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The Mediterranean Fever Gene Mutations and Its Association with HRQoL, Depression and Fatigue in Patients with Familial Mediterranean Fever Associated Spondyloarthropathies

Ailesel Akdeniz Ateşi ile İlişkili Spondiloartropatili Hastalarda Akdeniz Ateşi Gen Mutasyonlarının ve Yaşam Kalitesi, Depresyon ve Yorgunluk ile İlişkisi

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Abstract

Objective: Our aim was to evaluate the health-related quality of life (HRQoL), depression, fatigue, the Mediterranean fever (*MEFV*) gene mutations, and other disease-related variables in patients with Familial Mediterranean fever (FMF) associated spondyloarthropathies (SpA).
Materials and Methods: Consecutively, 45 patients with FMF associated SpA (41 females, 4 males) and 40 healthy controls were included. Metrological measures (finger-floor distance, dorsal Schober's test, occiput-wall distance and chest expansion) were determined. Axial and peripheral joint pain was evaluated by using visual analog scale (VAS), disease activity by Bath Ankylosing Spondylitis Disease Activity index and function by Bath Ankylosing Spondylitis Functional index. Short Form-36 and the multidimensional assessment of fatigue (MAF) scale, Beck depression index (BDI) and MAF scales were used to evaluate HRQoL, depression and fatigue.
Results: Mean ages of the patients was 43.73±8.7 (24-59) years. Both physical and mental HRQoL were found to be significantly worse in FMF associated SpA patients than in controls. Twelve patients (26.6%) had clinical depression with BDI scores ≥17. MAF score was high in patients with FMF associated SpA. The most frequent mutations were M694V and E148Q in patients with FMF associated SpA. No significant effect of MEFV gene mutations was seen on QoL, fatigue, depression, pain and disease-related variables.
Conclusion: FMF associated SpA significantly affects the QoL of its sufferers, as other chronic ilnesses. In this study, both physical and mental HRQoL were found to be significantly worse in FMF associated SpA patients than in controls, irrespective of the MEFV gene mutations. Depression was also seen in high rates in patients with FMF associated SpA. Further studies are needed to determine the effects of *MEFV* gene mutations on disease severity and QoL in FMF patients.
Keywords: Familial Mediterranean fever, healthy related quality of life, *MEFV* gene, spondyloarhtopathy

Öz

Amaç: Ailevi Akdeniz ateşine (AAA) eşlik eden spondililoartropatisi (SpA) olan hastalarda sağlıkla ilişkili yaşam kalitesi (HRQoL), depresyon, yorgunluk, Akdeniz ateşi geni (*MEFV*) mutasyonları ve diğer hastalıklarla ilişkili durumların değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: Kırk beş AAA spondilit hastası (41 kadın, 4 erkek) ve 40 sağlıklı kontrol çalışmaya dahil edildi. Metrolojik ölçümler (el parmak-zemin mesafesi, bel Schöber testi, oksiput-duvar mesafesi ve göğüs ekspansiyonu) değerlendirilerek kaydedildi. Aksiyal ve periferik eklem ağrısı görsel ağrı skalası (GAS) ile, hastalık aktivitesi Bath Ankilozan Spondilit Hastalık Aktivite indeksi (BASDAİ) ile, hastalık fonksiyonu Bath Ankilozan Spondilit Fonksiyonel indeksi (BASFİ) ile değerlendirildi. HRQoL, depresyon ve yorgunluk değerlendirilmesinde Kısa Form-36, Beck depresyon indeksi (BDI) ve multidimensiyonel yorgunluk değerlendirme (MAF) ölçekleri kullanıldı.
Bulgular: Çalışmaya dahil edilen hastaların yaş ortalaması 43,73±8,7 (24-59) yıl idi. Hem fiziksel hem de mental sağlıkla ilişkili yaşam kalitesi sonuçları kontrol grubuna göre anlamlı derecede kötüydü. On iki hastada (%26,6) BDI 17'nin üzerinde olup klinik olarak depresyon saptandı. Yorgunluk skorları yüksek olarak saptandı. AAA'ya eşlik eden SpA hastalarında en sık rastlanan gen mutasyonları M694V ve E148Q idi. MEFV gen mutasyonlarının QoL, yorgunluk, depresyon, ağrı ve diğer hastalıkla ilişkili değişkenler üzerinde önemli bir etkisi görülmedi.

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Sonuç: AAA eşlik eden SpA diğer kronik hastalıklar gibi yaşam kalitesini önemli derecede etkilemektedir. Bu hastalarda MEFV gen mutasyonlarından bağımsız olarak hem fiziksel hem de mental sağlıkla ilişkili yaşam kalitesi belirgin şekilde bozulmuş ve depresyon oranları da belirgin artmıştır. AAA hastalarında MEFV gen mutasyonlarının hastalık şiddeti ve yaşam kalitesi üzerindeki etkileri konusunda daha fazla çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Ailevi Akdeniz ateşi, sağlıkla ilgili yaşam kalitesi, *MEFV* geni, spondiloartropati

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disease characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation with an increased incidence in Eastern Mediterranean countries (1). The most common types of acute attacks include musculoskeletal symptoms and arthritis in patients with FMF (2,3). The most common type of joint involvement is usually self-limiting, monoarticular involvement affecting the knees, ankles or hips; however sacroiliitis, which is the hallmark of spondyloarthropathies (SpA), is also seen in higher frequencies than expected in patients with FMF (4). FMF associated SpA may have inflammatory low back pain, recurrent enthesitis, unilateral or bilateral sacroiliitis and spine involvement with minimal radiological findings (5). The rate of coexistence of FMF and spondylitis in adult patients has been reported as 0.5-12.5% (2).

The *Mediterranean fever* (*MEFV*) gene is localized at the 16p13.3 chromosome, and encodes for pyrin/mare, which belongs to a class of proteins involved in the regulation of apopitosis, cytokine processing, and inflammation, and in patients with FM, more than 330 mutations in this gene have been demonstrated (6,7). The M694V, M680I, V726A, E148Q, and M694I are the most common FMF gene variations in Turkey (8). *M694V* gene is reported to be the leading variation among Turkish and Sephardic Jews and it has been demonstrated that arthritis and sacroiliitis are commonly associated with the presence of M694V (9).

Incidence of FMF gene mutations has also been investigated in several types of other chronic inflammatory diseases such as multiple sclerosis (10), Behçet's disease (11), Chrone's disease (12), rheumatoid arthritis (13), ulcerative colitis (14) and Henoch-Schonlein purpura (15). These studies revealed not only an increased incidence of FMF gene mutations in patients with these autoinflammatory diseases, but also increased severity of the diseases in patients with FMF gene mutations.

Health-related quality of life (HRQoL) measures are used to evaluate the outcomes for many diseases with an increasing trend. It is obvious that researches on HRQoL contribute to the development of new health policies in addition to treatments. Although HRQoL in FMF has been investigated in many studies in the literatüre, no study has been found about FMF associated SpA (16-19).

This study aimed to evaluate the clinical characteristics, HRQoL, depression and fatigue in patients with FMF associated SpA. Besides, the associations between these parameters and MEFV gene variations were also studied.

Materials and Methods

The cross-sectional, prospective study was conducted in FMF associated SpA patients that were recruited from the outpatient clinic of Physical Medicine and Rehabilitation Clinic and Rheumatology Clinic.

Clinical Research Ethics Committee approval was acquired from University of Ankara Yıldırım Beyazıt Faculty of Medicine (decision no: 53, date: 28.04.2021) and it was carried out in accordance with the principles of Declaration of Helsinki. All patients and control participants gave written, informed consent.

Study Participants

The patients were diagnosed according to the Tel Hashomer and ASAS criteria (20,21). Forthy five patients (4 males, 41 females; mean age range 24 to 59 years) that presented with sacroiliitis, and/or inflammatory spinal pain and were diagnosed with FMF. The control groups were comprised of 40 healthy valuntary (4 males, 36 females; mean age range 23 to 60 years) participants. Between may 2021 and august 2021 were consecutively included in the study.

Inclusion criteria as follows: Patients with a diagnosis of FMF had magnetic resonance imaging (MRI) evidence of sacroiliitis. And/or inflammatory spinal pain and non-radiographic axial SpA and concomitant FMF were included in the study.

Exclusion criteria were as follows: Malignancy history, renal involvement, ankylosing spondilit, psoriatic arthritis, enteropathic arthritis, reactive arthritis, pregnancy, hypermobility syndrome, fibromyalgia syndrome or other systemic inflammatory rheumatic diseases.

FMF patients were classified into two groups according to the MEFV gene mutation analyses: (1) patients who had M694V gene mutation and (2) patients who had no M694V gene mutation. Finally, FMF patients were divided into four subgroups based on four prevailing MEFV mutations: (1) patients with homozygous M694V gene mutation, (2) patients with heterozygous M694V gene mutation, (3) patients with MEFV gene different homozygous mutations, and (4) patients with MEFV gene different heterozygous mutations.

G* Power version 3.1.2 (Heinrich Heine-Universität Düsseldorf, Düsseldorf, Germany) was used to calculate the sample size. Before starting work, effect size was calculated (18) and power analysis was done; alpha (H0): 0.05 power (1-ß) (H1)>0.90 effect size: 0.69. It was calculated that there should be 39 participants for each group and 78 participants in total. Power analysis revealed that 39 patients needed for FMF associated SpA group, and 39 participants needed for control group in 90% statistical power.

Assessments

Detailed patient examinations were performed by the same physican. Demographical, clinical and laboratory findings in patients with FMF spondylitis were recorded. Duration of morning stiffness (minute), presence of nocturnal pain, history of peripheral arthritis, symptom durations, and metrological measures (finger-floor distance, lumbar schober, occiput-wall distance, and chest expansion) were assessed.

Standard pelvic radiographs and MRI were obtained in all patients to assess the sacroiliac joints.

Laboratory tests; a complete blood cell count, blood chemistry panel, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen levels, and *MEFV* gene results were determined in available records. Medications and smoking history were also recorded.

DNA analyses were performed in Genetic Diseases Evaluation Center, Ankara City Hospital, Turkey. DNA was isolated from peripheral blood lymphocytes by standard procedures and amplified with sequence-specific primers using the polymerase chain reaction technique. The amplicons are then sequenced at capillary electrophoresis Applied Biosystems® 3500xL Genetic Analyzer (Thermo Fisher Scientific®, UK) and were analysed at Applied Biosystems™ GeneMapper® Software 5 for MEFV gene mutations, the disease activity and functional status of patients with FMF spondylitis were evaluated by Bath Ankylosing Spondylitis Disease Activity index (BASDAI) and the Bath Ankylosing Spondylitis Functional index (BASFI) (22,23).

Peripheral and axial joint pain were assessed by visual analog scale (VAS). Accordingly, the value 0 indicates that there is no pain, and the value 10 indicates the most severe pain (0-10 cm). The patients were asked to mark their subjective pain levels on a 10-cm scale (24). HRQoL was assessed by using Short Form-36 (SF-36), which is a widely applied instrument for measuring health status and consists of eight dimensions: physical functioning, social functioning, role physical, role emotional, mental health, vitality, bodily pain and general health perceptions. Scores range from 0 (worst) to 100 (best) with higher scores indicating better health status (25). Physical score of SF-36 (PCS) and mental score of SF-36 (MCS) also determined in patients and controls.

Beck depression index (BDI) was used to evaluation of depression. Clinical depression was diagnosed in patients with BDI scores of 17 or over (26).

The Multidimensional Assessment of Fatigue (MAF) scale was used to assess fatigue. MAF is a self-administered questionnaire developed to measure five dimensions of self-reported fatigue: degree (MAF1), severity (MAF2), distress (MAF3), impact on activities of daily living (MAF4) and timing (MAF5). It contains 16 items. The MAF score ranged from 0 (no fatigue) to 50 (severe fatigue) (27).

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 (IBM, Armonk, New York, USA) statistical software. Descriptive data were expressed as mean ± standard deviation, minimum, maximum, median. Shapiro-Wilks test was used to assess whether the parameters were normally distributed or not. The normality of data distribution was checked by Kolmogrov-Smirnov test. The Mann-Whitney U test was used to test differences among groups. Comparative analyses of demographic characteristics were computed using either the Mann-Whitney U test or the chi-squared test were used to compare the categorical data between the groups. Spearman and Pearson correlation tests were used to determine the relationships between the independent variables and the dependent variables. The Kruskal-Wallis H test (sometimes also called the "One-Way ANOVA on ranks") is a rank-based nonparametric test. We used it to determine if there were statistically significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable. The level of significance was set at $p<0.05$.

Results

Mean ages of the patients was 43.73±8.7 (24-59) years. There were no statistically significant differences in terms of gender, age and body mass index (BMI) between the patients with FMF associated SpA and controls ($p>0.05$). All of our patient groups participating in the study had sacroiliitis and spinal pain. Table 1 shows the demographical, clinical and laboratory findings in patients with FMF associated SpA. Mean BDI score was found as 13.97±8.2 (0-39). Twelve (26.6%) patients with BDI scores ≥17 had clinical depression. It was also seen that HLA-B27 test was obtained in 27 of 45 patients and found to be positive in 1 patient. Table 2 summarizes the MEFV gene mutations in patients with FMF associated SpA.

A comparison of patients with FMF associated SpA and healthy controls showed that patients with FMF associated SpA had lower scores in all subgroups of SF-36 than controls. There were statistically significant differences in all subgroups SF-36, PCS and MCS subgroup scores. The results were summarized in Table 3.

Table 4 shows the correlation between SF-36 subgroups, disability scores, clinical variables, and demographical characteristics of patients with FMF associated SpA. $P<0.05$ and $r2<-0.3$ or $p<0.05$ and $r2>0.3$ values were representing the statistically significant correlations. Axial and peripheral VAS, BASDAI, BASFI, BDI, BMI, fatigue and morning stiffness scores were found to be significantly correlated with PCS subgroups scores of SF-36. Age, fibrinogen level, ESR and CRP values was not correlated with PCS subgroups scores of SF-36 ($p>0.05$). Anti-depressant medications and FMF medications were not correlated with PCS. Age, MAF total and BDI scores were found to be correlated with MCS subgroups scores of SF-36 (*$P<0.05$ and $r<-0.3$ or $p<0.05$ and $r>0.3$). MAF subgroups were not correlated with MCS and PCS subgroups scores of SF-36 (Table 4).

Table 5 shows the comparison of HRQoL, fatigue, depression and disease-related variables in MEFV gene subgroups, however no statistically significant difference was found.

Table 1. Demographical, clinical and laboratory findings in FMF associated SpA

Variables	Mean ± SD, (min-max)
Symptom duration (years)	7±7.3, (1-15)
Morning stiffness (minutes)	39.22±40.7, (0-150)
Metrological measures	
Finger-floor distance	14.91±14.3, (0-50)
Dorsal Schober's	4.93±1.3, (2-10)
Occiput-wall distance	6.13±1.7, (0-10)
Chest expansion	4.82±1.2, (2-9)
MAF subgroups	
MAF-1 (degree)	6.68±2.1, (1-10)
MAF-2 (severity)	6.73±2.2, (1-10)
MAF-3 (distress)	6.55±2.1, (1-10)
MAF-4 (ADLs)	4.70±1.7, (1.9-9.6)
MAF-5 (timing)	6.65±2.1, (0-10)
MAF total	30.93±9.1, (2.5-46.8)
BASDAI	5.40±1.8, (0.7-8.9)
BASFI	3.79±1.9, (0-8)
Axial VAS	6.24±2.1, (1-10)
Peripheral VAS	5.14±2.6, (0-10)
Fibrinogen	22.45±84.7, (204-614)
ESR (mm/h)	16.06±14.1, (1-53)
C-reactive protein (mg/dL)	0.78±1.3, (0.1-8)
Beck depression inventory	13.97±8.2, (0-39)
Depression % (n)	26.6 (12)
Anti-depressant use % (n)	11.1 (5)
Medications	
Colchicine or/and NSAID % (n)	68.9 (31)
Colchicine + DMARD % (n)	28.9 (13)
Colchicine + biological therapies % (n)	2.2 (1)
Smoking % (n)	33.3 (15)
Joint pain % (n)	77.8 (35)

FMF: Familial Mediterranean fever, SpA: Spondyloarthropathies, ESR: Erythrocyte sedimentation rate, NSAID: Non-steroidal anti-inflammatory drugs, DMARD: Disease modifying antirheumatic drugs, SD: Standard deviation, MAF: Multidimensional Assessment of Fatigue, VAS: Visual analog scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, ADL: Activities of daily living

Discussion

The HRQoL is commonly impaired in many chronic rheumatologic diseases. Likewise FMF affects the QoL of its sufferers. This study investigated the HRQoL, fatigue, depression and disease-related variables in patients with FMF associated SpA. It was seen that QoL of the patients with FMF associated SpA was significantly worse than the controls. We also evaluated the effect of MEFV gene mutations on these parameters, however no significant relation was found.

Many studies which investigated the HRQoL in patients with FMF. However there is no study regarding HRQoL in FMF associated SpA. Buskila et al. (19) has been the first author to demonstrated that total HRQoL score of FMF patients was significantly lower than that in the control group. Similar to this, Deger et al. (28) and Duruoz et al. (16) investigated HRQoL using SF-36 and found that physical HRQoL was significantly worse in FMF patients than in controls. Sahin et al. (18) demonstrated that FMF reduces quality of life both in physical and mental dimensions. In this study, both physical and mental HRQoLs were found to be significantly worse in FMF associated SpA patients than in controls.

Anxiety and depression were stataed to be more frequent in FMF patients than healthy subjects, with an incidence of 33% (28,29), Likewise depression frequency was found to be 26.6% and fatigue score was high in our patients with FMF associated SpA, but we could not compare them with normal subjects since BDI and MAF were not administered to control group since primary aim of the study was the comparison of QoL.

SpA considerably affects the HRQoL of the sufferers because of a variety of symptoms, such as pain, fatigue, limited spinal mobility and chest expansion. We have previously reported that HRQoL, fatigue, pain, spinal mobility and chest expansion were significantly affected in patients with ankylosing spondylitis (29). We have also compared the clinical characteristics, HRQoL and fatigue in patients with FMF spondylitis with our previous study's patient group (patients with ankylosing spondylitis). Occiput-wall distance was significantly higher, chest expansion was significantly lower and BASFI score was significantly higher in AS patients than in patients with FMF associated SpA. Both conditions were negatively affecting the QoL (both physical and psychosocial domains) and fatigue scores of the sufferers, however HRQoL, pain scores and fatigue did not differ significantly in-between. Although spinal mobility, chest

Table 2. MEFV gene mutations in patients with FMF associated SpA

n=28	
M694V/Homozygous (n=5) M694V/Heterozygous comp (n=4) M694V/Heterozygous wild (n=3) E148Q/Homozygous (n=3) E148Q/Heterozygous comp (n=4) E148Q/Heterozygous wild (n=3)	V726A/Homozygous (n=1) V726A/Heterozygous comp (n=1) M680I/Homozygous (n=1) M680I/Heterozygous comp (n=1) R761H/Heterozygous wild (n=2)

FMF: Familial Mediterranean fever, SpA: Spondyloarthropathies, MEFV: Mediterranean fever

Table 3. Comparison of demographical dates, clinical variables, and SF-36 subgroups between FMF associated SpA and controls

Variables	FMF associated SpA n=41	Healthy group, n=40	p-values
Age (years), mean ± SD	43.73±8.7	46.26±10.4	0.111
Body mass index, mean ± SD	28.27±6.5	28.90±4.3	0.229
Gender; female/male n (%)	41/4 (90.1)	40 (100)	0.116
Physical function, median (min-max)	55 (0-95)	75 (50-100)	<0.001*
Role physical, median (min-max)	25 (0-100)	75 (0-100)	<0.001*
Bodily pain, median (min-max)	32 (0-100)	70 (45-100)	<0.001*
General health, median (min-max)	35 (0-72)	55 (25-100)	<0.001*
Vitality, median (min-max)	35 (0-85)	52 (20-100)	<0.001*
Social function, median (min-max)	62.5 (12.5-100)	75 (50-100)	<0.001*
Role emotional, median (min-max)	0 (0-100)	93 (0-100)	<0.001*
Mental health, median (min-max)	52 (12-88)	56 (36-100)	<0.001*
Physical score of SF-36, mean ± SD	36.11±8	60.9±12.7	<0.001*
Mental score of SF-36, mean ± SD	37.39±8.3	62.56±11.9	0.007*

*p<0.05, FMF: Familial Mediterranean fever, SpA: Spondyloarthropathies, SF-36: Short Form-36, min-max: Minimum-maximum, SD: Standard deviation

Table 4. Correlation between SF-36 subgroups, disability scores, clinical variables, and demographical characteristics of patients with FMF associated SpA

Variables		PCS	MCS
Peripheral joint VAS	r-value p-value	-0.320 0.032*	-0.192 0.207
Axial VAS	r-value p-value	-0.482 0.001*	-0.130 0.399
BASDAI	r-value p-value	-0.50 <0.001*	-0.165 0.280
BASFI	r-value p-value	-0.556 <0.001*	-0.221 0.144
MAF total	r-value p-value	-0.312 0.037*	-0.402 0.006
Beck Depression inventory	r-value p-value	-0.616 0.000*	- 0.493 0.001*
Morning stiffness	r-value p-value	-0.495 0.001*	-0.032 0.837
Age	r-value p-value	-0.235 0.120	-0.368 0.013*
Body mass index	r-value p-value	-0.365 0.014*	-0.171 0.261
MEFV gene mutations	r-value p-value	-0.124 0.419	0.037 0.808

*p<0.05 and r<-0.3 or p<0.05 and r>0.3, SF-36: Short Form-36, PCS: Physical score of SF-36, MCS: Mental score of SF-36, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, MAF: Multidimensional Assessment of Fatigue, VAS: Visual analog scale, SpA: Spondyloarthropathies

expansion and functional status in patients with FMF associated SpA were better than in AS patients, HRQoL and fatigue were found to be equally affected.

HLA-B27 test was ordered in 27 of the FMF associated SpA patients and found to be positive only in one of them. Although the sample is small, it can be assumed that HLA B27 doesn't seem to be a primary causing factor in development of sacroiliitis/spondylitis in FMF patients.

It was seen that PCS subgroups scores of SF-36 significantly correlated with axial and peripheral joint pain, depression, fatigue, morning stiffness, BMI, BASDAI and BASFI; whereas MCS were found to be significantly correlated with age, depression and fatigue in this study.

Table 5. Comparison of HRQoL, MAF and demographical variables in MEFV subgroups				
Variables median (min-max)	**MEFV 694 group (n=12)**	**Other MEFV group (n=16)**	**MEFV negative (n=17)**	**p-values**
Morning stiffness (minute)	25 (0-120)	30 (10-200)	30 (0-120)	0.672
Metrological measures				
Finger-floor distance	12.5 (0-50)	14 (0-42)	10 (0-50)	0.990
Dorsal Schober's	5 (3.5-10)	5 (2-6)	5 (2.5-7)	0.530
Occiput-wall distance	6 (4-9)	7 (1-9)	6 (4-10)	0.864
Chest expansion	5 (3.5-9)	5 (2-6)	5 (3-6)	0.849
SF subgroups				
PCS	35.4 (18.1-47.9)	36.5 (19.7-58.5)	32.4 (25.3-52.9)	0.312
MCS	39.2 (24.8-47)	37.8 (27-51.6)	34.2 (17.3- 54.4)	0.750
MAF subgroups				
MAF-1 (degree)	7.5 (4-9)	7.5 (3-10)	7 (1-9)	0.312
MAF-2 (severity)	7 (4-10)	7 (3-10)	7 (1-9)	0.848
MAF-3 (distress)	6.5 (3-10)	7 (3-10)	7 (1-8)	0.575
MAF-4 (ADLs)	4.7 (1.8-8.9)	4.8 (2.7-9.3)	4 (1.9-7.7)	0.547
MAF-5 (timing)	6.2 (2.5-8.7)	7.5 (5-10)	6.2 (2.1-10)	0.161
MAF total	33.7 (20-42.9)	33.5 (13.6-46.8)	29.8 (2.5-38.9)	0.342
BASDAI	5.27 (2.3-8.9)	5.85 (2.1-8.8)	5.8 (0.7-7.8)	0.751
BASFI	3.6 (0-6.7)	3.9 (0.9-8)	4 (0.6- 7.4)	0.651
Axial VAS	6 (4-9)	7 (2-10)	6.5 (1-9.5)	0.844
Peripheral VAS	6 (0-9)	5 (1-10)	5 (0-10)	0.863

BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, MAF: Multidimensional Assessment of Fatigue, VAS: Visual analog scale, SF-36: Short Form-36, PCS: Physical score of SF-36, MCS: Mental score of SF-36, MEFV: Mediterranean fever, min-max: Minimum-maximum, HRQoL: Health-related quality of life, ADL: Activities of daily living

The M694V, E148Q M680I, V726A, and M694I are the most common genetic variations related with FMF in Turkey (8,9,30). Increases in the severity of the chronic inflammatory diseases in patients with FMF gene mutations had been reported in several other studies (10-15). We have also investigated the association of MEFV gene variations with HRQoL, depression, fatigue, pain and other disease-related variables in patients with FMF associated SpA. However, no significant effect of MEFV gene mutations on above mentioned parameters was found; FMF associated SpA negatively affected the QoL of the patients irrespective of MEFV gene mutations. Similar to this, it was shown in the previous studies that there were no significant differences between MEFV gene carriers and non carriers regarding the clinical and demographic characteristics (31,32).

There are only a few studies in literature which systematically investigated the association between FMF and SpA. In other studies from Turkey, the frequency of sacroiliitis in FMF patients was reported to be 7-10.5% (9). Especially the *M694V* gene, the leading variation among Turkish and Sephardic Jews, has been reported to be associated with arthritis and sacroiliitis (9). Similarly, the most frequent mutations were M694V and E148Q in our patients with FMF associated SpA.

The study is single-centered and the control group consists of healthy participants. If the FMF patient group was considered as the control group in the study, our results could have been more valuable Another limitation is that; our assessment of disease activity may have been adversely affected by the variety of medical treatments.

Conclusion

FMF spondylitis significantly affects the QoL of the sufferers, as much as other chronic ilnesses do. In this study, both physical and mental HRQoL were found to be significantly worse in FMF associated SpA patients than in controls, irrespective of the MEFV gene mutations. Depression was also seen in high rates in patients with FMF associated SpA. Further studies are needed to determine the effects of MEFV gene mutations on disease severity and QoL in FMF patients.

Ethics

Ethics Committee Approval: Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee approval was obtained for the study with the number of 26379996/54 (decision no: 53, date: 28.04.2021).

Informed Consent: All subjects who met the study criteria were informed of the nature of the study and a written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G.A., B.M.A., F.F., Ş.E., G.G.C., Concept: Ş.E., F.F., B.M.A., Design: B.M.A., F.F., Data Collection or Processing: G.G.C., Ş.E., F.F., Analysis or Interpretation: G.G.C., B.M.A., Literature Search: S.G.A., Writing: S.G.A.

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