ORIGINAL ARTICLE

Rheumatology Quarterly

Kezban Armağan Alptürker. Familial Mediterranean Fever in Erzincan

DOI: 10.4274/qrheumatol.galenos.2023.43434
Rheumatology Quarterly 2023;1(2):57-62

CHARACTERISTICS OF PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER IN ERZINCAN PROVINCE: A CROSS-SECTIONAL STUDY FROM A SINGLE CENTER

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Abstract

Aim: Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent attacks of fever, peritonitis, and pleuritis. The disease usually occurs in the first two decades of life. It is frequently seen in the Central-North Anatolian Region of the country. In this study, it was aimed to investigate the first complaints, age at diagnosis, delay in diagnosis, most common clinical findings, and *MEFV* gene of patients with FMF living in Erzincan province.

Material and Methods: In this cross-sectional study, patients diagnosed with FMF who applied to rheumatology and physical medicine and rehabilitation outpatient clinics between January 2023 and May 2023 were included. Demographic data and genetic features were collected from patient interviews and medical records.

Results: The study comprised 142 (64 female, 78 male) patients with the diagnosis of FMF. The mean age of the patients was 31.60±9.91 years. In the patient group, the mean age of first attack was 16.39±7.55, delay in diagnosis was 3.57±2.35. Genetic analysis revealed that 24% of the patients were homozygous for M694V, followed by heterozygous M694V mutation (12.6%). The most common clinical symptoms in patients were peritonitis (86.6%). All patients were using colcicine.

Conclusion: It was observed that FMF patients treated with Erzincan were similar to the results of studies in Turkey in terms of mutation type and clinical complaints. Delay in diagnosis was found to be shorter compared with other studies. This study is important because it is the first comprehensive study in Erzincan province.

Keywords: Familial Mediterranean fever, genetic mutation, clinical features, Erzincan

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, or erysipelas-like skin lesions. The disease typically progresses with attacks and is mostly self-limiting attacks lasting between one and three days. Abdominal pain is the most common symptom of fever in patients with FMF. The disease usually occurs in the first two decades of life, and rarely it can start after the age of 40. The disease usually occurs in the first two decades of life, and rarely it can start after the age of 40 (1).

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Received: 05.06.2023 **Accepted:** 07.06.2023 **Publication Date:** 20.06.2023

Although the disease is Mediterranean-originated, it is frequently seen in the Central-North Anatolian Region of the country. The prevalence of consanguineous marriages in Turkey also increases the incidence of FMF, which is a genetically transmitted disease. FMF prevalence in Turkey is nearly 1:400 to 1:1000 (2). FMF is inherited autosomal recessively and the responsible gene, MEFV (Mediterranean fever), is localized in the short arm of chromosome 16 and encodes a protein (pyrin) found especially in granulocytes (3). The most common mutation in patients in the Turkish population is M694V and followed by M680I, V726A, and E148Q (4). There is no diagnostic test for the diagnosis of FMF and clinical features make the diagnosis. Diagnosis is made by the typical features of attacks, patients' response to colchicine, family history, and exclusion of other causes of periodic fever (5,6). The Tel-Hashomer and Livneh criteria were originally developed for diagnosis in adult FMF patients. If patients have atypical clinical symptoms, genetic analysis may be required if clinical criteria are not sufficient and if it is necessary to confirm the diagnosis (7). One of the devastating complications of FMF in the long term is the development of amyloidosis. Because of the amyloid deposition, mainly the kidneys are involved, and other organs may also be affected (8). Colchicine has also been found to be effective in preventing FMF attacks, reducing the frequency of attacks, and preventing the development of amyloidosis (9). Early recognition of the disease is essential to reduce the progression to kidney failure, which is the most feared complication of the disease. In this study, it was aimed to investigate the first complaints, age at diagnosis, delay in diagnosis, most common clinical findings, and *MEFV* gene of patients with FMF living in Erzincan province. This study will contribute to the earlier detection of the disease and thus to the prevention of complications.

MATERIAL AND METHODS

In this cross-sectional study, patients aged between 18 and 65 years who were diagnosed with FMF according to Tel-Hashomer criteria and who were referred to the Erzincan Binali Yıldırım University Mengücek Gazi Training and Research Hospital Rheumatology and Physical Medicine and Rehabilitation clinic between January 2023 and May 2023 were included. Permission was obtained from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee with the decision dated 22/12/2022 and numbered 2022-08/1. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients consented to the use of their information in this study. Main demographic and clinical data including (age, gender, first complaints and onset time, age of diagnosis, number of attacks in the last 1 year, treatments they received and whether they benefited from the treatment, and accompanying autoimmune diseases, family histories) and clinical features were recorded. The age at the first attack of the disease was recorded, and the age at the time of diagnosis was accepted as the age of diagnosis. Laboratory values, *MEFV* gene analysis, and HLA-B27 test results were recorded from the hospital database. Patients with a suspicious diagnosis were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) 22.0 package program. Quantitative variables were expressed as mean ± standard deviation or median (minimum and maximum) as appropriate. and qualitative variables were presented as numbers and percentages. Chi-square test's were used to analyze categorical data. Student's t-test and Mann-Whitney U test were used to analyze continuous data. At the $p \leq 0.05$, all results were considered statistically significant.

RESULTS

A total of 142 (68 female, 74 male) FMF patients were enrolled in this study. The male/female ratio was 1.21. The mean age of patients (aged between 4 and 63) were 31.60±9.91 (in female was 30.67±9.06) years). Age at the onset of symptoms, age at diagnosis, and delay in diagnosis were not statistically different between the genders ($p>0.05$). Haemoglobin, mean platelet volume, erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A levels were higher in male patients ($p<0.05$). When family history was questioned in terms of FMF, 69.7% (99 patients) of all patients had a positive family history. Comparison of demographic and laboratory characteristics between gender in FMF are summarized in Table 1. One hundred patients (70.4%) stated that their first attack was before the age of 18. Two patients stated that their first attack was after the age of 40. Due to the delay in the diagnosis, 8 (4 female patients and 4 male) (5.6%) patients were diagnosed over the age of 40. Adult patients (23 patients) were diagnosed most frequently by internal medicine physicians in secondary care clinics. One hundred and thirteen patients (79.5%) responded well to colchicine therapy (tablets contain 0.5 mg, 2-3 times a day). Twenty-nine (20.4%) colchicine-intolerant patients were switched to alternative colchicine (2 times a day, tablets contain 1 mg). One hundred and ten patients (77.5%) showed good compliance with the treatment, while 22.5% of them had irregular usage of colcicine. All irregular users relapsed after a mean period of 1.89±1.24 months. Seventeen (12%) patients were using Anakinra in addition to colcicine, and 7 (4.9%) patients were using canakinumab. When

Table 1. Comparison of the demographic and laboratory characteristics between gender in familial Mediterranean fever (FMF)

Variables	Female (n=64, %45)	Male (n=78, %55)	p
Age (years) (min-max)	30.67±9.06 (18-51)	32.37±10.56 (18-63)	0.316
Age at the onset of symptoms (mean ± SD) yr	15.89±8.23	16.80±6.98	0.471
Age at diagnosis (mean ± SD) yr	19.56±9.61	20.28±8.60	0.632
Delayed diagnosis (mean ± SD) yr	3.70±2.22	3.46±2.45	0.541
The duration of follow-up (mean ± SD) yr	9.12±4.22	11.64±7.46	0.182
Positive family history (n, %)	45 (70%)	59 (75%)	0.473
Attack frequency (number/year);(min-max)	1.09±0.91 (1-6)	1.46±1.43 (1-8)	0.081
Hemoglobin (g/dL)	12.78±1.18	13.55±1.57	**0.012**
WBC (10^3/µL)	7.17±2.12	7.44±2.92	**0.474**
MPV (fL)	9.52±0.71	10.02±1.21	**0.040**
Serum amyloid A (mg/dL)	26.75±30.52	41.92±59.27	**0.049**
ESR (mm/hour)	24.18±9.18	31.74±16.04	**0.021**
CRP (mg/dL)	8.67±4.04	13.11±8.67	**0.023**
HLA B-27 (n, %)	20 (31.2)	24 (30.7)	0.147

SD: Standard deviation, yr: Year, min-max: Minimum-maximum, WBC: White blood cell, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HLA: Human leukocyte antigens

comorbid diseases were questioned in FMF patients, 37 (13 female, 24 male) (26%) patients had spondyloarthritis (SpA), 6 (4.2%) patients had Behcet's disease, 5 (3.5%) patients had Inflammatory Bowel disease (IBD), and 4 (2.8%) patients had systemic lupus erythematosus (SLE). The patients in the study (87 patients) were diagnosed in childhood (<18 years), fever (42 patients, %42.8) was often the first and only symptom in their attacks. The complaints of the patients during the attacks were recorded. The most common clinical finding during an FMF attack was that abdominal pain (peritonitis) was detected in 86.6% of patients. This was followed by arthralgia (61.2%) and fever (60.5%). There was no gender difference between fever and abdominal pain. Arthralgia was more common in male patients (p=0.13). Arthralgia was more common in male patients, and the difference was significant (p=0.13). The difference was significant in arthritis (p=0.35) and ankle involvement was the most common joint involvement. Twenty-one (14.7%) patients had abdominal operations (9 were acute appendicitis) and the difference between genders was significant (p=0.09). The patients in the study (87 patients) were diagnosed in childhood (<18 years), fever often the first and only symptom in their attacks. A comparison of the clinical features of the patients with FMF is shown in Table 2. The *FMF* gene test results of 138 patients were accessed from computer records. The most frequently observed mutation was M694V homozygous mutation (34 pateints, 24%) patients, followed by heterozygous M694V mutation (18 patients, 12.6%). Heterozygous P369S (4 patients, 2.8%) and heterozygous

Table 2. Comparison of the clinical features of patients with FMF

Clinical symptoms	Female n=64 (%)	Male n=78 (%)	Total n=142 (%)
Clinical findings in attack abdominal pain	57 (89)	66 (84.6)	123 (86.6)
Fever	36 (56.2)	50 (64.1)	86 (60.5)
Arthralgia	32 (50.0)	55 (70.5)	87 (61.2)
Arthritis	10 (15.6)	24 (30.7)	34 (23.9)
Pleuritis	11 (17.1)	12 (15.3)	24 (16.9)
Myalgia	19 (29.6)	23 (29.4)	42 (29.5)
ELE	5 (7.8)	7 (8.9)	12 (8.4)
Back pain	20 (31.2)	28 (35.9)	48 (33.8)
The abdominal operation (n%)	4 (2.8)	17(12)	21 (14.7)
Good response to colchicine	54 (84.3)	56 (71.7)	110 (77.5)
Secondary amyloidosis	2 (1.4)	2 (1.4)	4 (2.8)
Renal failure	3 (4.6)	5 (6.4)	8 (5.6)
Sakroileitis	8 (12.5)	14 (18)	22 (15.5)

n: Number, ELE: Erysipelas-like erythema, FMF: Familial Mediterranean fever

V726A (4 patients, 2.8%) mutations were rarer. Genotypic distribution of MEFV mutations in patients with FMF is shown in Table 3. Twenty-three patients had proteinuria (>200 mg/day in 24-hour urine). Renal amyloidosis was found in the biopsy results of 4 patients with nephrotic proteinuria. Two of the patients who developed amyloidosis had homozygous M694V mutations, 1 had heterozygous M694V mutation, and one had M694V/E148Q mutation. Three patients with a diagnosis of amyloid were male and had a family history of FMF. The clinical features of the most common mutation (homozygous M694V) in patients are summarized in Table 4.

Table 3. Genotypic distribution of MEFV mutations in patients with Familial Mediterranean fever

Mutations detected	The number of patients (%)
Homozygous M694V	34 (24%)
Heterozygous M694V	18 (12.6%)
Homozygous M680I	14 (10%)
Heterozygous M680I	10 (7%)
M694V/M680I	10 (7%)
M694V/V726A	7 (4.9%)
M694V/R202Q	7 (4.9%)
M694V/E148Q	6 (4.2%)
M680I/E148Q	7 (4.9%)
M680I/R202Q	6 (4.2%)
Heterozygous E148Q	6 (4.2%)
Heterozygous R202Q	5 (3.5%)
Heterozygous P369S	4 (2.8%)
Heterozygous V726A	4 (2.8%)

Table 4. Clinical features of patients with homozygous M694V

Variables	Number of the patients=34 (%)
Male sex (%)	24 (70.5)
Age at the onset of symptoms (mean ± SD) yr	16.01±6.09
Age at diagnosis (mean ± SD) yr	18.46±6.98
Delayed diagnosis (mean ± SD) yr	2.46±1.72
Positive family history (n, %)	25 (73.5)
Secondary amyloidosis (n, %)	2 (5.8)
SD: Standard deviation, yr: Year, n: Number	

DISCUSSION

In this study, demographic, clinical characteristics and recorded data in the files of patients with FMF followed up in a single center were analyzed. Although FMF was observed in certain ethnic groups originating in the Mediterranean and Middle East regions, it is seen more intensely in provinces such as Sivas, Tokat, and Erzincan in the country. The results of the study conducted by the Turkish FMF group showed that the incidence of the disease was almost equal in both sexes (M/F: 1.2/1) (9,10). In this study, in which 142 patients (64 females, 78 males) were evaluated, the male/female ratio was found to be 1.21/1, which is similar to the literature.

FMF usually occurs at a young age, the first attack occurs before ten years of age in approximately 60% of the patients, and onset in the majority of patients (90%) begins before the age of 20 years. Rarely, the first complaints may start over the age of 40 years (10). In a recently published large cohort of Armenians, the proportion of patients with onset ≥40 years was 3.4% (11). The mean age of first attack in the patients in the study was 16.39±7.55 (female 15.89±8.23, male 16.80±6.98), and 2 (1.4 %) patients had their first attack over the age of 40 years. The variable nature of the disease, the different clinical presentation in each patient, and the exacerbation of symptoms cause a diagnostic challenge in FMF. It causes considerable diagnostic delay even in endemic areas. In a nationwide study conducted in Turkey, the age at diagnosis was 16.4±11.5 years, and the diagnosis delay time was 6.9±7.6 years (12). Tamir et al. (13) reported the median delay in diagnosis for FMF populations as 8 years. The diagnostic delay of the patients in the study was shorter, unlike these studies. The diagnostic delay of the patients in the study was shorter, unlike the other studies. The mean delay in diagnosis in all patients was 3.57±2.35 (female: 3.70±2.22, male: 3.46±2.45) years ($p<0.05$). The reason for the delay in diagnosis in female patients compared with male patients was considered to be the inability to recognize abdominal pain attacks because they coincided with monthly menstrual periods. Although FMF has a heterogeneous clinical spectrum, fever and peritonitis are the most common symptoms reported in over 90% of patients of all ages and ethnicities (13,14). The clinical picture and laboratory findings are compatible with acute peritonitis. The fever usually 38-40 °C during the attack and lasts for 12-72 hours. Fever often the only symptom in childhood but may not accompany every FMF attack (14). In the study, the most common finding during FMF attack was abdominal pain in 123 (86.6%) patients, followed by arthralgia (861.2%) and fever (60.5%). The incidence of arthritis in Mediterranean fever is 40-70% and it is usually lower extremity involvement (9,15). Ankles (12.6%) and knees (7.0%) were more

frequent involvement in the patients, and similar to studies, arthralgia (61.2%) was a more common symptom than arthritis (23.9%) in the patients group. Studies show that the incidence of sacroiliitis is high in FMF patients and its close relationship with SpA. It was emphasized in studies that axial signs of symptoms were more severe in HLA-B27-positive cases (16). The patients in the study, 48 (33.8%) patients with FMF had inflammatory low back pain. When the magnetic resonance imaging (MRI) results of patients with inflammatory low back pain were examined, findings consistent with sacroiliitis were observed in 22 (15.5%) patients. In the whole patient group, 44 (30.9%) patients were HLA B-27 positive, and there was no significant difference between genders. The rate of HLA B-27 positivity was found to be 37.5% (18 patients) in patients with inflammatory low back pain. Many cases have been reported that underwent laparotomy considering acute abdomen with findings such as fever, abdominal pain, distension and tenderness in abdominal examination and air-fluid levels in standing abdominal X-ray (17). In a study conducted in Turkey, it was reported that the young population applied to the emergency department with acute abdomen and approximately 19% of these patients were operated on considering acute appendicitis (6,18). Before the diagnosis of FMF, a total of 21 (14.7%) patients were operated for acute abdomen, while 15 (10.5%) patients were operated for acute appendicitis. The gene that causes FMF (Mediterranean fever gene, *MEFV*) is located on the short arm of chromosome 16p13.3. The frequencies of 8 mutations (M694V, M680I, E148Q, V726A, A744S, R202Q, R761H, T267I) reported to be frequently encountered in the *MEFV* gene in the literature were investigated. Although the MEFV mutation in Turkish patients showed great variability, the most common mutation was M694V between 14.7% and 53.8% of MEFV alleles. This is followed by V726A, M680I and E148Q.8,9. Dundar et al. (19) found in a cohort showed that the most frequent mutations were M694V, E148Q and M680I, respectively. M694V homozygous mutation (24%) was the most frequently detected mutation in the study group, followed by M694V heterozygous mutation (12.6%) and homozygous M680I (10%) respectively. It was similar to the literature in terms of frequently found mutations. Heterozygous E148Q (4.2%) was found to be less in number than in the literature. In a study conducted in Turkey, the incidence of sacroiliitis on X-ray was found to be 10.5%. In the evaluation of clinical findings according to mutation type in the study, male sex (24 patients) was more dominant in patients with M694V homozygous mutations and sacroiliac joint involvements (18 patients) were found more frequently than all other mutation types. In contrast, sacroiliitis was evaluated with MRI in the study. Amyloidosis is the most serious complication of FMF and often affects the kidneys. It presents with proteinuria and leads to end-stage renal disease. According to the data of the FMF study, its incidence was found to be 12.9% (2,12). Differences in clinical cases and the development of amyloidosis are affected by the type of MEFV mutations and it has been associated with a severe course of the disease in some ethnic groups. In the study conducted in Turkey, FMF patients who are homozygous for M694V have a 6-fold risk of amyloidosis compared with FMF patients with other *MEFV* gene mutations. In addition, male gender and family history of amyloidosis were defined as another risk factors (9,12,20,21). In the study, two of 4 patients with renal amyloidosis had homozygous M694V mutation, one patient had heterozygous M694V mutation, and one patient had M694V/E148Q mutation, similar to the literature. Three patients with a diagnosis of amyloid were male and had a family history of FMF. One of these patients was diagnosed over the age of 40 and the first finding was proteinuria. The discovery of colchicine as an effective drug for FMF was a big step forward, and the response to this drug could also be used to confirm the diagnosis. Colchicine is the gold standard treatment that is effective in preventing attacks and protects against the development of amyloidosis (12,17). All patients were receiving at least 1 mg per day colchicine treatment. 77.5% of the patients showed good compliance with the treatment, 22.5% of them were on irregular colchicine use, and recurrence in irregular users recurred after a mean period of 1.89±1.24 months. It is defined as colchicine resistance with >6 attacks per year, and up to 5% of patients are considered to be resistant or inadequately responsive to colchicine (colchicine intolerance) (22). Blocking interleukin-1, which is involved in the pathogenesis of the disease, can be considered as alternative treatment options in resistant AAA cases and organ involvement (23). Twenty-four (16.9%) of the patients were using biological therapy (blocking the IL-1 cytokine) in addition to colcicine. FMF has many inflammatory disease comorbidities such as SpA, Behçet's disease, and ulcerative colitis. In one study, SpA prevalence was reported to be 0.4% in FMF (8,9). Among the vasculitides, it has been reported in some studies that the incidence of PAN and Henoch-Schönlein purpura is higher in FMF patients (24). In the study, 37 (13 female, 24 male) (26%) patients had SpA, 6 (4.2%) patients had Behçet's disease. Also, 5 (3.5%) patients had IBD and 4 (2.8%) patients had SLE. It was observed that FMF patients treated with Erzincan were similar to the results of studies in Turkey in terms of mutation type and clinical complaints. Delay in diagnosis was found to be shorter compared with other studies.

Study Limitations

Some strengths and limitations of the study should be addressed. The main limitation was the cross-sectional and single-center plan of the study. This prevented clear conclusions about the follow-up of the patients. Because it was a single-center, the number of patients was low.

CONCLUSION

FMF is a disease that is frequently observed in Erzincan province and its diagnosis can often be difficult. The fact that it is still a late-diagnosed disease and the delays in its referral to rheumatology causes patients to undergo unnecessary operations and increase the risk of amyloidosis. The aim of this study was to provide earlier recognition of this disease, which is common in Erzincan province, to increase awareness about the disease, and thus to enable patients to find a chance for earlier treatment.

Acknowledgements

I would like to thank Dr. Emine Esra ERGÜL for her valuable support.

Ethics

Ethics Committee Approval: Permission was obtained from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee with the decision dated 22/12/2022 and numbered 2022-08/1.

Informed Consent: All patients consented to the use of their information in this study.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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