Relationship Between Familial Mediterranean Fever and Other Rheumatic Diseases: Coincidence or Coexistence?

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ABSTRACT

Background Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease affecting mainly the ethnic groups of the Mediterranean basin. It has been reported that it can coexist with various systemic inflammatory diseases. This study aimed to obtain information on rheumatic diseases that accompany FMF and evaluate the relation between FMF and such diseases.

Material and Methods Eighty-four patients diagnosed with FMF and have rheumatic disease comorbidity in the rheumatology clinic between January 2018 - March 2020 were included in this study.

Results The most common accompanying rheumatic disease was spondyloarthritis (SpA) with 36 patients. Vasculitis was the second common disease accompanying FMF with 22, followed by connective tissue disease (CTD) in 18, juvenile idiopathic arthritis in 4, gout in 3, and hidradenitis suppurativa in 1 patients. The most common MEFV mutation observed was M694V. The rate of patients in the SPA group with signs of fever was significantly higher than those in the vasculitis group. The median C-reactive protein value of the patients in the vasculitis group was significantly higher than the CTD group. There was no statistically significant difference between disease groups regarding to other clinical manifestations and laboratory findings. There was no statistically significant association between disease groups and MEFV mutations regarding to genotype and allelic distribution.

Conclusions In this study, the relation between FMF and various rheumatic diseases was determined. Two new conditions, eosinophilic granulomatous polyangiitis and scleroderma were detected. The associations may be just coincidental or an extension of the common underlying pathology. To be aware of this association is important to early diagnosis and appropriate treatment.

Keywords: Familial Mediterranean fever, MEFV mutation, rheumatic diseases.

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DOI: 10.46310/tjim.982632
Introduction

Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent polyserositis and fever attack.\(^1\) FMF prevalence varies between 1:200-1,000 depending on geographic regions, and it mostly occurs in middle eastern and Mediterranean regions.\(^2\) Several clinical diagnostic criteria sets have been proposed to diagnose FMF (Tel-Hashomer, Livneh, pediatric criteria, and new Eurofever/PRINTO classification criteria). The oldest and the most widely used criteria set is the Tel Hashomer.\(^3,4\) It is considered an autosome recessive disease, but about one-fourth of patients are heterozygote, suggesting genetic heterogeneity. FMF is caused by mutations in the MEFV gene located on chromosome 16.

MEFV codes a protein termed pyrin. In the presence of MEFV gene mutations, as a result of uncontrolled pyrin activation, caspase 1 is activated, and IL-1\(\beta\) expression is enhanced, and hence an exaggerated inflammatory response arises.\(^5\) Although the phenotype-genotype correlation of FMF remains to be elucidated, certain variants of the MEFV gene play an important part in pathogenesis. At present, all reported MEFV variants and the associated phenotypes are recorded in the INFEVERS database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), and there are around 385 known sequence variants of MEFV.\(^5\) The most common mutations are V726A, M680I, M694V, M694I in exon 10, and E148Q in exon 2. M694V prevalence is between 20% and 65%, and it is the most common and pathogenic variant of all FMF mutations.\(^6\) The pathogenic effect of E148Q is uncertain and its presence in over 1% of the healthy population suggests that it may be a benign polymorphism. The most critical member of the inflammasome family plays an essential role in the etiopathogenesis of FMF is the nucleotide-binding domain-like receptor (NLRP3). When activated, NLRP3 leads to cleavage and activation of IL-1\(\beta\) in response to many inflammatory stimuli. It is also responsible for many other inflammatory conditions and diseases.\(^7,8\) Whether increased inflammation in FMF patients sets the stage for some inflammatory and non-inflammatory conditions is still debatable. According to previous data, it has been reported that in %12-17, 2 of FMF patients, there may be coexisting systemic inflammatory conditions. The analysis of probable comorbidities is essential for understanding their effect on clinical presentation and if they share a common etiological pathway. This study aimed to obtain information on rheumatic diseases accompanying FMF and evaluate the relationship between these diseases and FMF.

Material and Methods

Study Population and Design

Among a group of 400 FMF patients followed up at one center, 84 patients were determined to have rheumatic disease comorbidity by reviewing their medical records. Eighty-four patients over 18 diagnosed with FMF and have rheumatic disease comorbidity in the rheumatology clinic between January 2018 - March 2020 were included in this study. The accompanying rheumatological diseases were spondyloarthritis (SpA) in 36 patients (ankylosing spondylitis [AS] 32, psoriatic arthritis [PSA] 3, and inflammatory bowel disease-associated SpA 1 patients), vasculitis in 23 patients (its distribution was as follows: Behçet’s disease [BD] 12, leukocytoclastic vasculitis [LCV] 2, Henoch-Schoenlein purpura [HSP] 5, Takayasu arteritis [TA] 1, eosinophilic granulomatous polyangiitis [EGPA] 1, polyaerteritis nodosa [PAN] 1 patient), connective tissue disease (CTD) present in 13 (Sjogren syndrome [SS] 6, systemic lupus erythematosus [SLE] 1, scleroderma [SSc] 3, mixed connective tissue disease [MCTD] 3, rheumatoid arthritis [RA] 5 patients, juvenile idiopathic arthritis [JIA] in 4, gout in 3, hidradenitis suppurativa [HS] in 1 patients). Sex, age, duration of disease, comorbidities, family history, clinical symptoms (fever, peritonitis, pleuritis, pericarditis, arthritis, myalgia, erysipelas-like rash), genotype data (if present), laboratory results, radiological findings, and treatment information were recorded. Data on accompanying rheumatic diseases were obtained from hospital records. All current and past rheumatic comorbidities were taken into consideration and supported by health system records. Patients with a diagnosis of FMF but without rheumatic disease were excluded. All the data were compared among a total of 5 groups (vasculitis, SpA, CTD, gout, and JIA)
This study was conducted by following the principles of the Helsinki Declaration, and written informed consent was obtained from all participants. Approval for the study was obtained from the ethics committee with the decision dated 22.04.2020 and numbered 2020/182.

**Classification Criteria**

FMF diagnosis was made according to The Tel-Hashomer criteria. It is evaluated as major and minor criteria. Major criteria are fever with peritonitis, pleuritis, and synovitis attacks; AA-type amyloidosis, response to colchicine treatment; Minor criteria are recurrent episodes of fever, erysipelas-like erythema, and history of FMF in a first-degree relative. For the definitive diagnosis, two major or one major and two minor findings should accompany.

We included patients, as defined by accepted diagnostic criteria at the time studies were identified. Patients diagnosed with SSc according to 2013 classification criteria, SS according to 2016 ACR/EULAR SS classification criteria, SLE according to SLICC 2012 classification criteria, RA according to 2010 ACR/EULAR RA classification criteria, BD according to the International Working Group criteria, SpA according to the 2009 ASAS classification criteria were included. Other patients were also defined according to diagnostic criteria accepted at the time of the study. Organ involvement was evaluated according to clinical symptoms and the results of various diagnostic tests.

**Laboratory Measurements**

Blood was analyzed to obtain CBC results, including the leukocyte, hemoglobin, platelet, lymphocyte, neutrophil, and monocyte counts. Urine protein, erythrocyte sedimentation rate (ESR; 0–20 mm/hour), and C-reactive protein (CRP; 0-8 mg/L) of the patient were recorded.

**Assessment of Genetic Analyses**

Results of all MEFV gene whole gene sequence analyses were retrieved from the database of our hospital. HLA-B27 and HLA-B51 genetic analysis data were obtained retrospectively from the hospital database system.

**Statistical Analysis**

All statistical analysis was performed using R version 3.6.0 (the R Foundation of Statistical Computing, Vienna, Austria; https://www.r-project.org). To assess the normality of the data, Shapiro-Wilk’s normality test and Q-Q plots were used, and also Levene’s test was used to check the homogeneity of the variances. Numerical variables were presented as mean±standard deviation (minimum-maximum) or median with interquartile range. Categorical variables were described as count (n) and percentage (%). One-way ANOVA (analysis of variance) followed by Tukey HSD post-hoc test and Kruskal-Wallis test followed by Dunn post-hoc test with Bonferroni correction was run to determine whether there was a statistically significant difference between numerical variables and groups (SPA, vasculitis, and CTD). Moreover, the Pearson chi-square test followed by two proportions Z-test with Bonferroni correction and Fisher-Freeman-Halton exact test were conducted to examine whether there was a statistically significant association between categorical variables and groups. The allelic distribution of the mutations according to groups were compared using three sample proportion tests with and without continuity correction. The significance level was set at 5%.

**Results**

Eighty-four patients with comorbid FMF and rheumatic disease were included in this study. 32 (38.1%) males and 52 (61.9%) female participants with a mean age of 38.36±13.68 (17-78). There were 18 patients over the age of 40. Musculoskeletal involvement was predominant in these patients, and they had a low penetrating mutation, except for two homozygous patients for M694V mutation. The demographical characteristics, clinical manifestation and laboratory findings of the patients were given in Table 1. The duration of FMF disease is 8±5 (1-24) years. The most common symptoms were decreasing order of frequency recurrent abdominal pain 98.8%, fever 22.6%, arthritis 17.9%, lower back pain 9.5%, pleuritis 7.1%, erysipelas-like erythema 3.6%. A family history of FMF was found in 39 (46.4%) out of 84. Mean proteinuria was found to be
239 mg/day. In three patients, proteinuria at the level of 500 mg or over was observed.

The most common accompanying rheumatological disease was SpA in 36 (43%) patients. AS was detected in 32 (38.9%), PSA in 3 (3.6%), and inflammatory bowel disease-associated SpA in 1 (1.2%) patient. Vasculitis was the second most common comorbid disease group in FMF with a rate of 26.2%. Its distribution was as follows: BD 12, LCV 2, HSP 5, TA 1, EGPA 1, PAN 1 patients. CTD present in 18 (21.4%) (SS 6, SLE 1, SSc 3, MCTD 3, RA in 5 [6%]), JIA in 4 (4.8%), gout in 3 (3.6%), HS in 1 (1.2%) patient (Table 2). 17 patients who had comorbid AS underwent HLA-B27 analysis and it was found to be positive in two patients. FMF patients with radiographically detected sacroiliitis, the rate of M694V mutation was high. Enthesitis is present in 11.9% of FMF patients accompanying SPA. Eleven patients with comorbid BD underwent HLA-B51 analysis, with positive results in 4 patients. One patient had neuro-BD, four vascular involvement, two joint and eye involvement, four isolated mucocutaneous involvement, and no gastrointestinal involvement in BD patients. Thrombosis was present in 30% of patients with BD, and of these, all but one had M694V mutation. Coexistence with SS was detected in six patients.
In five of these patients, there was a MEFV mutation in exon 10 without any life-threatening organ involvement. No serositis was detected in MCTD patients with M694V mutation. One SSc patient had limited, and two patients had widespread skin involvement. There was no interstitial lung disease and pulmonary hypertension. Two patients had M694V mutations in SSc patients. As a medical treatment, all patients used colchicine. Azathioprine was used in 11 (13.1%), anakinra in 1 (1.2%), anti-TNF in 7 (8.3%), DMARD in 45(53.6%), allopurinol in 2 (2.4%), cyclosporin in 1 (1.2%) patients.

There was a statistically significant difference between disease groups as determined by One-way ANOVA (F=7.741, p=0.001). A Tukey post hoc test revealed that the mean age of the patients in the CTD group was statistically significantly higher than the patients in the SPA group with signs of fever was significantly higher than those in the Vasculitis group (48.67±12.68 vs. 34.72±11.37, p=0.001). The other comparisons were not statistically significant after the Bonferroni adjustment (all p=0.016). There was no statistically significant difference between disease groups regarding to other clinical manifestations and laboratory findings (all p>0.05) (Table 1).

The genotype and allele frequency of FMF according to the MEFV mutations were given in Table 3. MEFV gene mutation was investigated in 70 (83.33%) patients. In these patients, the most common mutation was M694V heterozygote, which was found in 30 (42.85%) patients. M694V homozygote was found in 15 (21.42%), M680I heterozygote in 10 (14.28%), M680I homozygote in 2 (2.85%), E148Q homozygote in 1(1.42%), E148Q heterozygote in 1(1.42%), V726A homozygote in 0 (0%), V726A heterozygote in 5 (7.14%), the normal mutation in 1 (1.2%) patients.

Among the detected mutations, 13 (15.5%) of the patients were defined as compound heterozygous. A Fisher-Freeman-Halton exact test and a three-sample proportion test with and without continuity correction test showed that there was no statistically significant association between disease groups and MEFV mutations regarding to genotype and allelic distribution (all p>0.05) (Table 3).
Discussion

FMF, which is the most common inherited autoinflammatory disease, still has many unknown aspects, despite much information. In a few FMF patient series, there was a slight male predominance. In this study females were preponderant. Although FMF usually arises at young ages, it may rarely emerge after 40. Patients with late-onset have lower rates of mutation in exon 2 and exon 10 of the MEFV gene. They display higher rates of musculoskeletal system

Table 3. Comparison of genotype and allele frequency of FMF according to the MEFV mutations.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=84)</th>
<th>SPA (n=36)</th>
<th>Vasculitis (n=23)</th>
<th>CTD (n=18)</th>
<th>p-value</th>
<th>Gout (n=3)</th>
<th>JIA (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients included in the calculation(^1)</td>
<td>70</td>
<td>27</td>
<td>21</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M694V gene mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.776(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote</td>
<td>15 (33.3)</td>
<td>6 (31.6)</td>
<td>6 (40)</td>
<td>3 (27.3)</td>
<td>-</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>30 (66.7)</td>
<td>13 (68.4)</td>
<td>9 (60)</td>
<td>8 (72.7)</td>
<td>3 (100)</td>
<td>3 (75)</td>
<td></td>
</tr>
<tr>
<td>Allelic distribution</td>
<td>60/140 (42.86)</td>
<td>25/54 (46.3)</td>
<td>21/42 (50)</td>
<td>14/30 (46.67)</td>
<td>0.930(^2)</td>
<td>3/6 (50)</td>
<td>5/8 (62.50)</td>
</tr>
<tr>
<td>M680I gene mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.455(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote</td>
<td>2 (16.7)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>10 (83.3)</td>
<td>4 (66.7)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>-</td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td>Allelic distribution</td>
<td>14/140 (10)</td>
<td>8/54 (14.82)</td>
<td>3/42 (7.14)</td>
<td>3/30 (10)</td>
<td>0.483(^2)</td>
<td>-</td>
<td>1/8 (12.50)</td>
</tr>
<tr>
<td>E148Q gene mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote</td>
<td>1 (50)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Allelic distribution</td>
<td>3/140 (2.14)</td>
<td>2/54 (3.7)</td>
<td>1/2 (2.38)</td>
<td>0/30 (0)</td>
<td>0.566(^2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>V726A gene mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.999(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>3 (100)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Allelic distribution</td>
<td>5/140 (3.57)</td>
<td>0/54 (0)</td>
<td>2/42 (4.76)</td>
<td>3/30 (10)</td>
<td>0.076(^2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.286(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygote</td>
<td>4 (44.4)</td>
<td>1 (20)</td>
<td>2 (66.7)</td>
<td>1 (100)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>5 (55.6)</td>
<td>4 (80)</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Allelic distribution</td>
<td>13/140 (9.29)</td>
<td>6/54 (11.11)</td>
<td>5/42 (11.9)</td>
<td>2/30 (6.67)</td>
<td>0.747(^2)</td>
<td>2/6 (33.33)</td>
<td>-</td>
</tr>
<tr>
<td>Normal</td>
<td>1 (1.2)</td>
<td>1 (2.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No test</td>
<td>13 (15.5)</td>
<td>8 (22.2)</td>
<td>2 (8.7)</td>
<td>3 (16.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data were described as number (n) and percentage (%).

p-value\(^1\) shows the comparison of SPA, vasculitis, and STD groups (gout and JIA were excluded from statistical analysis due to the small sample size) and was calculated using Fisher-Freeman-Halton exact test.

p-value\(^2\) shows comparison of SPA, vasculitis, and CTD groups (gout and JIA were excluded from statistical analysis due to the small sample size) and was calculated using a 3-sample proportion test with and without continuity correction.

+Patients who did not show mutations and were not tested were excluded from the analysis for allelic distribution.

SPA: spondyloarthropathy, CTD: connective tissue disease, NA: not applicable.
symptoms and a lower rate of serositis during attacks; therefore, they are associated with milder disease responding to lower doses of colchicine. Consistent with the literature, in this study, in 18 patients diagnosed after 40, there were low penetrating mutations except for 2 cases who were M694V homozygote and musculoskeletal findings predominant.

In FMF, inflammation is not restricted to severe inflammation during periodic attacks, and chronic subclinical inflammation may continue between attacks. This chronic proinflammatory condition may play a triggering role in the development of some diseases. The coexistence of FMF with diseases such as SpA, BD, RA, SS, JIA, IBD, and PAN has been reported. Some of these inflammatory conditions may be regarded as coincidental, but some have reached important figures, suggesting an association between them. The exact mechanism of this association is unknown; however, it may be due to predisposing effects of impaired immune pathways in FMF. Mutations in NLR proteins are strongly associated with autoimmune diseases. In FMF, pyrin, which has undergone mutation, interacts with the inflammasome, activating caspase-1, which leads to overexpression of many cytokines, including IL-1β, IL-6, and IL-18. IL-1β upregulates IL-2 receptors, prolongs T cells' lifespan, and plays an important role in the proliferation of B cells and antibody production. IL-1β also has a key role in the differentiation of Th17 cells, essential in the adaptive immune system.

The SpA was the most common comorbid inflammatory condition in this study, with a rate of 43%. The SpA is a well-known MHC-I-apathy with a strong relation with HLA-B27 and completely overlaps with typical characteristics of neither autoimmune nor autoinflammatory diseases. SpA prevalence increases in FMF patients and their first-degree relatives. It has been reported that the prevalence of SpA is as high as 7% in FMF patients. The articular symptoms of FMF have characteristics overlapping with SpA, and the increased prevalence of SpA in FMF patients suggests a relation between the two disorders. Furthermore, it has been reported that sacroiliitis, which is the hallmark of SpA, are higher than expected rates in FMF patients with musculoskeletal symptoms. In a recent study, the incidence of sacroiliitis in FMF patients was established to be 2.6%.

Nevertheless, current data on HLA-B27 in the development of sacroiliitis in FMF patients are controversial. HLA-B27 was positive merely in 11% of our patients with SpA. This finding indicates that HLA-B27 does not have an essential role in the pathogenesis of FMF-associated SpA and that other pathophysiological mechanisms are required to explain the relation between SpA and FMF. A new study demonstrated the relationship between the IL1R2 gene and AS. Therefore, candidate gene and genome-wide association studies suggest that in addition to the IL-17 pathway associated with IL-23R, there is also an increased risk of AS in association with the IL-1 cytokine pathway. SpA associated endoplasmic reticulum-associated aminopeptidase 1 plays a role in the modulation of IL-1, IL-6, and TNF.

There is some evidence that M694V variation may be more common in FMF patients with sacroiliitis. A common result of the present study and the aforementioned studies is that the prevalence of M694V mutation is high among FMF and SpA patients. In this study, of 36 FMF patients with SpA, MEFV mutation analysis was performed in 28 patients. Besides, in FMF patients with radiographically detected sacroiliitis, the rate of M694V mutation was higher, similar to the literature. Furthermore, enthesitis, which is the hallmark of SpA, has been reported in FMF. Compared to AS, in FMF patients with SpA, peripheral arthritis and enthesitis occurred more commonly, and uveitis and syndesmophyte less commonly in the previous study. In this study, the rate of enthesitis was 11.9%.

Inflammasomes play a crucial role in the development of various skin diseases such as psoriasis and HS. In a recent population-based study by Hodak et al., a strong relationship between HS and FMF has been reported. In this study, there was one HS, one enteropathic arthritis, and three PSA patients. Ashida et al. demonstrated Th17 cells in the upper dermis of lesions similar to psoriasis in a patient with FMF. It is estimated that high IL-1 levels in FMF patients may lead to Th17 activation and direct stimulation of keratinocytes. The level
of IL-1 produced by active T lymphocytes is high in psoriasis lesions.\textsuperscript{21} FMF and IBD have many similar clinical and biological properties and may accompany FMF. MEFV mutation has been detected in IBD as well, making diagnosis more challenging.\textsuperscript{22}

Vasculitis is the second most common inflammatory disease occurring in FMF patients, with a rate of 26%.\textsuperscript{23} The relation between FMF and vasculitis has long been debated. The risk of vasculitis development seems to be increased in FMF patients. High serum IL-6 levels, which remain elevated even during relapse-free periods, have been reported. Although the exact pathogenesis of FMF-associated vasculitis remains unknown, an increase in serum levels of all pro-inflammatory cytokines, including IL-1\(\beta\), IL-6, IL-18, IL-33, and INF-\(\gamma\) and resulting in endothelial cell dysfunction (ECD), seems to be important. IL-1 is the most predominant among these cytokines, and high IL-1\(\beta\) activity may promote vasculitis in FMF patients. It has been demonstrated that IL-1\(\beta\) and TNF-\(\alpha\) mediate type II activation of endothelial cells and cause ECD by leading to the long-term inflammatory response. As reported in a recent comprehensive review, ECD, increased atherosclerotic burden, and thrombocyte activation are important characteristics of FMF and are maintained even in attack-free periods of FMF. A few reports have been published in the last few years, which relate subclinical inflammation to hypercoagulopathy and thrombosis in FMF. MEFV gene mutations associated with FMF may contribute to vasculitis in some FMF patients by producing high proinflammatory cytokine levels. The role played by environmental factors, especially streptococcal infections, seems to be important.\textsuperscript{24,25} Studies report the increased prevalence of HSP or PAN in both pediatric and adult FMF patients was published. The prevalence of HSP in FMF patients ranged from 2.7% and 7.2% in four studies in Turkey and Israel. In this study, 22 patients were diagnosed with vasculitis and FMF, and four of them had HSP. HSP findings emerged after the diagnosis of FMF, and the male/female ratio was 3/1. The literature demonstrated that most FMF patients reported having HSP or PAN as well had homozygote or compound heterozygote M694V mutations; our findings agreed with the literature.\textsuperscript{24,26} It has been reported that patients with HSP with MEFV mutations are younger and have higher rates of edema and acute phase responses than those without such mutations. Can \textit{et al.}\textsuperscript{27} stated that 45% of patients with HSP had MEFV mutations, but these mutations were unrelated to the clinical course and complications. Some authors suggested that HSP-like vasculitis in FMF is a specific feature of FMF.\textsuperscript{25} In agreement with Ben Chetrit \textit{et al.}\textsuperscript{28}, we established LCV in our patients, but no IgA accumulation was detected. PAN is the second most common FMF-associated vasculitis, involving 0.9–1.4% of patients.\textsuperscript{25} It has been reported that compared to other PAN patients, FMF-associated PAN arises at younger ages, has lower HBS antigen positivity, and peripheral nerve involvement is absent. However, myalgia, perirenal hematoma, and central nervous system involvement were more common, and the prognosis was more favorable.\textsuperscript{24,25} There is still no consensus on whether PAN occurring in FMF is coincidental or directly associated with it. M694 V is the most common mutation in patients with FMF and PAN. Consistent with the literature, symptoms of our 32-year-old male patient with M694V mutation, were mild. After HSP and PAN, BD is the third most common vasculitis encountered in FMF patients. Due to the absence of T and B cells in its pathogenesis, the episodic pattern of disease course, and abnormally increased inflammatory response, BD is a polygenic autoinflammatory disease. MEFV gene, IL-1, is an important cytokine in BD. BD and FMF share some common characteristics, such as geographical distribution and clinical symptoms. Tunca \textit{et al.}\textsuperscript{29} reported the prevalence of BD to be 0.5% among 2,838 FMF patients in Turkey. In 2017, it was stated by Watad \textit{et al.}\textsuperscript{30} that in patients with BD, the prevalence of FMF increases considerably. The male/female ratio in FMF and patients with BD varied between different studies. Watad \textit{et al.}\textsuperscript{30} reported a male/female ratio of 0.4 in FMF-BD. In our series, the M/F ratio was 1/3, with female predominance. FMF patients with or without accompanying BD presented with a similar FMF phenotype. In the literature, in BD accompanying FMF, the rate of gastrointestinal
and CNS involvement was found to be higher. In our patient series, one patient had neuro-BD, four vascular involvement, two joint and eye involvement, four isolated mucocutaneous involvement, and no GIS involvement. Whether FMF and BD are separate clinical entities or have common characteristics which cannot be ascribed to coincidence is still disputed. According to Ben-Chetrit and Yazıcı 

 concluded that FMF and BD coexisted in the same people more frequently than expected, and BD should be incorporated into other vasculitides widespread in FMF. Therefore, the overlapping of some disease features has suggested a common genetic susceptibility in BD and FMF, and both disorders suggest that there is a common genetic susceptibility in BD and FMF. Both disorders may represent the opposite poles of the same disease axis. It was also observed that MEFV mutations increased susceptibility to BD and increased the risk of venothrombotic events in patients with BD patients, suggesting that pyrin, which has undergone mutation, plays suggesting that pyrin, which has undergone mutation, may play a direct role in the pathogenesis of BD. In our series, thrombosis was present in 30% of patients with BD, and of these, all but one had M694V mutation. It has been proposed that these mutations may be associated with the pathogenesis of BD. In the study of Yazıcı et al. evaluating 100 patients with BD, MEFV mutations (M694V, E148Q, M680I, V726A) were detected in 27% of patients. The most common mutation was M694V. They also evaluated the relation between MEFV mutations and clinical data of BD, finding no relation. In the study of Taşliyurt et al., it was established that the rate of MEFV mutations in Turkish patients with BD was 39%, and it was thought that E148Q and M680I mutations might play a part in the pathogenesis of BD. The rates of uveitis were found to be significantly lower in patients with BD with MEFV mutations. Nevertheless, in this study, MEFV mutation was detected in two patients with uveitis. Livneh et al. determined that despite a single MEFV allele with mutation, BD was present in 10 out of 11 patients with clinical expression of FMF. There were four heterozygote patients in our series. However, studies with a larger sample size are warranted to demonstrate the role of MEFV mutations in the pathogenesis of BD.

In addition to these widespread vasculitis symptoms, some case reports on FMF patients with central nervous system vasculitis, coronary vasculitis, TA, Cogan syndrome, and cutaneous vasculitis. In this study, FMF coexisted with cutaneous vasculitis in four patients, with TA in one patient and EGPA in one patient. As far as we know, no association between FMF and EGPA has been reported so far. Although these cases are considered FMF-associated vasculitis, we believe that there is no adequate evidence to rule out a coincidental relationship with FMF.

Gout arthritis and FMF share some clinical and pathological characteristics such as classification as autoinflammatory disease, relations with the inflammasome short-term intermittent arthritis, and good response to colchicine and anti-interleukin-1 treatment. It has commonly been accepted that mono-sodium urate activates the NLRP3 inflammasome, leading to the production and release of proinflammatory cytokines. Sari et al. investigated the frequency of MEFV gene mutation in patients with gout arthritis and established that E148Q was the most commonly encountered mutation. However, this finding should be cautiously interpreted owing to the high prevalence of this mutation in the normal population (18.3%). Karaarslan et al. demonstrated high rates of MEFV gene mutation in 93 patients and concluded that MEFV gene mutations might play an essential part in the pathogenesis of the disease. In 3 patients with gout arthritis in this study, the most common MEFV mutation was M694V.

Although acute, non-erosive arthritis is one of the most important clinical findings of FMF, chronic arthritis may also occur in FMF patients. Pyrin may function as a sensor for the inactivation of Rho GTPase caused by pathogens in the impaired intestinal flora. Dysbiosis may lead to post-translational modification of autoantibodies and subsequently to RA development, and it was established in patients with RA. Therefore, dysbiosis of intestinal bacteria may trigger natural and adaptive immunity leading to RA and FMF. Anti-citrullinated protein antibodies (ACPA)
were found to be markedly more common in FMF patients. In three of our five cases with RA, ACPA levels were found to be high. In various studies, the prevalence of JIA in FMF patients varies between 3.6% and 8%. JIA was present in 5% of our patients. The rate of M694V mutation was found to be around 10% in JIA, and these cases were more severe and recalcitrant to treatment. In this study, in JIA cases, M694V mutation was present one patient as homozygote and three patients as heterozygote. Hence, in children assumed to have JIA, it is recommended that MEFV gene mutations be screened.

Although CTD and FMF coexist very rarely, there are a few cases reported in the literature. In this study, there were six cases of SS, one case of SLE, three cases of SSc, and three cases of MCTD. In a large Turkish cohort with 32,716 FMF patients, four cases of SLE were detected. In patients with SLE with pericardial/pleural effusion, MEFV gene variants were more common. In a multi-center study including 3,000 Turkish FMF patients, no case of SLE was detected. A recent study demonstrated carrier status of MEFV gene mutations protected from more severe kidney involvement while enhancing excessive inflammatory symptoms such as fever and pleuritis. In contrast, Deniz et al. showed that exon 10 mutations were associated with SLE nephritis. In our cases with lupus, there was no nephritis and pleuritis. Some evidence regarding the relation between FMF and SS. Tanaka et al. found higher IL-18 levels in patients with concurrent SS and FMF and suggested that FMF-associated irregular IL-18 production and chronic inflammation are related to the development of SS. Coexistence with SS was detected in six patients in our cohort. In five of these patients, there was a MEFV mutation in exon 10 without any life-threatening organ involvement. It has been stated that MEFV mutation may contribute to the clinical symptoms of MCTD, including serositis, through the alteration in pyrin inflammasome function. No serositis was detected in our MCTD patients with M694V mutation. There was no concurrence with SSc in the literature reported so far. One SSc patient had limited, and two patients had widespread skin involvement. There was no interstitial lung disease and pulmonary hypertension. Two patients had M694V mutations. In countries where FMF is endemic, in connective tissue disease patients with atypical clinical symptoms such as unexplained acute phase response, intermittent abdominal and back pain, and inadequate response to treatment, FMF should be borne in mind. The number of patients was too few to conclude the relationship between MEFV gene mutation and CTD development.

This study has some limitations. As it is a single-center cross-sectional study, it is not possible to generalize these results to the general population. Moreover, the research included a relatively small number of patients (n=84). In this regard, the results and conclusions should be interpreted with caution. Finally, there were patients without any genetic analysis.

Conclusion

A wide range of other rheumatic diseases associated with FMF has been described. The high correlation reported between them reflects the similarities in clinical presentation in conjunction with probable common genetic and ethnic background. We also established two new conditions, i.e., EGPA and scleroderma, which may be associated with FMF. This concurrence may only be coincidental or reflect an extension of the underlying pathology of FMF. The determination of pathological pathways connecting FMF to these diseases requires further investigations to be conducted.

Learning Points

FMF can coexist with various rheumatic diseases. Related diseases might have a causality relationship with FMF. They can be due to common genetic predisposition, immune dysfunction, or autoinflammation itself. The healthcare provider must be aware of these associations to detect them timely, treat them appropriately, and improve the prognosis.
**Acknowledgments**

We acknowledge our patients for the consent to publish this research for teaching medical professionals to help their patients better. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of Interest**

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Authors’ Contribution**

Study Conception: DT, SY, ML; Study Design: DT, SY, ML; Supervision: DT, SG, ML; Materials: DT, SG; Data Collection and/or Processing: DT, SY, ML; Statistical Analysis and/or Data Interpretation: DT, SY; Literature Review: DT; Manuscript Preparation: DT; Critical Review: DT, SY.

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