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MEFV Mutations And Clinical Findings in Patients With Familial Mediteranean Fever: The Emergency Department Experiences

Murat Toprak[1], Mehmet Reşit Oncu[2]

[1]*Van Yüzüncü Yıl University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Van, Türkiye*
[2] [1]*Van Yüzüncü Yıl University Faculty of Medicine, Department of Emegency Medicine, Van, Türkiye*

Abstract

Introduction: We examined emergency department utilization patterns by identifying the characteristics of FMF cases in the emergency department and analyzing the relationship between genotype-related characteristics and clinical findings.

Materials and Methods: One hundred and thirty-five patients with FMF were evaluated. The present study included adult Turkish patients (≥18 years old) who had been diagnosed according to the Tel Hashomer and Livneh criteria. A comprehensive data set encompassing demographic and clinical information was meticulously compiled for the entire patient cohort from the clinic's database and medical records.

Results: A total of 135 patients (81 [60%] female/54 [40%] male) with FMF were included to study. The mean age was 28.19±9.71 years and the disease duration was 6.62±5.38 years. The most common allele freuquency was identified as M694V, present in 36 (26.5%) patients. The other mutations were listed as R202Q (14%), M680I (5.9%), E148Q (8.4%) and V726A (12.5%) respectively. While patients with M694V gene mutations have more severe clinical symptoms (constipation, fatigue, erysipelas-like erythema, scrotal pain, appendicitis surgery), E148Q and V726A gene mutations shows milder clinical symptoms. A correlation was identified between M694V and appendectomy, arthritis/arthralgia, and constipation.

Conclusion: Abdominal pain and fever was the most frequent symptom. M694V, E148Q, R202Q, M680I, and V726A were the most common mutations in FMF patients. Appendectomy, arthritis/ arthralgia and constipation were significantly correlate in patients with M694V mutations.

Key words: Emergency; familial mediterranean fever; genetic mutation; clinical symptom.

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic periodic fever syndrome and characterized by recurrent episodes of fever, serositis, arthritis, dermal manifestations, and long-term renal complications (1). Its prevalence is very high among people non-Ashkenazi Jews, Armenians, Turks and Arabs (2). Since the definition of MEFV gene mutations underlying FMF in 1997, around 310 sequence variants in MEFV gene have been detected (3). In trials conducted in Turkish population, the most common mutations were reported as M694V, E148Q, M680I and V726A (4, 5). Colchicine therapy, as a standard treatment of FMF has been clinically proven to reduce the frequency and severity of acute attacks and prevent the development of amyloidosis in FMF patients (6).
FMF is an autoinflammatory multisystem disease (7). Fever, abdominal pain and joint involvement are the most common clinical findings, while others are less common (7, 8). Pleural attacks, usually acute and one-sided, and erysipelas-like erythema, (painful, hot, swollen, distinct red lesions of the skin on the lower extremities), appear in a third of FMF patients during their life (8). Headache or diffuse myalgia and malaise can also occur (9). Recurrent orchitis and meningitis are uncommon presentations. The most important complication is renal failure (10). Prior to the diagnosis of FMF, 30–50% of the patients undergo unnecessary surgical interventions such as appendectomy, or cholecystectomy (11). While there were studies on the clinical symptoms of FMF patients in emergency departments (12-13), there were few studies that correlated clinical and genetic mutations. The present study was conducted with the objective of enhancing the comprehension of emergency care health service utilisation among individuals afflicted with FMF at a population level. To analyse the relationship

***Corresponding Author:** Murat Toprak, Medical Faculty of Van Yüzüncü Yıl University, Department of Physical Medicine and Rehabilitation, 65080 Van, Turkey. **E-mail :** dr.murattoprak@gmail.com **Orcid:** Murat Toprak 0000-0002-6490-4645, Mehmet Reşit Oncu 0000-0001-9296-2554

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between genotype-related features and clinical findings, including recurrent fever, abdominal pain, arthritis/arthralgia, myalgia, proteinuria and/or amyloidosis, in FMF cases presenting to the emergency department.

Material and Methods

A retrospective service evaluation was undertaken of all patients who attended the Emergency department in Van Yüzüncü Yıl University hospital, between December 2019 and June 2020. One hundred and thirty-five patients with FMF were the subjects of the present study. Patients over the age of 18 who were diagnosed according to the Tel Hashomer and Livneh (14) criteria were included in the study. The present study was conducted in accordance with the Helsinki Principles. A comprehensive data set encompassing demographic and clinical information was meticulously retrieved from the hospital database, encompassing all patients included in the study. The clinical and demographic characteristics encompassed the following: age, gender, age at onset/diagnosis, disease duration, time to diagnosis, attack characteristics (fever, erysipelas-like erythema, pleuritis, febrile myalgia, peritonitis, pericarditis, diarrhea, constipation, and arthritis), predominant attack types (serositis and musculoskeletal), appendectomy history, and colchicine dose. MEFV mutation results were obtained from the medical records of the subjects.

Ethical Approval: In our study, written consent was obtained from all the cases participating in our study, in accordance with the Declaration of Helsinki. Ethics Committee permission was obtained Van Yüzüncü Yıl University Ethical Approval Medical Faculty Clinical Research Ethics Committee with the decision dated 13.09.2019 and numbered 03.

Statistical Analysis: Data is expressed as mean ± standard deviation or n (%). For determination linear relationships among the variables, the Pearson correlation analysis was carried out. An investigation was conducted into the relationships between MEPV and the other evaluation parameters, with Pearson correlation analysis being utilised to facilitate this investigation. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software version 23.0 was utilised for the statistical analyses, with a significance level of 5% being considered.

Results

A total of 135 patients (81 [60%] female/54 [40%] male) with FMF were included to study. The mean age was 28.19±9.71 years and the disease duration was 6.62±5.38 years. The clinical and laboratory characteristics are summarized in Table 1.

Table 1: Clinical and laboratory characteristics of FMF patients

Characteristics	
Age, mean±SD	28.19±9.71
Symptom onset age, mean±SD	14.22±6.96
Disease duration, mean±SD	6.62±5.38
Gender, Female /Male (n,%)	81 (60%)/54 (40%)
Symptoms;	
Fever, (n,%)	128 (94.8%)
Abdominal pain, (n,%)	132 (97.8%)
Chest pain, (n,%)	67 (49.6%)
Vomiting, (n,%)	43 (31.8%)
Diarrhea, (n,%)	31 (22.9%)
Constipation, (n,%)	53 (39.2%)
Fatigue, (n,%)	104 (77%)
Arthritis / arthralgia, (n,%)	92 (68.1%)
Myalgia, (n,%)	61 (45.2%)
Erysipelas-like erythema, (n,%)	61 (45.2%)
	44 (32.6%)
	6 (4.4%)
Headache, (n,%)	44 (32.6%)
Scrotal pain, (n,%)	6 (4.4%)
Polyneuropathy, (n,%)	17 (12.6%)
Appendectomy, (n,%)	29 (21.48%)
Hepatomegaly, (n,%)	6 (4.4%)
Splenomegaly, (n,%)	5 (3.7%)
ESH, mean±SD	14.81±10.71
Leucocyt, mean±SD	7.64±2.14
CRP, mean±SD	22.43±20.02
Fibrinogen, mean±SD	273.25±85.98
Proteinuria/hematuria, (n,%)	22 (16.3%)
Amyloidosis, (n,%)	5 (3.7%)

ESH; erythrocyte sedimentation rate, CRP: C-reactive protein, SD; standard deviation

Mutational analysis of the MEFV gene was conducted on a total of 135 patients. The most prevalent allele frequency was identified as M694V, present in 36 (26.5%) patients. The other mutations were catalogued as R202Q (14%), M680I (5.9%), E148Q (8.4%) and V726A (12.5%) respectively. The frequency of alleles is specified in Table 2.

Table 2: The frequency of MEFV gene alleles in the studied group

Allele	Number of allele, (n, %)
M694V	36 (26.5%)
R202Q	19 (14%)
M680I	8 (5.9%)
E148Q	11(8.4%)
V726A	17 (12.5%)
Others	44 (32.4%)
Total	135 alleles

MEFV; Mediterranean fever (MEFV) gene

As demonstrated in Table 3, patients who possess the M694V gene mutation present with more severe clinical symptoms, including constipation, fatigue, erysipelas-like erythema, scrotal pain and appendectomy. In contrast, patients who possess the E148Q and V726A gene mutations exhibit milder clinical symptoms. As illustrated in Table 4, M694V demonstrated a correlation with appendectomy, arthritis/arthralgia, and constipation.

Discussion

The present study examined the clinical manifestations and genetic mutational analyses of patients with FMF in the emergency department. The present study corroborates three significant conclusions: Firstly, the most prevalent alleles frequency were identified as M694V (26.5%), R202Q (14%), V726A (12.5%), E148Q (8.4%) and M680I (5.9%); Secondly, the most prevalent symptoms were determined to be abdominal pain, fever, myalgia/arthralgia and fatigue, with prevalence rates of 97.8%, 94.8%, 81.5% and 77%, respectively; Thirdly, the most prevalent mutation observed in conjunction with the clinical findings (appendectomy, arthritis/arthralgia and constipation, in particular) was M694V. In certain studies (4, 5, 15), these five mutations (M694V, M680I, M694I, V726A and E148Q) are responsible for more than 85% of FMF cases. In addition, Coskun et al. (16) evaluated MEFV gene mutations in 1058 pediatric patients and the four most common mutations (M694V (36.50%), E148Q (32.77%), V726A (14.09%), and M694I (4.41%). The results obtained in this study were consistent with those of the aforementioned study. FMF is a disease that progresses in recurrent attacks. Attacks are mostly seen in the form of fever and polyserositis, and ends spontaneously within an average of 2-4 days. There may also be shorter or longer attacks. It has been observed that approximately 50% of patients experience this attack 10 to 30 times per year. Some attacks are severe enough to require an emergency application, while others may progress more mildly. Patients are generally asymptomatic, except for attacks. Acute abdominal pain is one of the most common causes of consultation in the emergency department and is a frequent cause of medical and surgical ambulatory visits (17). Abdominal pain occurs at some point during the lives of more than 90% of FMF patients (14). A plethora of studies have evaluated abdominal pain in FMF patients (2, 11, 14, 17-21). Prior to the diagnosis of FMF, 30–50% of the patients undergo unnecessary surgical interventions such as appendectomy, or cholecystectomy (2, 11, 18). The frequency of appendectomies in FMF patients was documented in a number of studies, with percentages of 16% (20), 19% (5, 18), 26.6% (19), and 39% (11) recorded, respectively. Furthermore, the prevalence of FMF in patients presenting to the emergency department with acute abdominal pain was found to be 2% (2). Furthermore, Kısacık et al. (21) established that FMF were identified in 7.7% of patients with negative appendectomy. In the present study, the most prevalent cause was abdominal pain, with a frequency of appendectomy of 21.48%. FMF may be an important cause of emergency admissions for acute abdominal pain in a country where this disease is common (2). In these patients, secondary causes are more likely than direct consequences of FMF. Potential contributors include; Severe abdominal pain leading to decreased bowel motility, dehydration during attacks, use of analgesics or opioids, chronic subclinical inflammation, or comorbid conditions that may affect gastrointestinal motility. Several studies in the literature showed that M694V is the most common MEFV mutation and confers the severe clinical phenotype (2, 11). As anticipated, M694V was the most prevalent mutation among patients exhibiting associated clinical symptoms in the present study. Furthermore, the correlation between the M694V mutation and appendectomy

Table 3: Frequency of clinical features in MEFV gene mutations

	M694V	M680I	R202Q	E148Q	V726A	OTHERS	p
Age,mean±SD	28,75±7.27	23.5±4.3	31.11±10.9	24.36±46.3	34.65±12.3	23.57±4.9	.021
Disease duration, mean±SD	5.61±3.91	6.5± 4.12	7.42±4.41	6.45±5.97	7.71±5.97	6.71±5.15	.763
Fever (n,%)	36 (100%)	18 (94.7%)	19 (100%)	9 (81.8%)	13 (76.5%)	33 (75%)	.006
Abdominal pain (n,%)	36 (100%)	8 (100%)	19 (100%)	9 (81.8%)	16 (94.1%)	44 (100%)	.022
Chest pain (n,%)	30 (83.3%)	6 (75%)	13 (68.4%)	4 (36.3%)	3 (17.6%)	11 (25%)	.003
Vomiting (n,%)	27 (75%)	4 (50%)	7 (36.8%)	2 (18.2%)	2 (11.7%)	1 (2.2%)	.002
Diarrhea (n,%)	17 (47.2%)	3 (37.5%)	3 (15.8%)	2 (18.2%)	1 (5.9%)	5 (11.4%)	.014
Constipation (n,%)	29 (80.5%)	3 (37.5%)	5 (26.3%)	3 (27.2%)	2 (11.7%)	11 (25%)	.ooo
Fatigue (n,%)	30 (83.3%)	7 (87.5%)	17 (89.5)	10 (90.9%)	12 (70.6%)	28 (63.6%)	.000
Arthritis/ arthralgia (n,%)	29 (80.5%)	6 (75%)	15 (78.9%)	10 (90.9%)	13 (76.5%)	19 (43.2%)	.009
Myalgia (n,%)	22 (61.1%)	8 (100%)	9 (47.4%)	6 (54.5%)	11 (64.7%)	5 (71.4%)	.033
Erysipelas-like erythema (n,%)	26 (72.2%)	4 (50%)	10 (52.6%)	7 (63.6%)	7 (41.2%)	7 (15.9%)	.000
Headache (n,%)	11 (30.6%)	6 (75%)	8 (42.1%)	5 (45.5%)	9 (52.9%)	5 (11.4%)	.005
Scrotal pain (n,%)	4 (11.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4.5%)	.000
Proteinuria/ hematuria (n, %)	16 (44.4%)	1 (12.5%)	2 (10.5%)	1 (9.1%)	1 (5.8%)	1 (2.3%)	.548
Polyneuropath (n,%)	6 (16.7%)	2 (25%)	2 (10.5%)	2 (18.2%)	1 (5.8%)	4 (9.1%)	.005
Appendectomy (n,%)	26 (72.2%)	(0%)	0 (0%)	0 (0%)	0 (0%)	3 (42.9%)	.000
Amyloidosis (n,%)	3 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5.6%)	.401

MEFV; Mediterranean fever (MEFV) gene, $p < 0.001$

was found to be statistically significant. The most significant clinical observation in FMF is the presence of fever. The occurrence of fever is a hallmark feature of almost all FMF patients. Fever is characterised by its recurrent nature, with a typical temperature of >38 °C (100.4 °F), and may reach a maximum of 40 °C. The usual cycle is spontaneous rapidly rising followed by plateau and rapid decrease over a course of 1–3 days (1,7). Fever was the most prevalent symptom, manifesting in approximately 93% to 100% of cases (4, 7, 9). In this study, high-grade fever was observed in 94.8% of patients. Arthralgia and arthritis represent the prevalent manifestation of (FMF) and occur in two-thirds (70%) of patients with FMF (5, 7, 8). As stated in the current studies, the most common joints in our patients were the knee, ankle and wrist joints. Arthritis was seen less frequently . Especially, recurrent arthritis attacks should suggest FMF. A plethora of studies have previously demonstrated that the frequency of arthritis and arthralgia is elevated in patients with M694V mutations (5, 7, 8, 9, 22) . The present study has identified the M694V mutation as a significant predisposing factor for patients with familial Mediterranean fever (FMF). Furthermore, a substantial correlation has been observed between arthritis and arthralgia on the one hand, and the M694V mutation on the other. The aetiology of chest pain is typically attributed to pleuritis and/or pericarditis. The frequency of chest pain in FMF patients varies on average by 25-40%. The pain is characterised as unilateral, with an acute onset and a duration of between one and four days. There is a rapid recovery period. As is the case in other studies (1, 7, 9), the M694V and M680I mutations were the most prevalent in the present patient cohort. The most significant long-term complication is amyloidosis, which can result in renal failure or death (1, 3). In the present study, proteinuria was observed in 22 patients (16.3%), while renal amyloidosis was identified in 5 patients (3.7%). The Turkey FMF Working Group reported that the frequency of amyloidosis was 12.9% (18). Kasifoglu et al. (23) analysed 2246 FMF patients, identifying 193 (8.6%) cases of amyloidosis that were confirmed through biopsy. In recent times, there has been an observed increase in the incidence of extrarenal manifestations of amyloidosis in patients with renal amyloidosis, which is indicative of a prolonged life expectancy, and this is attributable to the advent of biological treatments, dialysis and transplantation. As was the case in the study of the literature, the proteinuria/amyloidosis level was found to be higher in patients with the M694V mutation. However, a significant correlation was not identified between amyloidosis

Table 4: Correlation between clinical features and MEVF gene mutations

	M694V	M680I	R202Q	E148Q	V726A	Others
Fever	.101	.495	.271	.043	.518	.525
Abdominal pain	.291	.660	.478	.198	.273	.682
Chest pain	.452	.882	.561	.278	.189	.361
Vomiting	.002	.907	.353	.525	.462	.123
Diarrhea	.736	.479	.832	.734	.184	.055
Constipation	.001	.534	.673	.089	.048	.625
Fatigue	.294	.468	.164	.254	.499	.575
Arthritis/ arthralgia	.000	.164	.759	.401	.569	.195
Myalgia	.290	.046	.036	.312	.745	.848
Erysipelas-like erythema	.065	.583	.526	.758	.105	.024
Headache	.039	.081	.771	.985	.492	.152
Scrotal pain	.012	.186	.033	.117	.046	.218
Proteinuria/ hematuria	.325	.764	.202	.501	.388	.882
Polyneuropath	.390	.447	.163	.261	.002	.244
Appendectomy	.000	.394	.213	.396	.720	.841
Amyloidosis	.492	.567	.356	.497	.387	.594

MEFV; Mediterranean fever (MEFV) gene, *: $p< 0.001$, **: $p<0.005$

and M694V. M694V has been identified as the most prevalent and pathogenic mutation. It was observed that the M694V mutation was associated with a more severe disease course in comparison to other mutations. From a clinical perspective, the patient is more likely to undergo an appendectomy, demonstrate musculoskeletal involvement, and experience constipation. The pathogenic effect of the E148Q mutation is uncertain. In the E148Q mutation, the clinic becomes more benign and the risk of developing amyloidosis is lower. We did not observe any clinical effects with E148Q. MEFV mutation analysis does not completely solve the problem. There are typical clinical findings and there may be cases where no mutation is detected. Clinical findings are of paramount importance in the diagnosis of the condition. It has been established that a significant proportion of patients diagnosed with FMF exhibit atypical presentations, which can result in difficulties in interpreting the indication for genetic testing. Furthermore, these patients may be asymptomatic despite carrying sequence variants, thereby raising concerns regarding prophylaxis and treatment (3). Despite the negative gene mutation test result in these patients, the presence of mutations that have not yet been detected should be considered, and diagnosis should be made based on the typical clinical presentation. The early recognition of FMF disease by physicians working in emergency units has the potential to prevent unnecessary interventions (2).

Study limitations: The limitations of the present study are as follows: The design of the study was retrospective, and the sample size was relatively small. Secondly, it is important to note that applications related to FMF may have been confused with those of patients who applied to the emergency room for FMF-related reasons, despite these being unrelated. Third, the data pertaining to the patients was retrieved from the relevant documentation and the hospital's registration system. The possibility that some data may not be saved to the file or system indicates the possibility that patient data may be missing. Fourth, genetic mutations of FMF patients were not evaluated in detail (homozygous, heterozygous and compound). Finally, The study was conducted in a single centre, which is a limitation in terms of generalising the results to other centres or patient profiles.

Conclusion

The most prevalent symptoms exhibited by patients suffering from Familial Mediterranean Fever (FMF) when presenting to the emergency department were abdominal pain and fever. The most prevalent mutations observed in FMF patients were M694V, E148Q, R202Q, M680I, and V726A. A statistically significant correlation was identified between appendectomy, arthritis, arthralgia and constipation in patients who possessed M694V mutations. Adherence to FMF treatment guidelines may reduce ED visits, hospitalisation, and healthcare expenditure.

Ethical approval: Ethics Committee permission was obtained from Van Yüzüncü Yıl University Medical Faculty Clinical Research Ethics Committee with the decision number 03 on 13.09.2019.

Conflict of interest: The authors have no conflict of interest regarding this study.

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Author contributions: Concept (MT, MRO), Design (MT, MRO), Data Collection and/or Processing (MT, MRO), Analysis and/or Interpretation (MT, MRO)

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