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THE EVALUATION OF HEALTH STATUS OF FAMILIAL MEDITERRANEAN FEVER PATIENTS WITH HOMOZYGOUS M694V MUTATION

Ayşegül Çakar[1], Lale Saka Baraz[2], Demet Yalçın Kehribar[3], Metin Özgen[4]

[1]Gölcük Necati Çelik State Hospital, Clinic of Internal Medicine, Kocaeli, Türkiye
[2]Manisa City Hospital, Clinic of Internal Medicine, Manisa, Türkiye
[3]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, İzmir, Türkiye
[4]İzmir Ekonomi University, Medical Point Hospital, Department of Rheumatology, İzmir, Türkiye

Abstract

Aim: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent episodes of fever, serositis, and systemic inflammation. The M694V mutation in the *MEFV* gene is associated with a more severe disease phenotype, including early onset, frequent attacks, and an increased risk of amyloidosis. This study aimed to evaluate the clinical features, comorbidities, and treatment outcomes of FMF patients homozygous for the M694V mutation.

Material and Methods: A retrospective analysis was conducted on 183 FMF patients homozygous for the M694V mutation, diagnosed and followed at our hospital between 2014 and 2022. Data on demographics, clinical characteristics, laboratory findings, and treatment modalities were collected.

Results: The most common symptoms were abdominal pain (88%), joint pain (78%), and arthritis (46%). Proteinuria and amyloidosis were detected in 22.4% and 7.1% of patients, respectively. The average age of symptom onset was 14.1 years, with a mean annual attack frequency of 2.75. Comorbidities were present in 24% of patients, including spondyloarthritis and inflammatory bowel disease. Colchicine was the mainstay treatment (94.5%), while 21.8% required IL-1 inhibitors. Eight patients (4.4%) died during follow-up, five due to amyloidosis-related complications.

Conclusion: M694V homozygous FMF patients exhibit a severe disease presentation associated with this variant with frequent attacks, high amyloidosis risk, and significant comorbidities. While colchicine remains essential, biologics are increasingly used for colchicine-resistant cases. Early diagnosis, individualized treatment, and regular monitoring are crucial to improving patient outcomes.

Keywords: Familial Mediterranean fever, M694V, homozygous, phenotype, genotype

Address for Correspondence: Lale Saka Baraz, MD, Manisa City Hospital, Clinic of Internal Medicine, Manisa, Türkiye
E-mail: lalesaka-6@hotmail.com **ORCID ID:** orcid.org/0000-0003-4387-6929
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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder characterized by recurrent episodes of fever, serositis, and systemic inflammation. It is predominantly observed in populations of the Mediterranean basin, including Turks, Armenians, Arabs, and Jews, where its prevalence can reach as high as 1 in 200 to 1 in 1,000 individuals (1). The disease is caused by mutations in the *MEFV* gene, which encodes pyrin, a protein involved in regulating the inflammatory response (2).

Among the more than 300 identified variants in the *MEFV* gene, M694V is the most extensively studied and clinically significant variant. Homozygosity for the M694V mutation has been consistently associated with a more severe disease phenotype, including early onset, higher frequency of attacks, and increased risk of amyloidosis, a life-threatening complication of FMF (3,4). Despite recognizing its clinical importance, the full spectrum of manifestations in M694V homozygous individuals remains underexplored, particularly in diverse populations.

Recent advances in understanding the molecular mechanisms of FMF have underscored the role of pyrin in inflammasome activation and interleukin (IL)-1β secretion, linking specific *MEFV* mutations to distinct inflammatory profiles (5). This genotype-phenotype correlation is pivotal for tailoring therapeutic strategies, particularly the use of colchicine and emerging biologics such as IL-1 inhibitors (6). However, the variability in clinical presentations even among individuals with the same genotype suggests the involvement of additional genetic, epigenetic, and environmental factors (7-11).

The present study aims to comprehensively evaluate the clinical characteristics of M694V homozygous FMF patients, providing insights into the phenotypic diversity and potential modifiers of disease expression. By systematically analyzing a cohort of these individuals, we seek to identify patterns that may enhance diagnostic accuracy and guide personalized treatment approaches.

MATERIAL AND METHODS

Design and Patient Enrollment

This study was conducted retrospectively. Patients diagnosed with FMF and carrying the M694V homozygous mutation who were admitted for diagnosis and/or follow-up to our rheumatology department between January 2014 and December 2023 were retrospectively analyzed. The diagnosis of FMF was established using the Eurofever/PRINTO classification criteria (11). Approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (approval number: 2023/207, date: 28.08.2023). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, and their confidentiality was maintained throughout the study.

Patient data were accessed using our university hospital information system "MIA" and telephone interviews. A total of 183 patients aged 18 years and older were included in the study. Data on patient demographics, clinical histories (hospital and outpatient records), laboratory results, and medication reports were reviewed.

Patient Selection and Data Collection

While determining clinical and demographic characteristics, the entire cohort of 183 patients was considered. The analyzed variables included age, age at symptom onset, age at diagnosis, gender, genotype, initial attack frequency, family history of FMF, the presence of FMF-related complications such as proteinuria and amyloidosis, symptoms including abdominal pain, chest pain, joint pain, arthritis, erysipelas-like erythema, calf pain, associated diseases, colchicine therapy, biological agent use, and comorbid conditions. Based on established clinical guidelines, proteinuria was defined as urinary protein excretion of 500 mg/day or higher. The inclusion criteria were a diagnosis of FMF, being over 18 years old, and having the M694V homozygous mutation. Patients with insufficient data records, malignancies, or chronic infections were not included in the study. Colchicine resistance is defined according to the 2016 European Alliance of Associations for Rheumatology recommendations, as the persistence of one or more attacks per month despite adherence to an adequate dose of colchicine for at least six months, or the presence of ongoing subclinical inflammation (elevated C-reactive protein or serum amyloid A) between attacks.

Statistical Analysis

IBM SPSS Statistics 25.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for data analysis. Continuous variables are reported as mean ± standard deviation, while categorical data, including demographic and clinical characteristics, are expressed as frequencies and percentages. The Student's t-test was applied to variables with a normal distribution when making comparisons between genders. Statistical significance was defined as a p-value of less than 0.05 across all analyses.

RESULTS

Clinical Features

Among 183 patients with M694V homozygous mutation and a diagnosis of FMF, the most common symptom was abdominal pain, reported by 147 patients (88%). Other symptoms included

joint pain (78%), arthritis (46%), chest pain (33.3%), erysipelas-like lesions (32%), and calf pain (28%). Proteinuria and amyloidosis were detected in 22.4% and 7.1% of patients, respectively. In the study, the mean follow-up duration was 13.3±9.7 years (min 2 years-max 48 years) and the median age at death was 48 years (min 19 years-max 64 years). Detailed clinical findings are summarized in Table 1.

Ages of Symptom Onset and Diagnosis

In this cohort, the reported age of symptom onset was 14.1±11.2 years, and the age of diagnosis was 20.0±14.1 years. The mean time interval from symptom onset to diagnosis was 5.9±4.8 years. In this cohort, the mean age of symptom onset was 12.9 years in females and 8.5 years in males (p=0.146). Similarly, the mean age of diagnosis was 21.0 years in females and 19.1 years in males (p=0.364).

Attack Frequency

The average annual attack frequency for FMF-diagnosed patients with the M694V homozygous mutation is approximately 2.75 attacks per year; among them, 44.3% reported no attacks. The maximum recorded attack frequency was 24 attacks per year in two patients. Approximately 12% of the patients currently report having an attack frequency of more than once per month. There was no significant difference in attack frequency between genders (p=0.442).

Family History

A total of 123 patients reported having a first-degree relative with FMF.

Comorbid Conditions

Comorbidities were observed in 24% (45) of patients, though the percentage of each comorbid disease observed is separately detailed elsewhere. The most common accompanying disease are: spondyloarthritis (n=17), rheumatoid arthritis (n=7), Behçet's disease (n=5), systemic lupus erythematosus (n=3), inflammatory bowel disease (n=2), and others. Seven patients also had a history of acute rheumatic fever.

Table 1. Clinical findings of FMF-diagnosed patients with M694V homozygous mutation (n=168)

Clinical finding	Present (n)
Abdominal pain	147 (88%)
Chest pain	65 (39%)
Arthralgia	131 (78%)
Arthritis	78 (46%)
Erysipelas-like erythema	53 (32%)
Calf pain	47 (28%)
Amyloidosis	13 (8%)
Proteinuria	41 (24%)
FMF: Familial Mediterranean fever	

Diagnosis and Treatment

The majority of diagnoses were based on clinical symptoms supported by genetic testing. Among 177 patients with available data, 94.5% were on colchicine treatment. Biological agents, particularly IL-1 antagonists (21.8%) and tumor necrosis factor-α inhibitors (3.7%), were used in patients with additional inflammatory or autoimmune conditions.

Surgical History

Surgical interventions were documented in 17.5% of patients, including appendectomies (14.7%), cholecystectomies (1.6%), and splenectomies (1.6%).

Mortality

Eight patients (4.4%) died during follow-up. Among them, five had amyloidosis. Causes of death included complications related to amyloidosis, renal failure, infection, and malignancy. Four patients had undergone renal transplantation.

DISCUSSION

FMF is a prototype autoinflammatory disorder resulting from mutations in the *MEFV* gene. This study evaluates the clinical characteristics of patients who are homozygous for the M694V mutation, one of the most severe and clinically significant variants of *MEFV* responsible for FMF. The study provides valuable insights into the phenotype-genotype relationship and the challenges associated with the treatment of these patients by examining key clinical features, comorbidities, and treatment patterns. In this M694V homozygous cohort, abdominal pain (88%) and joint pain (78%) emerge as the primary symptoms, consistent with previous studies highlighting these features as prominent signs of FMF (12). The high prevalence of erysipelas-like erythema (32%) and calf pain (28%) in the dermatologic and musculoskeletal systems, indicates the significance of these symptoms in the disease spectrum, especially in M694V homozygous patients (1). Early symptom onset (mean age: 14.1 years) and late diagnosis (mean age: 20.0 years) emphasize the disease burden due to delays in diagnosis (13).

In this study, the annual attack frequency in M694V homozygous FMF patients was 2.75 attacks per year on average, with considerable variability observed among patients. Nearly half of the patients in the M694V homozygous cohort reported

no attacks, while a small subgroup experienced frequent recurrences (>12 attacks/year), suggesting suboptimal disease control or colchicine resistance (14). These findings are in line with reports linking M694V homozygosity to more severe disease and frequent, intense inflammatory episodes (15). Additionally, the significant variability in attack frequency among patients with the same genotype provides valuable insight into the genotype-phenotype relationship. The reason why some patients with the same genetic mutation experience no attacks while others have frequent attacks remains unclear, highlighting the need for further research. It is evident that factors beyond the *MEFV* gene influence disease activity. Additional studies are required to better understand the genotype-phenotype correlation in FMF.

A serious complication of FMF, amyloidosis, was detected in 7% of M694V homozygous patients, consistent with global estimates for untreated or inadequately managed FMF cases (16). Proteinuria was observed in 22.4% of patients, emphasizing the importance of routine kidney monitoring in this population. These findings reflect the known relationship between M694V homozygosity and an increased risk of amyloidosis, due to persistent subclinical inflammation and inadequate control of the IL-1β pathway (17). Early initiation of colchicine therapy significantly reduces the risk of amyloidosis; however, even in treated patients, amyloidosis may persist, highlighting the need for alternative treatments in colchicine-resistant cases (18).

In the M694V homozygous FMF cohort, 21.8% of patients used biological agents, particularly IL-1 inhibitors, reflecting the increased awareness of colchicine resistance. These agents have shown promising results in managing refractory cases, particularly in reducing attack frequency and preventing amyloidosis (19). However, barriers such as treatment costs, accessibility, and potential side effects limit their widespread use. Overcoming these barriers requires cost-effectiveness studies and patient education programs (20).

This study also identified a high prevalence of comorbidities at 24%, including ankylosing spondylitis, systemic lupus erythematosus, and inflammatory bowel disease, among other autoinflammatory and autoimmune disorders. This underscores the genetic susceptibility and shared inflammatory pathways between FMF and other immune-mediated diseases (21). These comorbidities often complicate treatment and highlight the need for comprehensive, individualized treatment approaches (22). Additionally, no significant differences were found between sexes in terms of attack frequency, symptom onset age, or diagnosis age, indicating that disease expression is generally similar in both males and females (23). However, the observed variability in clinical presentations even among patients with the same genotype supports the role of epigenetic and environmental factors in modulating FMF phenotypes (24-27). These findings emphasize the importance of studying these regulators to better understand disease heterogeneity and improve prognostic accuracy.

Study Limitations

Several limitations should be considered when interpreting these findings. First, the retrospective design may introduce selection bias, and there may be missing information in patient records and interviews. Second, the single-center study design limits the generalizability of the findings to larger populations. Another limitation is the lack of a comparison non-homozygous M694V group, which could have provided clearer insight into the effects of the homozygous M694V mutation on disease phenotype and facilitated a deeper understanding of the genotype-phenotype relationship. The clinical features of arthritis were not evaluated, which is also a limitation of our study.

CONCLUSION

This study comprehensively evaluated the clinical characteristics, comorbidities, and treatment outcomes of M694V homozygous FMF patients. The findings highlight the severe disease phenotype associated with this genotype, characterized by frequent attacks, early symptom onset, and a high-risk of amyloidosis. While colchicine remains the cornerstone of FMF management, the increasing use of IL-1 inhibitors underscores the need for personalized treatment strategies to address colchicine resistance and refractory cases.

Key takeaways from this study include the significant variability in symptom presentation and attack frequency among patients with shared genetic profiles, in FMF. This highlights the critical role of additional genetic, epigenetic, and environmental factors in modulating FMF expression. Furthermore, despite the higher use of biological treatments in M694V homozygous FMF patients, the high prevalence of comorbidities emphasizes the need for treatment and monitoring approaches tailored to the mutation status of these patients.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (approval number: 2023/207, date: 28.08.2023). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ç., D.Y.K., M.Ö., Concept: A.Ç., D.Y.K., Design: A.Ç., D.Y.K., M.Ö., Data Collection or Processing: A.Ç., D.Y.K., Analysis or Interpretation: A.Ç., L.S.B., M.Ö., Literature Search: A.Ç., D.Y.K., M.Ö., Writing: A.Ç., L.S.B., D.Y.K., M.Ö.

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