Frequency distribution of valvular heart involvement in children under 16 years of age with familial Mediterranean fever: a genotype-based analysis

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Abstract:

Background and Objective: Considering the genetic heterogeneity of FMF and its diverse clinical manifestations, it is necessary to investigate the frequency distribution of heart valve involvement based on different MEFV genotypes. This study aims to fill the gap in knowledge about the cardiovascular burden of FMF in children, particularly focusing on how different genotypes affect the prevalence and type of valvular heart disease.

Methods: In this study, a cross-section of 40 children under 16 years of age with Mediterranean fever, echocardiographic parameters of the patients: Myocardial performance index, pulmonary hypertension, ejection fraction, changes in heart valves, pericardial effusion and changes in the great vessels of the heart, left ventricle mass ,, was investigated. SPSS software version 27 was used for data analysis.

Results: mild tricuspid regurgitation was observed in 2 cases (5%) of patients and mild pulmonary insufficiency was observed in 3 cases (7.5%) of patients. Analysis of available data showed that heart valve involvement has a significant and strong relationship with E148Q genotype (P=0.002 and r=0.635).

Conclusion: Our study highlights a significant and strong association between E148Q genotype and heart valve involvement in children under 16 years of age with FMF. These findings emphasize the importance of genetic factors in the cardiovascular manifestations of FMF and the need for genotype-specific clinical management.

***Keywords:** familial Mediterranean fever, genotype, MEFV, heart valve involvement, E148Q*

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Background and Objective

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disorder that primarily affects populations in the Mediterranean region, including Jews, Armenians, Turks, and Arabs.[1] FMF is characterized by recurrent episodes of fever, serositis (inflammation of serous membranes), and arthritis.[2] If inadequately managed, it can lead to severe complications. The disease is predominantly caused by mutations in the *MEFV* gene, which encodes pyrin, a protein involved in the regulation of inflammation. Mutations in this gene result in uncontrolled inflammation, leading to the clinical manifestations of FMF.[3,4]

The *MEFV* gene, located on the short arm of chromosome 16, is highly polymorphic, with over 300 identified mutations. However, five mutations account for the majority of FMF cases: M694V, M680I, V726A, E148Q, and M694I. These mutations vary in frequency and clinical severity.[5] Notably, the M694V mutation is associated with a severe phenotype characterized by frequent and intense inflammatory attacks and a higher risk of secondary amyloidosis. The genotype of an individual significantly influences the clinical manifestations, severity, and treatment response in FMF.[6]

FMF is not limited to periodic fever and serositis. It also has significant cardiovascular implications.[7] Chronic inflammation, a hallmark of FMF, is a recognized risk factor for various cardiovascular diseases, including atherosclerosis, myocarditis, and pericarditis.[8] In recent years, there has been growing interest in the potential involvement of heart valves in FMF patients.[9] Valvular heart disease, including conditions such as tricuspid insufficiency, mitral valve prolapse, and aortic regurgitation, can significantly impact the prognosis and quality of life of FMF patients, particularly in children who are still in their developmental years.[7]

Children with FMF represent a unique subset of the FMF population. Disease onset during childhood can affect a child's growth and development.[5] Understanding the frequency and nature of valvular heart involvement in these patients is crucial for early diagnosis and intervention. The association between specific *MEFV* gene mutations and the risk of valvular heart disease remains an active area of research. Previous studies have suggested that certain mutations may predispose individuals to specific types of cardiac involvement, but comprehensive data in pediatric populations remain limited.[10]

Earlier studies have reported varying degrees of cardiac involvement in FMF patients, with some focusing on myocardial function and others on pericardial and valvular abnormalities.[4] For instance, a study by Muraru et al. (2002) found that FMF patients with the M694V mutation had higher levels of inflammatory markers and a greater risk of cardiac involvement compared to other mutations.[11] Similarly, research by AbdelAziz et al. (1996) highlighted the severity of clinical manifestations in M694V homozygous patients, including an increased prevalence of amyloidosis and related cardiac complications.[12]

In the context of valvular heart disease, studies have reported differing findings.[9] A study by Arslanoglu et al. (2009) pointed to an increased prevalence of mitral valve prolapse in FMF patients,[13] while another study by Vampertzi et al. (2004) identified a higher incidence of aortic regurgitation in this population.[14] However, these studies often involved adult patients, and data specific to pediatric populations remain scarce.[6]

The pathophysiology of cardiac involvement in FMF is complex and multifactorial. Chronic inflammation plays a central role, leading to endothelial dysfunction, increased vascular permeability, and subsequent cardiac tissue remodeling. Overproduction of pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) can directly damage cardiac tissues, resulting in fibrosis and valvular abnormalities.[15] Genetic factors further modulate these inflammatory

responses, with specific *MEFV* mutations being associated with more severe inflammatory phenotypes.[11]

Identifying specific genotype patterns of valvular cardiac involvement in pediatric FMF patients can enhance clinical decision-making. For instance, children with the M694V mutation may benefit from more intensive cardiac monitoring and early intervention strategies to mitigate the risk of myocardial dysfunction.[12] Conversely, patients with non-M694V mutations may require focused screening for valvular abnormalities and appropriate management to prevent long-term complications.[14]

Given the genetic heterogeneity of FMF and its diverse clinical manifestations, it is essential to examine the distribution of valvular heart involvement based on different *MEFV* genotypes. This study aims to address the knowledge gap regarding the cardiovascular burden of FMF in children, specifically focusing on how different genotypes influence the prevalence and type of valvular heart disease. By elucidating these relationships, we hope to improve the clinical management and prognosis of pediatric FMF patients. The primary objective of this study is to determine the frequency distribution of valvular heart involvement in children under 16 years of age with FMF, categorized based on their specific *MEFV* genotypes.

Methods

Study Design

This study was conducted as a descriptive cross-sectional study after obtaining ethical approval from the Ethics Committee of Ardabil University of Medical Sciences. It included children under the age of 16 diagnosed with Familial Mediterranean Fever (FMF) who visited Kosar Clinic, affiliated with Ardabil University of Medical Sciences, from the beginning of April 2022 to the end of March 2023. Patients were enrolled based on specified inclusion and exclusion criteria.

Eligibility Criteria

The inclusion criteria were as follows: children under 16 years of age, a confirmed diagnosis of FMF based on relevant laboratory tests and verification by a pediatric rheumatologist, consent to participate in the study, and genetic testing to determine FMF genotype. The exclusion criteria were congenital heart diseases, a history of cardiac surgeries during infancy, vascular anomalies, ongoing treatment for pulmonary disorders, and immunocompromised conditions.

Sampling

Due to the limited number of FMF cases in children under 16, the census sampling method was employed to maximize sample size. During the specified time frame, 40 eligible patients were referred to Kosar Clinic and were enrolled in the study after meeting the inclusion and exclusion criteria.

Procedure

In the first step, a data collection form, including a checklist and questionnaire, was designed based on the study objectives. In the second step, the required information was gathered for each patient, including age, sex, height, disease duration, type of medication used, regular colchicine usage, other disease manifestations, and laboratory findings. Echocardiographic parameters of the patients were also assessed. Standard transthoracic echocardiography (TTE) was performed using M-mode, 2D, tissue Doppler imaging (TDI), and pulsed Doppler techniques. TDI is essential for evaluating diastolic ventricular function. Left ventricular diameters, including left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD), were measured in the parasternal long-axis view to calculate LVEF (left ventricular ejection fraction) and LVSF (left ventricular shortening fraction). Abnormal values were defined as LVEF ≤ 54% and LVSF ≤ 28%. Normal LVEF and LVSF ranges were considered 54–75% and 28–38%, respectively. TDI was used to evaluate myocardial longitudinal movement during systolic and diastolic phases of the left ventricle. Pulsed Doppler was utilized to measure diastolic blood flow velocity alongside TDI. In the apical four-chamber

view, pulsed Doppler recorded the E-wave velocity (early diastolic filling) and A-wave velocity (atrial contraction). A normal E/A ratio of 1–3 was considered. TDI measured myocardial fiber velocity in longitudinal motion during systole and diastole in the apical four-chamber view. Sample volume placement on the septal side of the mitral valve allowed measurements of ė (early diastolic velocity), ȧ (late diastolic velocity), and ś (systolic velocity). The E/ė ratio was calculated to estimate left ventricular filling pressure, with E/ė > 14 considered a sensitive non-invasive echocardiographic marker for increased left ventricular filling pressure. An ė ≤ 8 cm/s indicated left ventricular diastolic dysfunction. The myocardial performance index (MPI) was calculated as a sensitive measure of systolic and diastolic dysfunction of the left ventricle. TDI-derived MPI was calculated by dividing the sum of isovolumic contraction time and isovolumic relaxation time by ejection time, using the sample volume positioned at the septal mitral annulus in the apical four-chamber view. Normal MPI values for the left ventricle are 0.35 ± 0.03 in children and 0.39 ± 0.05 in adults.

Statistical Analysis

The collected data were analyzed using SPSS version 27. Quantitative variables were described using mean and standard deviation, while qualitative variables were summarized as frequencies and percentages. Pearson correlation was employed to assess the association between genotype and valvular involvement. A P-value < 0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the Ethics Committee of Ardabil University of Medical Sciences. Following the approval and coordination with Kosar Clinic authorities, sampling commenced. The study objectives were explained to the patients and their parents, and informed consent forms were signed by the parents. No costs were incurred by patients for cardiac evaluations. All data were collected with utmost honesty and confidentiality.

Results

In this study, 40 patients diagnosed with Familial Mediterranean Fever (FMF) were evaluated, with a mean age of 11.23 ± 1.3 years (range: 3–16 years). Of the participants, 58% (23 patients) were male, and 42% (17 patients) were female. All patients were on colchicine therapy. Genetic analysis revealed the presence of the M694V genotype in 45% (18 patients). Additionally, M680I was found in 11 patients, V726A in 3 patients, E148Q in 5 patients, and M694I in 3 patients. Two patients had no identifiable genetic mutations (Figure 1).

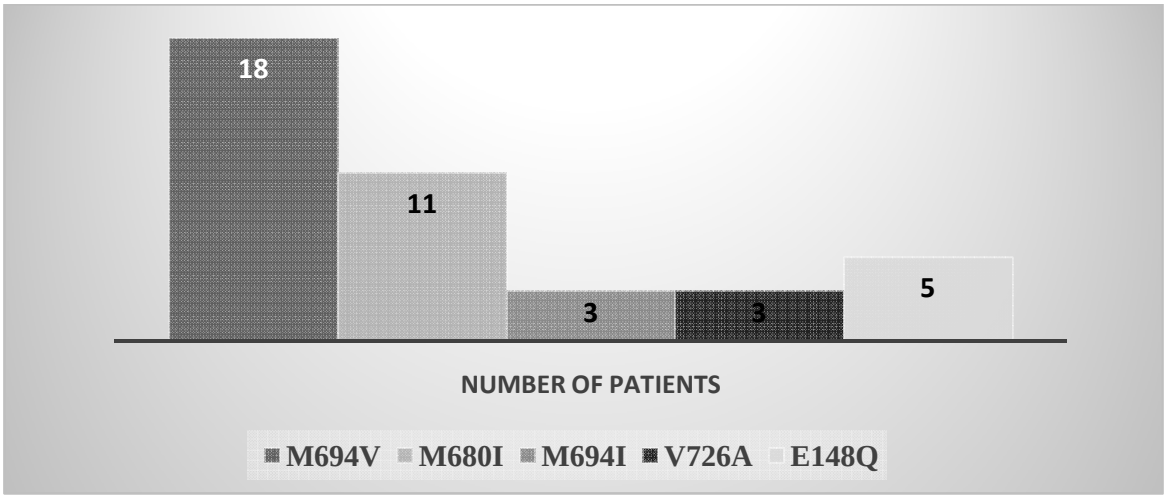

Figure 1: Frequency distribution of genetic mutations in children with Familial Mediterranean Fever.

Table 1: Clinical and laboratory characteristics of patients.

Variable	*Minimum*	*Maximum*	*Mean ± SD*
Weight (kg)	*13*	*85*	*43 ± 12.06*
Height (cm)	*100*	*180*	*139.43 ± 26.54*
LVEF (%)	*57.11*	*74.11*	*66.89 ± 5.9*
LVSF (%)	*27.12*	*39.05*	*36.74 ± 5.007*
MPI-TDI	*0.14*	*0.41*	*0.31 ± 0.09*
Ea (cm/s)	*11.84*	*30.21*	*-16.73 ± 7.73*
Aa (cm/s)	*6.24*	*20.6*	*9.92 ± 4.42*
Sa (cm/s)	*7.52*	*18.35*	*12.26 ± 3.1*
E/A (ratio)	*1.16*	*3.43*	*0.16 ± 0.005*
E/ė (ratio)	*2.99*	*8.86*	*4.53 ± 1.17*

In 82.5% (33 patients), Tei index values obtained via echocardiography were within the normal range (0.35 ± 0.03). However, 17.5% (7 patients) exhibited Tei index values > 0.38. The mean left ventricular ejection fraction (LVEF), within the normal range of 54%–75%, was 66.86 ± 5.9%. The left ventricular shortening fraction (LVSF), typically between 28% and 38%, averaged 36.74 ± 5.007% in this study. Pulsed Doppler assessments of mitral valve flow velocities were normal in all patients, with E-wave and A-wave velocities within the standard ranges. Tissue Doppler imaging (TDI) showed normal velocities during early and late diastolic phases. Tricuspid annulus velocities were above 17 cm/s in all patients, consistent with normal findings (Table 1).

Mild tricuspid regurgitation (MTR) was observed in 2 cases (5%), and mild pulmonary insufficiency (MPI) was noted in 3 cases (7.5%). Statistical analysis showed a significant association between cardiac valve involvement and the E148Q genotype (P = 0.002).

Table 2: Distribution of cardiac valve abnormalities by genotype.

Genotype	*MTR(%)*	*MPI(%)*
M694V (18 patients)	*1 (0%)*	*0 (0%)*
M680I (11 patients)	*0 (0%)*	*0 (0%)*
V726A (3 patients)	*0 (0%)*	*0 (0%)*
E148Q (5 patients)	*1 (0%)*	*4 (0%)*
M694I (3 patients)	*0 (0%)*	*0 (0%)*
No genetic mutation(2patients)	*0 (0%)*	*0 (0%)*

MTR: Mild Tricuspid Regurgitation;
MPI: Mild Pulmonary Insufficiency

Discussion

Our study examined the distribution and frequency of valvular heart involvement in children under 16 years of age diagnosed with Familial Mediterranean Fever (FMF), with a focus on their genotype. Among the 40 children evaluated, mild tricuspid regurgitation was observed in 2 patients (5%), and mild pulmonary regurgitation in 3 patients (7.5%). Our analysis revealed a significant and strong association between valvular heart involvement and the E148Q genotype.

The prevalence of valvular heart involvement observed in our study is consistent with previous research findings, though the focus on pediatric populations and genotype-specific analyses provides novel insights. For example, Yiğit et al. (2002) [11] and AbdelAziz et al. (1996)[12] documented various cardiac manifestations in FMF patients, primarily in adult cohorts. These studies highlighted the increased cardiovascular risks in FMF due to chronic inflammation. However, our study uniquely contributes by focusing on younger populations and identifying a robust correlation between the E148Q genotype and valvular heart disease.

In contrast, Romano et al. (2004)[13] identified a higher prevalence of aortic regurgitation in FMF patients, though their study did not specifically examine pediatric cases or genotype-specific correlations. Similarly, Arslanoglu et al. (2009)[17] reported an increased incidence of mitral valve prolapse but emphasized adult patients. Therefore, our findings expand the understanding of cardiac involvement in FMF in pediatric populations and underscore the importance of genetic factors in these manifestations.

The pathophysiology of valvular heart disease in FMF is complex and multifaceted, primarily driven by chronic inflammation. Mutations in the MEFV gene associated with FMF, including E148Q, lead to dysregulated production of pyrin, a protein playing a critical role in the innate immune response.

Pyrin mutations result in overactivation of the inflammasome, a multiprotein

complex responsible for the activation of pro-inflammatory cytokines such as interleukin-1β (IL-1β).[1-3]

Chronic overproduction of IL-1β and other pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), leads to systemic inflammation, which can extend to the cardiovascular system.[17] This sustained inflammatory state causes endothelial dysfunction, increased vascular permeability, and the development of fibrotic changes in cardiac tissues. As observed in our study, these alterations can manifest as valvular heart disease, including tricuspid regurgitation and pulmonary regurgitation.[18]

A key finding of our study is the strong association between the E148Q genotype and valvular heart involvement. Although the E148Q mutation is generally not as strongly associated with severe FMF phenotypes as M694V, it appears to have a significant impact on cardiac involvement. This may be due to specific mechanisms by which different pyrin mutations influence inflammatory activity and cytokine production. The E148Q mutation may create a pro-inflammatory environment particularly affecting cardiac valves, contributing to the observed valvular lesions.[19]

Identifying genotype-specific cardiovascular risks in pediatric FMF patients has important clinical implications. For children with the E148Q genotype, our findings suggest the need for closer cardiovascular monitoring and early intervention strategies. Regular echocardiographic evaluations can help detect valvular abnormalities at an early stage, allowing timely management to prevent progression to more severe cardiac complications.

Furthermore, these findings highlight the importance of genetic testing in FMF patients. Identifying specific MEFV mutations can enable clinicians to better predict potential cardiovascular risks and tailor their management approaches accordingly. This personalized approach can improve patient outcomes and enhance the quality of life for children with FMF.[20]

Previous genetic studies have primarily focused on the M694V mutation due to its strong association with severe FMF phenotypes and amyloidosis. However, our study emphasizes the significant role of the E148Q mutation in valvular heart disease. This contrast with earlier findings suggests that different MEFV mutations may have distinct pathogenic mechanisms, warranting further research to elucidate these differences.[6-11]

Our study was conducted as a single-center investigation and suffered from a limited sample size due to time constraints. Future research should aim to replicate our findings in larger, multicenter cohorts to confirm the observed genotype-specific associations and further explore the underlying mechanisms. Longitudinal studies could provide insights into the progression of valvular heart disease in FMF patients and the long-term impact of different MEFV mutations. Additionally, evaluating the potential benefits of targeted anti-inflammatory treatments, such as IL-1 inhibitors, in preventing or mitigating cardiac involvement in FMF could be highly valuable.

Conclusion

Our study highlights a significant association between the E148Q genotype and valvular heart involvement in children under 16 years of age with FMF. These findings underscore the importance of genetic factors in the cardiovascular manifestations of FMF and the need for genotype-specific clinical management. By improving our understanding of the genetic basis of valvular heart disease in FMF, we can enhance patient care and outcomes in this vulnerable population.

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