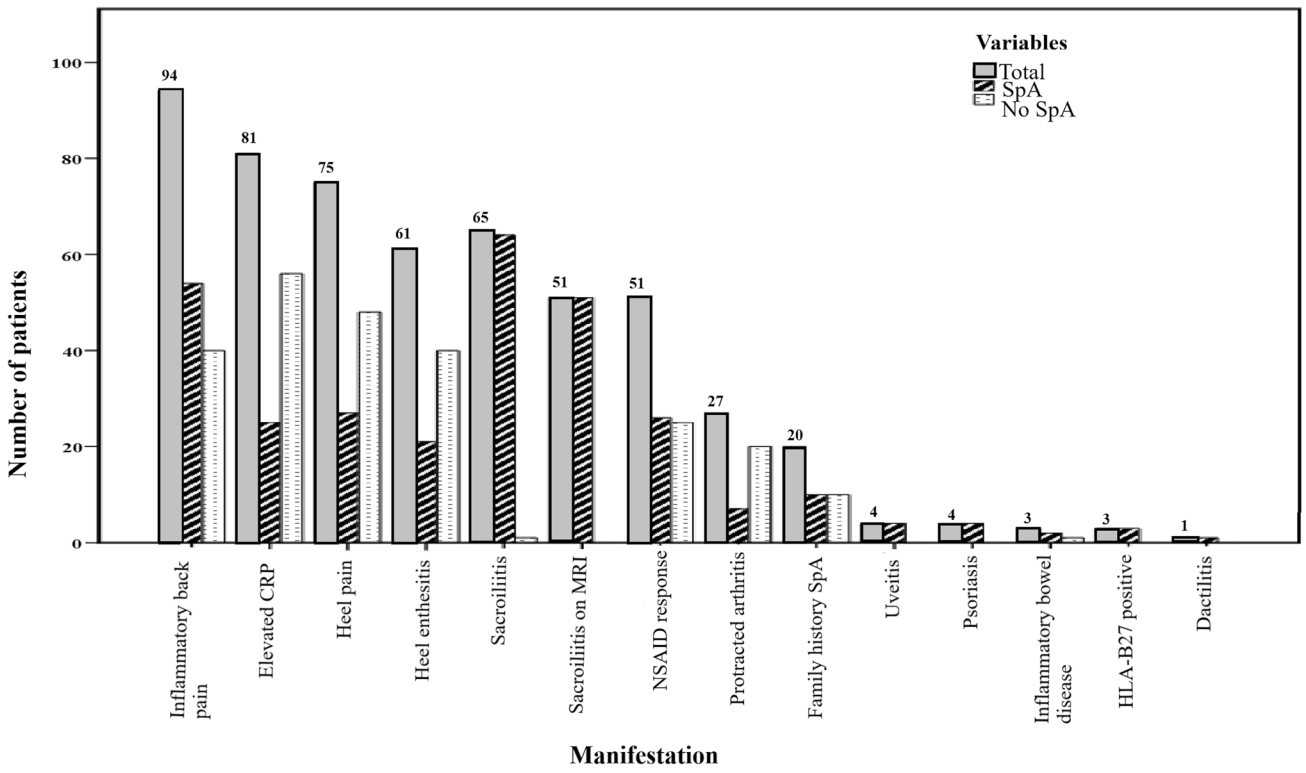

Fig. 1 Spondyloarthropathy manifestations with numbers in the study population. (*SpA* spondyloarthropathy, C-reactive protein, *NSAID* Non-steroidal anti-inflammatory drugs, *MRI* magnetic resonance imaging.)

the patients with protracted arthritis compared to those without [4.3 (3–10.35) vs 3.13 (0–6), $p < 0.001$]. Colchicine resistance rate was significantly higher in patients with protracted arthritis compared to those without (57.7% vs 19% $p < 0.001$). ISSF and PrasS were significantly higher in patients with protracted arthritis compared to those without [2 (0.5–4.5) vs 1 (0–2), 5 (3.75–8) vs 4 (3–5), respectively, $p < 0.001$ for both]. Table 5 shows the comparisons of the patients with protracted arthritis and without.

Univariate analysis discovered the CRP, ESR, amyloidosis, colchicine resistance, ISSF, and PrasS relations with protracted arthritis (Table 5), then ISSF remained to be the only determinant of protracted arthritis in the multivariate analysis [ß 1.74 (95%Cl 1.10–2.77), $p < 0.001$].

Discussion

To our knowledge, this is the first study to evaluate the demographic, disease-related, and treatment characteristics of adult FMF patients with any of SpA's. The SpA frequency was 26.1%, and 22.6% of the total were classified as axSpA in this study. Sacroiliitis (22.9%), established heel enthesitis (21.6%), and protracted arthritis (9.5%) which are typical manifestations of SpA were found to be common in patients with FMF. Additionally, this study emphasizes the importance of these non-episodic findings in patients with FMF regardless of SpA. To identify and select the patients with SpA from the FMF cohort, well-defined ASAS criteria were used systematically. When we listed the SpA manifestations among the patients with and without SpA, a meaningful number of patients without SpA displayed various manifestations, such as heel enthesitis, protracted arthritis, inflammatory back pain, elevated CRP, and family history of SpA.

The frequency of SpA in this cohort (26.1%) is generally higher than in the previous studies [3, 5, 9, 14–16]. Data on the co-variance of FMF and SpA have revealed highly variable rates. One with the largest sample size (3000 patients) reported an axSpA prevalence rate of 0.4% [5], however, the ratio increased as the sample size decreased in general [3, 5, 9, 14, 15]. The reason for the variable frequencies may be related to the fact that in recent years, rheumatologists have more frequently screened for sacroiliitis in parallel with the increase in the knowledge of the association between FMF and sacroiliitis. Another reason may be the differences among the SpA screening methods. Those studies mostly assessed axSpA/AS, and little is known regarding peripheral pSpA in FMF. In addition, some of them presented the SpA prevalence in FMF and some the FMF prevalence in AS. We believe that our study offers an objective SpA frequency

Table 2 The comparison of the patients with and without SpA[a]

	SpA[b] (*n*: 74)	No SpA[b] (*n*: 209)	*p*[c]
Age, years	40.22 (SD 12.10)	36.94 (SD 12.28)	0.045
Sex, female	53 (71.6%)	156 (74.6%)	0.611
FMF diagnosis duration, years	9 (4–17.75)	9 (4–20)	0.785
MEFV Exon 10 mutations, *n*	34 (45.9%)	108 (51.7%)	0.398
M694V	28 (37.8%)	85 (40.7%)	0.67
M694V homozygous	8 (10.8%)	26 (12.4%)	0.711
V726A	3 (4.1%)	24 (11.5%)	0.068
M680I	5 (6.8%)	21 (10%)	0.4
MEFV Exon 2 mutations, *n*	23 (31.1%)	85 (40.7%)	0.145
R202Q	18 (24.3%)	54 (25.8%)	0.797
E148Q	6 (8.1%)	29 (13.9%)	0.195
CRP, mg/L (intervals)	3.17 (3–8.6)	3.13 (0–5.73)	0.177
ESR, mm/h (intervals)	19.5 (8–32)	18(8–28)	0.427
Amyloidosis, *n*	3 (4.1%)	7 (3.3%)	0.725
Colchicine dose, mg	1.5 (1.25–2)	1.5 (1–2)	0.839
Colchicine resistance, *n*	17 (25.8%)	38 (22 %)	0.533
Number of attacks (last 3 months)	1 (0–2)	0 (0–2)	0.707
ISSF, median	1 (0–2)	1 (0–2)	0.038
ISSF, mean	1.40 (1.39)	1.04 (1.21)	
Pras score	4 (3–5.75)	4 (3–6)	0.646
Heel pain, *n*	27 (37.5%)	48 (23.8%)	0.025
Heel enthesitis on X-ray, (*n*: 109)	21 (28.4%)	40 (19.1%)	0.097
Arthritis, *n*	28 (37.8%)	72 (35.1%)	0.676
Protracted arthritis	7 (9.6%)	20 (9.8%)	0.958
DMARD use for arthritis	7	11	0.256
Biologic use for arthritis	5	2	0.017
Steroid use for arthritis	1	6	0.67

SpA: spondyloarthropathy, FMF: familial Mediterranean fever, MEFV: Mediterranean fever, ISSF: International severity score for FMF, DMARD: disease modifying antirheumatic drug, SD: standard deviation

[a]MEFV mutations detected in > 5% of the study population are presented

[b]Median with quartiles (25–75%), otherwise indicated by (%) or (SD)

[c]Significance in pairwise comparisons by Student's *t*, Mann–Whitney *U*, or Kruskal–Wallis tests

rate since it aimed to identify all SpA cases and screened all FMF cases.

Whether FMF and SpA are coexisting diseases and whether they are components of each other are still contentious. Studies investigating the association between these diseases and cytokines and genes have revealed an AS risk associated with the IL-1 cytokine pathway in addition to associations with the IL-23R and IL-17 pathways [33–36]. There is also evidence implicating the *M694V* mutation in the pathogenesis of AS [37, 38]. Studies by Kasifoglu et al. and Akar et al. found an association between sacroiliitis and *M694V* mutations [8, 9], but they reported the frequency of sacroiliitis to be as low as 7% and was conducted with a limited population in accordance with the selection criteria. Although in some studies, sacroiliitis not associated with *HLA-B27* in patients with FMF [5] has distanced authors from the SpA diagnosis [15], in others, the fact that sacroiliitis did not respond to colchicine or IL-1 blockers and was instead treated with anti-TNF drugs has suggested associations with a concomitant disease [39]. In contrast to these, our study neither confirmed such a genetic association nor found an association with exons. On the other hand, the findings of subclinical inflammation during the inter-attack periods in some FMF patients led to the idea that the close interactions of innate and adaptive immune systems preparing the environment for other chronic inflammatory diseases. The results in our study support that protracted arthritis is associated with subclinical inflammation and colchicine resistance. On the other hand, the presence of sacroiliitis, heel enthesitis, and even SpA did not support that hypothesis.

This study specifically examined the non-episodic manifestations, such as persistent enthesitis detected on X-ray, sacroiliitis detected in patients with IBP for at least

Table 3 Relations between heel enthesitis and familial Mediterranean fever characteristics

	Heel enthesitis[a]		Univariate analysis[b]	Multivariate analysis[c]
	Present (*n*: 61)	Not detected (*n*: 222)	OR (95% Cl)	OR (95% Cl)
Age, years	42.67 (9.46)	36.45 (12.66)**	1.04 (1.02–1.06)**	1.03 (1.01–1.06)*
Sex, female	48 (78.7%)	161 (72.5%)	0.71 (0.36–1.41)	–
FMF diagnosis duration, years	9.5 (4–22)	9 (4–19)	1.01 (0.98–1.03)	–
MEFV Exon 10 mutation, *n*	30 (49.1%)	112 (50.4)	0.95 (0.54–1.67)	–
M694V	26 (42.6%)	87 (39.2%)	1.15 (0.65–2.15)	–
M694V homozygous	8 (13.1%)	26 (11.7%)	1.14 (0.49–2.66)	–
V726A	2 (3.3%)	25 (11.2%)	0.27 (0.06–1.16)	–
M680I	8 (13.1%)	18 (8.1%)	1.71 (0.70–4.15)	–
MEFV Exon 2 mutation, *n*	23 (37.7%)	85 (38.3%)	0.98 (0.54–1.75)	–
R202Q	15 (24.6%)	57 (25.7%)	0.94 (0.49–1.82)	–
E148Q	10 (16.4%)	25 (11.3%)	1.54 (0.69–3.42)	–
CRP, mg/L (intervals)	3.23(3–6.3)	3.13 (0–6)	0.99 (0.95–1.02)	–
ESR, mm/h (intervals)	20.5 (9–27.75)	17 (8–28)	1.01 (0.99–1.02)	–
Amyloidosis, *n*	2 (3.3%)	8 (3.6%)	0.91 (0.19–4.38)	–
Arthritis	22 (36%)	78 (35.1%)	1.01 (0.56–1.83)	–
Colchicine dose, mg	1.5 (1–2)	1.5 (1–2)	1.01 (0.63–1.60)	–
Colchicine resistance, *n*	10 (16.4%)	44 (19.8%)	0.73 (0.34–1.57)	–
Attack count (last 3 months)	0 (0–1)	1 (0–2)	0.92 (0.77–1.09)	–
ISSF	1 (0–2)	1 (0–2)	0.93 (0.73–1.18)	–
Pras score	3 (2–5)	4 (3–6)*	0.84 (0.72–0.99)*	0.90 (0.76–1.06)

MEFV Mediterranean fever, *ISSF* International severity score for FMF, *SD* standard deviation

[a]Median with quartiles (25–75%), otherwise indicated by (%) or (SD). Student's *t*, Mann–Whitney *U*, or Kruskal–Wallis tests were used for the comparisons

[b]Univariate logistic regression analysis

[c]Multivariate logistic regression analysis, model $p < 0.001$, R2: 0.068. (parameters that were found to be significant in univariate analysis were included)

*$p < 0.05$, **$p < 0.01$

3 months, and protracted arthritis. Among them, sacroiliitis has been frequently studied before in connection with FMF and our sacroiliitis frequency is compatible with the literature [8, 40]. Established heel enthesitis was seen at a rate of 21.6% in our cohort and was independent of the presence of SpA diagnosis. There has been an increasing amount of literature regarding the presence of enthesitis in patients with FMF. A study by Sen et al. using the Maastricht Ankylosing Spondylitis Enthesitis Score reported enthesitis frequency to be 22.6% in patients with FMF [7], which is similar to the frequency of heel enthesitis in our study. In addition, its association with ISSF scores has been confirmed by regression analysis. The association of enthesitis with MEFV mutations has also been an issue of interest, and several studies have not found associations (similar to ours) [7, 19]. In contrast, another study conducted with a small sample size found ultrasonography-detected enthesitis scores to be associated with *M694V* mutations but not with other mutations and found the most common involvement to be that of the Achilles tendon [6]. However, those studies had various assessment methods to evaluate enthesitis. In addition, it is still not precisely known whether enthesitis and sacroiliitis may also occur as episodic signs, like episodic arthritis. Thus, our non-MEFV-related results might be better explained by our evaluation methods investigating the established signs. Further research aiming to shed light on this could focus on self-limiting enthesitis and sacroiliitis.

In this cohort, 35% of the FMF patients were found to have arthritis, a rate slightly lower than the previously reported frequencies in Turkey [41, 42]. Apart from the classical self-limiting FMF arthritis, our study found a 9.5% frequency of protracted arthritis. Since it is known that protracted arthritis may need a disease-modifying antirheumatic drug or anti-TNF agent therapy [43, 44], we investigated protracted arthritis separately from all other forms of arthritis. The protracted arthritis frequency reported previously in childhood is slightly lower than our protracted arthritis frequency [45]. Regarding adults, studies on the associations

Table 4 Relations between sacroiliitis and familial Mediterranean fever characteristics

	Sacroiliitis[a]		Univariate analysis[b]
	Present (*n*: 65)	Not detected (*n*: 218)	OR (95% Cl)
Age, years	39.17 (11.92)	37.38 (12.40)	1.01(0.99–1.03)
Sex, female	46 (70.8%)	163 (74.8%)	1.22 (0.66–2.26)
FMF diagnosis duration, years	7 (4-17)	9 (4-20)	0.99 (0.97–1.02)
MEFV Exon 10 mutation, n	32 (49.2%)	110 (50.5%)	0.95 (0.55–1.66)
M694V	26 (40%)	87 (39.9%)	1.00 (0.57–1.77)
M694V homozygous	6 (9.2%)	28 (12.8%)	0.69 (0.27–1.77)
V726A	3 (4.6%)	24 (11%)	0.39 (0.11–1.34)
M680I	5 (7.7%)	21 (9.6%)	0.78 (0.28–2.16)
MEFV Exon 2 mutation, n	21 (32.3%)	87 (39.9%)	0.72 (0.40–1.29)
R202Q	17 (26.2%)	55 (25.2%)	1.05 (0.56–1.97)
E148Q	4 (6.2%)	31 (14.2%)	0.40 (0.13–1.67)
CRP, mg/L (intervals)	3.21(3–9.44)	3.13 (0–5.46)	1.00 (0.99–1.01)
ESR, mm/h (intervals)	18 (8–30.5)	19 (8–28.25)	1.00 (0.98–1.02)
Amyloidosis, *n*	3 (4.6%)	7 (3.2%)	1.46 (0.37–5.81)
Arthritis	23 (35.4%)	77 (36%)	0.97 (0.55–1.74)
Colchicine dose, mg	1.5 (1.12–1.5)	1.5 (1–2)	0.92 (0.58–1.45)
Colchicine resistance, n	13 (22.8%)	42 (23.1%)	0.98 (0.48–2.00)
Attack count (last 3 months)	0 (0–2)	0 (0–2)	0.99 (0.87–1.14)
ISSF	1 (0–2)	1 (0–2)	1.18 (0.96–1.47)
Pras score	4 (3–5)	4 (3–6)	0.97 (0.84–-1.12)

MEFV Mediterranean Fever, *ISSF* International severity score for FMF, *SD* standard deviation

[a]Median with quartiles (25–75%), otherwise indicated by (%) or (SD). Student's *t*, Mann–Whitney *U*, or Kruskal–Wallis tests were used for the comparisons, all p values > 0.05

[b]Univariate logistic regression analysis, all p values > 0.05

of protracted arthritis are still insufficient. Although an association between FMF arthritis and M694V mutations has been previously defined in the literature [39], publications on protracted arthritis fail to elucidate clinical relationships [11, 21]. One of the major advantages of this study is that it reveals the relations between protracted arthritis and FMF characteristics. Patients with protracted arthritis had a higher CRP level, disease severity score, and colchicine resistance rate than those without. Finally, ISSF was the best-associated factor with protracted arthritis among the FMF characteristics in multivariate analysis.

Finally, we have three main novelties in this study: First, our main study population is FMF patients with any of the SpA's. Second, instead of focusing on the SpA features between SpA patients and FMF patients with SpA, it investigates which FMF features differ between FMF patients with and without SpA and which FMF features are associated with the main features of SpA. In this regard, heel enthesitis and protracted arthritis may be considered shared manifestations. On the other hand, this study has some limitations, particularly its retrospective design. The fact that data on dactylitis, arthritis, and extra-heel enthesitis were collected from anamnesis may somewhat reduce its reliability (patients may not remember childhood symptoms). Although none of our patients had extra-heel enthesitis in the classification entry criteria, we could not give the prevalence of extra-heel enthesitis. Therefore, prospective studies are needed to confirm the results. Another limitation is the small number of *HLA-B27* tests performed, which prevented commenting on this genetic relationship. Future studies involving larger sample sizes and genetic analysis are needed to answer the question "Concomitance of FMF and SpA or Manifestation of SpA-like characteristics in FMF?" Despite this, our study included one of the largest sample sizes and investigated all the manifestations of SpA and their association with FMF in a large cohort of adult patients with FMF.

In conclusion, this study presented the phenotypic features of SpA observed in patients with adult FMF. Our results show that the frequency of common manifestations of SpA and the frequency of patients who meet the classification criteria for axSpA and pSpA are not low. This emphasizes that in clinical practice related to these concomitant or associated diseases, the presence of one of the diseases must lead to an inquiry of the other. SpA and "shared manifestations" may have an impact on FMF,

Table 5 Relations between protracted arthritis and familial Mediterranean fever characteristics

	Protracted arthritis[a]		Univariate analysis[b]	Multivariate analysis[c]
	Present	Not detected	OR (95% Cl)	OR (95% Cl)
	(*n*: 65)	(*n*: 250)		
Age, years	40.92 (12.76)	37.39 (12.19)	1.02(0.99–1.06)	–
Sex, female	5 (18.55%)	67 (26.8%)	0.62 (0.22–1.70)	–
FMF diagnosis duration, years	11 (4–21)	9 (4–19)	1.02 (0.98–1.05)	–
MEFV Exon 10 mutation, *n*	9 (33.3%)	130 (52%)	0.46 (0.20–1.07)	–
M694V	7 (25.9%)	103 (41.2%)	0.50 (0.20–1.22)	–
694V homozygous	3 (11.1%)	29 (11.6%)	0.95 (0.27–3.36)	–
V726A	2 (7.4%)	25 (10%)	0.72 (0.16–3.22)	–
M680I	1 (3.7%)	25 (10%)	0.35 (0.04–2.66)	–
MEFV Exon 2 mutation, n	12 (44.4%)	93 (37.2%)	1.35 (0.61–3.01)	–
R202Q	8 (29.6%)	62 (24.8%)	1.28 (0.53–3.06)	–
E148Q	6 (22.2%)	28 (11.2%)	2.26 (0.84–6.09)	–
CRP, mg/L (intervals)	4.3 (3-10.35)**	3.13 (0–6)	1.04 (1.01–1.07)*	1.02 (0.97–1.06)
ESR, mm/h (intervals)	24 (10–38.5)	18 (8–28)	1.03 (1.01–1.06)*	–
Amyloidosis, *n*	4 (14.8%)	4 (1.6%)	10.70 (2.51–45.61)**	3.25 (0.45–23.33)
Colchicine dose, mg	1.5 (1.25–2)	1.5 (1–2)	1.21 (0.60–2.44)	–
Colchicine resistance, *n*	15 (57.7%)**	40 (19%)	5.79 (2.47–13.57)**	2.26 (0.67–7.60)
Attack count (last 3 months)	1 (0–2)	0 (0–2)	1.10 (0.94–1.29)	–
ISSF	2 (0.5–4.5)**	1 (0–2)	1.81 (1.38–2.38)**	1.74 (1.10–2.77)*
Pras score	5 (3.75–8)**	4 (3–5)	1.33 (1.11–1.58)**	0.86 (0.65–1.14)

MEFV Mediterranean FeVer, *ISSF* international severity score for FMF, *SD* standard deviation

[a]Median with quartiles (25–75%), otherwise indicated by (%) or (SD). Student's t, Mann–Whitney U, or Kruskal–Wallis tests were used for the comparisons

[b]Univariate logistic regression analysis

[c]Multivariate logistic regression analysis, model $p < 0.001$, R2: 0.228. (parameters that were found to be significant in univariate analysis were included)

*$p < 0.05$, **$p < 0.01$

whereas it can be argued that these manifestations and the presence of SpA were not found to be associated with MEFV mutations. Additionally, older age is the main predictor of enthesitis, and disease severity is linked with protracted arthritis.

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Data availability The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability The code used to analyze the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Authors declare no conflict of interest, financial support or relationships.

Ethics approval This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The xxx University Ethics Committee approved this study. The approval date and number were 04.12.2020 and 09.2020.1255, respectively.

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References

1. Ben-Chetrit E, Levy M (1998) Familial Mediterranean fever. Lancet 351:659–664. https://doi.org/10.1016/S0140-6736(97)09408-7
2. Grateau G, Duruöz MT (2010) Autoinflammatory conditions: when to suspect? How to treat? Best Pract Res Clin Rheumatol 24(3):401–411. https://doi.org/10.1016/j.berh.2009.12.009
3. Atas N, Armagan B, Bodakci E et al (2020) Familial Mediterranean fever is associated with a wide spectrum of inflammatory disorders: results from a large cohort study. Rheumatol Int 40:41–48. https://doi.org/10.1007/s00296-019-04412-7
4. Yildiz M, Adrovic A, Tasdemir E et al (2020) Evaluation of co-existing diseases in children with familial Mediterranean fever. Rheumatol Int 40:57–64. https://doi.org/10.1007/s00296-019-04391-9
5. Langevitz P, Livneh A, Zemer D et al (1997) Seronegative spondyloarthropathy in familial Mediterranean fever. Semin Arthritis Rheum 27:67–72. https://doi.org/10.1016/S0049-0172(97)80007-8
6. Tufan A, Mercan R, Tezcan ME et al (2013) Enthesopathy in patients with familial Mediterranean fever: increased prevalence in M694 v variant. Rheumatol Int 33:1933–1937. https://doi.org/10.1007/s00296-013-2669-4
7. Sen N, Yilmaz M, Mercan R et al (2021) Enthesitis may be one of the signs of severe disease in familial Mediterranean fever. Clin Rheumatol 40:1479–1485. https://doi.org/10.1007/s10067-020-05392-x
8. Kaşifoğlu T, Çalişir C, Cansu DÜ, Korkmaz C (2009) The frequency of sacroiliitis in familial Mediterranean fever and the role of *HLA-B27* and MEFV mutations in the development of sacroiliitis. Clin Rheumatol 28:41–46. https://doi.org/10.1007/s10067-008-0980-3
9. Akar S, Soysal O, Balci A et al (2013) High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection. Arthritis Res Ther 15:R21. https://doi.org/10.1186/ar4154
10. Borman P, Gökoğlu F, Taşbaş O et al (2009) Familial Mediterranean fever-related spondyloarthropathy. Singapore Med J 50:e116–e119. https://doi.org/10.4328/jcam.3083
11. Sneh E, Pras M, Michaeli D et al (1977) Protracted arthritis in familial Mediterranean fever. Rheumatol 16:102–106. https://doi.org/10.1093/rheumatology/16.2.102
12. Yildiz M, Tune SE, Sahin M et al (2006) Evaluation of joints using Tc 99m-MDP bone scintigraphy in patients with familial Mediterranean fever: should bone scans be used for diagnosis and follow-up? Rheumatol Int 26:220–223. https://doi.org/10.1007/s00296-004-0555-9
13. Yazici A, Ozdemir Isik O, Temiz Karadag D, Cefle A (2021) Are there any clinical differences between ankylosing spondylitis patients and familial Mediterranean fever patients with ankylosing spondylitis? Int J Clin Pract 75:e13645. https://doi.org/10.1111/ijcp.13645
14. Akkoc N, Gul A (2011) Familial mediterranean fever and seronegative arthritis. Curr Rheumatol Rep 13:388–394. https://doi.org/10.1007/s11926-011-0191-9
15. Merashli M, Noureldine MHA, Tfayli Y et al (2018) Ankylosing spondylitis among familial Mediterranean fever patients. Endocrine, Metab Immune Disord - Drug Targets 18:148–154. https://doi.org/10.2174/1871530317666171003155517
16. Eshed I, Rosman Y, Livneh A et al (2014) Exertional leg pain in familial mediterranean fever: a manifestation of an underlying enthesopathy and a marker of more severe disease. Arthritis Rheumatol 66:3221–3226. https://doi.org/10.1002/art.38797
17. Rudwaleit M, Van Der Heijde D, Landewé R et al (2009) The development of assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 68:777–783. https://doi.org/10.1136/ard.2009.108233
18. Rudwaleit M, Van Der Heijde D, Landewé R et al (2011) The Assessment of Spondyloarthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 70:25–31. https://doi.org/10.1136/ard.2010.133645
19. Yılmaz Ö, Kısacık B, Ozkan F et al (2013) Does enthesopathy relate to M694V gene mutation in patients with Familial Mediterranean fever? Clin Rheumatol 32:1593–1598. https://doi.org/10.1007/s10067-013-2316-1
20. Majeed HA, Rawashdeh M (1997) The clinical patterns of arthritis in children with familial Mediterranean fever. QJM - Mon J Assoc Physicians 90:37–43. https://doi.org/10.1093/qjmed/90.1.37
21. Migita K, Hisanaga S, Izumi Y et al (2017) Protracted arthritis in a Japanese patient with familial Mediterranean fever. Mod Rheumatol 27:905–909. https://doi.org/10.3109/14397595.2015.1031722
22. Bodur H, Yurdakul FG, Çay HF et al (2020) Familial Mediterranean fever: assessment of clinical manifestations, pregnancy, genetic mutational analyses, and disease severity in a national cohort. Rheumatol Int 40:29–40. https://doi.org/10.1007/s00296-019-04443-0
23. Ben-Zvi I, Livneh A (2011) Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat Rev Rheumatol 7:105–112. https://doi.org/10.1038/nrrheum.2010.181
24. Duruoz MT, Unal C, Bingul DK, Ulutatar F (2018) Fatigue in familial Mediterranean fever and its relations with other clinical parameters. Rheumatol Int 38:75–81. https://doi.org/10.1007/s00296-017-3882-3
25. Livneh A, Langevitz P, Zemer D et al (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40:1879–1885. https://doi.org/10.1002/art.1780401023
26. Demirkaya E, Acikel C, Hashkes P et al (2016) Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis 75:1051–1056. https://doi.org/10.1136/annrheumdis-2015-208671
27. Pras E, Livneh A, Balow JE et al (1998) Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet 75:216–219. https://doi.org/10.1002/(SICI)1096-8628(19980113)75:2%3c216::AID-AJMG20%3e3.0.CO;2-R
28. Woolf AD (2014) History and physical examination. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology, 6. Elsevier Health Sciences, Philadelphia, pp 209–224
29. Sarı İ, Birlik M, Kasifoğlu T (2014) Familial Mediterranean fever: an updated review. Eur J Rheumatol 1:21–33. https://doi.org/10.5152/eurjrheum.2014.006
30. Sieper J, Van Der Heijde D, Landewé R et al (2009) New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the assessment of spondyloarthritis international society (ASAS). Ann Rheum Dis 68:784–788. https://doi.org/10.1136/ard.2008.101501
31. Maksymowych WP, Lambert RGW, Østergaard M et al (2019) MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI

working group. Ann Rheum Dis 78:1550–1558. https://doi.org/10.1136/annrheumdis-2019-215589
32. Taylor W, Gladman D, Helliwell P et al (2006) Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 54:2665–2673. https://doi.org/10.1002/art.21972
33. Sims AM, Timms AE, Bruges-Armas J et al (2008) Prospective meta-analysis of interleukin 1 gene complex polymorphisms confirms associations with ankylosing spondylitis. Ann Rheum Dis 67:1305–1309. https://doi.org/10.1136/ard.2007.081364
34. Ben-Chetrit E, Peleg H, Aamar S, Heyman SN (2009) The spectrum of MEFV clinical presentations–is it familial Mediterranean fever only? Rheumatol 48:1455–1459. https://doi.org/10.1093/rheumatology/kep296
35. Reveille JD (2011) The genetic basis of spondyloarthritis. Ann Rheum Dis 70:i44–i50. https://doi.org/10.1136/ard.2010.140574
36. Masters SL, Simon A, Aksentijevich I, Kastner DL (2009) Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 27:621–668. https://doi.org/10.1146/annurev.immunol.25.022106.141627
37. Zhong L, Song H, Wang W et al (2017) MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: a meta-analysis. PLoS ONE 12:e0182967. https://doi.org/10.1371/journal.pone.0182967
38. Li Z, Akar S, Yarkan H et al (2019) Genome-wide association study in Turkish and Iranian populations identify rare familial Mediterranean fever gene (MEFV) polymorphisms associated with ankylosing spondylitis. PLoS Genet 15:e1008038. https://doi.org/10.1371/journal.pgen.1008038
39. Avar-Aydın PO, Ozcakar ZB, Aydın F et al (2022) The expanded spectrum of arthritis in children with familial Mediterranean fever. Clin Rheumatol 41:1535–1541. https://doi.org/10.1007/s10067-022-06082-6
40. Cefle A, Kamali S, Sayarlioglu M et al (2005) A comparison of clinical findings of familial Mediterranean fever patients with and without amyloidosis. Rheumatol Int 25:442–446. https://doi.org/10.1007/s00296-004-0471-z
41. Tunca M, Ozdogan H, Kasapcopur O et al (2005) Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 84:1–11. https://doi.org/10.1097/01.md.0000152370.84628.0c
42. Sayarlioglu M, Cefle A, Inanc M et al (2005) Characteristics of patients with adult-onset familial Mediterranean fever in Turkey: analysis of 401 cases. Int J Clin Pract 59:202–205. https://doi.org/10.1111/j.1742-1241.2004.00294.x
43. Bakkaloglu SA, Aksu T, Goker B et al (2009) Sulphasalazine treatment in protracted familial Mediterranean fever arthritis. Eur J Pediatr 168:1017–1019. https://doi.org/10.1007/s00431-008-0875-y
44. Bilgen SA, Kilic L, Akdogan A et al (2011) Effects of anti-tumor necrosis factor agents for familial Mediterranean fever patients with chronic arthritis and/or sacroiliitis who were resistant to colchicine treatment. J Clin Rheumatol 17:358–362. https://doi.org/10.1097/RHU.0b013e31823682f5
45. Brik R, Shinawi M, Kasinetz L, Gershoni-Baruch R (2001) The musculoskeletal manifestations of familial Mediterranean fever in children genetically diagnosed with the disease. Arthritis Rheum 44(6):1416–1419