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Cardiac functions and pericardial thickness changes in familial Mediterranean fever patients

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Abstract

Background The goal of the study is to ascertain how the pericardium and heart functions alter in patients with familial Mediterranean fever (FMF) both during the acute phase and the period of subclinical inflammation.

Methods During the study, 99 patients diagnosed with FMF (35 of whom were in an FMF attack period) were recruited to this study, and 24 completely healthy children in the same age group—who did not have FMF and had not any cardiac condition that applied to visit the pediatric cardiology outpatient clinic for routine follow-up—were included as the control group.

Results In patients with FMF, there was no discernible relationship between genetic abnormalities and pericardial thickness ($p > 0.05$). A significant difference was not observed in the diastolic and systolic cardiac function values between the control group and the FMF patients, with the exception of the parameters related to ejection time (ET), contraction time (IVCT), and relaxation time (IVRT). It was observed that pericardial thickness was greater in FMF patients than in study participants who did not have FMF, and this difference is statistically significant ($p < 0.05$).

Conclusions It was determined that the effects of cardiac inflammation continued in children with FMF, even if they were asymptomatic. Therefore, it should be part of the follow-ups.

Key points

- In our study, cardiac functions and pericardial thickening of 99 FMF patients with and without attack were prospectively investigated.
- In ongoing follow-up of patients with FMF, we found that inflammation, which affects all serosas, also affects the pericardium during the attract and nonattack phase.
- We believe that cardiac functions, including the status of the pericardium, should be monitored as part of the long-term follow-up of FMF.

Keywords Children, FMF, Cardiac functions, Pericardial involvement

Background

The autosomal recessive autoinflammatory illness known as familial Mediterranean fever (FMF) is characterized by recurring episodes of fever, joint pain, abdominal pain, and chest pain. FMF is prevalent in Mediterranean-bordering nations and primarily affects Jews, Turks, Arabs, and Armenians. The FMF mutation carrier rate is reported to be 1:4.3 in Arabs, 1:3.5 in Jews, and 1:5 in Armenians, North Africa, Iraq, and Turkey [1–3].

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Debilitating serositis attacks is the primary symptom of FMF, and even when there is no attack, inflammation may still be present [1]. According to recent research, a mutation in the Mediterranean fever (MEFV) gene on its 16th chromosome causes FMF disease [3]. This gene produces the inflammatory protein pyrin, also known as marenostrin. This protein's mutation prevents both apoptosis and the suppression of inflammation [4, 5].

Endothelial dysfunction resulting from inflammation and thickening of the intima-media is critical risk factors for the early detection of atherosclerosis and other cardiovascular diseases [6, 7]. Conduction disorders, rhythm anomalies, pericarditis, and pericardial effusion may develop as comorbidities in FMF patients due to cardiovascular system involvement. It has also been reported that FMF increases carotid intima thickness, causes left ventricular diastolic dysfunction, and is linked to atherosclerosis [5, 6]. This study was conducted to determine the changes in cardiac function and pericardial involvement in patients with FMF during periods with attacks and without attacks.

Methods

Patients who applied to the Pediatric Rheumatology Polyclinic were the participants of this study. Ninety-nine patients diagnosed with FMF (35 of whom were in an FMF attack period) were recruited to this study during their follow-up, and 24 completely healthy children in the same age group—who did not have FMF and had applied to the Pediatric Cardiology Outpatient Clinic for routine follow-up—were included as the group with control.

The treatment plan, demographic data, and clinical and laboratory analyses (including fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complete blood count) were documented for each participant. By evaluating FMF patients, it is possible to determine how their cardiac functions change during an FMF attack and the proportion of FMF cases with pericardial involvement. Furthermore, pericardial involvement can be determined by comparing the pericardial thickness of FMF patients (both during the attack and non-attack periods) with that of the control group.

Inclusion criteria are as follows:

- Patients with AAA diagnosed by the Tel Hashomer and Ankara criteria
- Patients with FMF during the not attack phase.
- The family authorizes you to work.

Exclusion criteria are as follows:

- The study did not include patients who could not obtain a conclusive diagnosis.

Control group

- The control group consisted of children in the same age range who were admitted to the Pediatric Cardiology Outpatient Clinic for routine follow-up, were in perfect health, and did not have a chronic illness.

Based on the Ankara and Tel Hashomer criteria, FMF was diagnosed among the study's patients [8–11]. The study was conducted prospectively, and approval was obtained from the Rectorate Non-Interventional Research Ethics Committee (Date: 19 November 2014, Decision 63684) before starting the study.

The same pediatric cardiologist examined the cardiovascular systems and assessed the ECG and ECHO recordings of all patients in the FMF and control groups. After the child had rested for 10 min and the room temperature was between 20 and 23°, an ECG recording was performed using a "Trismed Cardipia 400 brand" 6/12 channel monitor ECG equipment, while the child was in the supine position. As per usual practice, electrodes were positioned in their anatomical placements. An ordinary ECG assessment was carried out. As axis calculations, we assessed R-R distance, rhythm, QRS voltage, T-wave measurements, P distance, PR interval, S-T change, QRS interval, and QT interval. After a typical ECG assessment, QTc, or heart rate-corrected QT time, was computed. Every measurement was done by hand. The distance between the isoelectric line and the start of the Q wave was determined to be the QT interval. The modified Bazett formula was utilized to compute the corrected QT (QTc).

Before and after the assault, an echocardiogram was taken utilizing a GE medical imaging system, which included a Vivid 7 Pro ECO equipment with a 3-MHz probe. The American Society of Echocardiography's M-mode standardization committee's recommendations were followed for taking M-mode echocardiographic measurements. When the cursor was at the level of the left ventricle's mitral valve, M-mode measurements were taken in the parasternal long-axis window [12]. Ejection fraction (EF), fractional shortening (FS), interventricular septal thickness at end-diastole (IVSd) and end-systole (IVSs), left ventricular posterior wall thicknesses at end-diastole (LVPWd) and in systole (LVPWs), cardiac mass (LVPdMass), E wave (premature filling of the left ventricle), A wave, E/A wave ratios, IVRT (isovolumetric relaxation time), IVCT (isovolumetric contraction time), ET (ejection time), DT (deceleration time), pericardial thickness, and amount of pericardial effusion were assessed and recorded [13].

Utilizing a transthoracic M-mode ECHO, left posterior ventricular wall pericardial effusion and pericardial

thickness—calculated as the mean of three assessments made by the same pediatric cardiologist—were assessed using M-mode measures in the parasternal long-axis window [14–16].

Statistical analysis

For this study's data analysis, a computer environment running version 16.0 of the Statistical Package for Social Sciences statistical program (SPSS) for Windows was utilized. The number of cases (%) for nominal variables, the mean ± standard deviation, and the median (lowest-highest) values for non-normally distributed continuous variables are displayed for data that is normally distributed. Means were compared using the Student's *t*-test, medians were compared using the Mann-Whitney *U*-test, and percentages were compared using the chi-square test. At $p < 0.05$, the outcomes were deemed statistically significant.

Results

In this study, 123 volunteers who fulfilled the study's requirements were involved. Of these 123 participants, 99 were evaluated as FMF patients, and 24 comprised the control group. Of the FMF patients, 64 (64.64%) were not in an attack period, and 35 (35.35%) were patients in an FMF attack period.

The male-to-female ratio was 1.3 among the 99 FMF patients in the study group, with 56 (56.5%) being male and 43 (43.5%) being female. Table 1 displays the FMF cases' demographic information.

Table 1 Statics indicating difference ages, males, and females

	FMF no-attack period	FMF attack period	*P*
Age (years)	9.2 ± 3.7[a]	10.5 ± 3.6	$p > 0.05$
Boys/girls	1.29	1.3	$p > 0.05$

[a] The values are given as the mean standard deviation

There was no statistically significant difference in age and gender between FMF patients with relapse, patients without exacerbation, and the control group ($p > 0.05$).

When the clinical findings on the patients who were in an FMF attack period were evaluated at the time of the attack, abdominal pain was the most common symptom (94.2%, $n = 33$). Next were fever (91.4%, $n = 32$), joint pain (48.5%, $n = 17$), and chest pain (20%, $n = 7$).

The patient group with FMF—those who were not in an attack period and those in an FMF attack period—was evaluated on specific laboratory parameters (Table 2).

There was a significant correlation between pericardial thickness and fibrinogen on the one hand and CRP levels on the other ($p < 0.05$). However, white blood cells, ESR, and the annual number of attacks before and after FMF diagnosis did not significantly correlate ($p > 0.05$).

The genetic mutation analyses of the FMF patients in this study revealed that 13 (13.13%) of the patients had homozygous mutations, 72 (72.72%) had heterozygous mutations, and 14 (14.14%) did not have any mutations (Table 3).

The E148Q mutation, which was found on one or two alleles in 32 FMF patients (32.32%), is the most prevalent mutation in our FMF patients. V726A 21 (21.21%), R202Q 18 (18.18%), M694V 17 (17.17%), and M680I 4 (4.04%) were among the other frequently occurring mutations. No discernible relationship could be established between genetic abnormalities and pericardial thickness due to the small number of cases.

With the exception of IVRT, IVCT, and ET, there was no significant difference in the systolic and diastolic cardiac function values between the FMF patients and the control group participants, according to the participants' cardiac evaluation (Table 4).

On examining the electrocardiographic evaluations, all participants exhibited sinus rhythms, and no arrhythmia was observed. The electrocardiogram (ECG) characteristics of P distance, T wave, QRS voltage, and QTc did not show a statistically significant difference between the FMF patients and the control group participants (*p*

Table 2 Laboratory values for the two FMF patient groups

	FMF no-attack period	FMF attack period	*P*
Hemoglobin (g/dl)	12.9 ± 1.1[a]	12.7 ± 1.1	$p > 0.05$
hematocrit (K/μL)	39 ± 3.3	39.1 ± 3.1	$p > 0.05$
Platelets (K/μL)	309.953 ± 79.541	304.028 ± 94.283	$p > 0.05$
White cell count (K/μL)	7.770 ± 2.278	10.022 ± 4.931	**$p < 0.05$**
Fibrinogen (mg/dL)	278 (200–370)[b]	455 (204–681)	**$p < 0.05$**
ESR (mm/h)	8 (1–56)	27 (3–92)	**$p < 0.05$**
CRP (mg/h)	3.2 (3–61)	27 (3.2–164)	**$p < 0.05$**

[a] Normal distribution data are presented as mean standard deviation [b]Non-normal distribution data are presented as median (smallest-largest)

Table 3 FMF cases distributed based on genetic alterations

	FMF no-attack period	FMF attack period
E148Q heterozygote	13	5
V726A homozygote	0	1
R202Q heterozygote t	4	0
M694V heterozygote	3	3
M680I homozygote	1	0
R202Q homozygote	5	2
M694V/V726A heterozygote	1	1
M680I/V726A heterozygote	1	0
V726A/M694I heterozygote	5	2
V726A/E148Q heterozygote	3	2
E148Q/R4048Q heterozygote	1	0
M694V homozygote	1	2
M694V/E148Q heterozygote	3	1
M680I heterozygote	0	1
M694V/M694L heterozygote	0	1
V726A homozygote	0	1
M694L/M694I heterozygote	0	1
M680IGC homozygote	0	1
R761H/M694I heterozygote	3	3
M694V/M680I heterozygote	0	1
A7445 heterozygote	1	1
K695R heterozygote	1	2
R202Q/V726A heterozygote	1	2
V726A/E167D heterozygote	2	0
E148Q/R202Q heterozygote	2	2
No mutation detected	13	1

Table 4 Comparison of cardiac function values for all study participants

	FMF patients	Control group	*P*
EF (%)	66.83 ± 5.08	69.04 ± 7.31	$p > 0.05$
FS (%)	36.38 ± 3.99	36.75 ± 5.22	$p > 0.05$
IVSd (cm)	0.70 ± 0.18	0.81 ± 0.13	$p > 0.05$
IVSs (cm)	0.97 ± 0.24	0.84 ± 0.10	$p > 0.05$
LVPWd (cm)	0.70 ± 0.19	0.81 ± 0.11	$p > 0.05$
LVPWs (cm)	1.02 ± 0.25	1.06 ± 0.19	$p > 0.05$
LVdMass (ASE) (g)	82.27 ± 45.02	96.69 ± 26.06	$p > 0.05$
E wave (cm/minute)	1.00 ± 0.14	1.03 ± 0.10	$p > 0.05$
A wave (cm/minute)	0.63 ± 0.13	0.66 ± 0.14	$p > 0.05$
E/A ratio	1.61 ± 0.32	1.51 ± 0.40	$p > 0.05$
IVRT (msn)	81 (36–147)	44 (30–96)	$p < 0.05$
IVCT (msn)	73 (44–214)	93 (69–266)	$p < 0.05$
ET (msn)	199 (22–332)	84 (60–118)	$p < 0.05$
DT (msn)	96 (60–221)	109 (79–118)	$p > 0.05$

EF Ejection fraction, *ET* Ejection time, *FS* Fractional shortening, *IRP* Idiopathic recurrent pericarditis, *IVCT* Isovolumetric contraction time, *IVRT* Isovolumetric relaxation time, *IVSd* Interventricular septal thickness at end-diastole, *IVSs* End-systole, *LVPWd* Left ventricular posterior wall thicknesses at end-diastole, *LVPWs* Left ventricular posterior wall thicknesses at end-diastole in systole, *LVPdMass* Cardiac mass

Table 5 Comparison of ECG values of the two FMF patient groups

	No. in an FMF attack period	FMF attack period	*P*
RR distance (mm)	17 (11–29)	17 (12–25)	$p > 0.05$
QRS voltage (mv)	1.2 (0.4–2.5)	1.2.(0.7–1.9)	$p > 0.05$
T wave (s)	0.12 (0.04–0,20)	0,16 (0.08–0.20)	$p > 0.05$
P distance (s)	0.08 (0.04–0.12)	0,08 (0.06–0.08)	$p > 0.05$
PR distance (s)	0.14 (0.12–0.20)	0,16 (0.12–0.16)	$p > 0.05$
QRS width (s)	0.06 (0.04–0.08)	0.06 (0.04–0.08)	$p > 0.05$
QTc (s)	0.37 (0.33–0.41)	0.38 (0.35–0.41)	$p < 0.05$

> 0.05). The FMF patients had a longer PR distance than the participants in the control group, and this difference was shown to be statistically significant ($p < 0.05$).

The ECG measurements of individuals with FMF who were not experiencing an attack period and those who were experiencing one did not show a statistically significant difference in the RR distance, QRS voltage, P distance, T wave, or PR distance ($p > 0.05$). It was shown that there was a statistically significant ($p < 0.05$) difference in the QTc measurement between the patients who were in an FMF attack period and the ones who were not (Table 5).

Systolic and diastolic cardiac functions did not significantly differ among the FMF patients whose cardiological evaluations were analyzed (those who were not experiencing an attack period as well as those who were).

When the study participants were evaluated for pericardial involvement, none of the FMF patients was diagnosed with pericarditis or effusion. However, regarding pericardial thickness, it was observed that pericardial thickness was greater in FMF patients than in the healthy participants, and this difference was found to be statistically significant ($p < 0.05$). The pericardial thickness in the patient group that was not experiencing FMF attacks was 0.46 (0.27–0.78) mm and 0.61 (0.38–0.92) mm in the patient group experiencing FMF attacks. The pericardium was thicker in the latter, especially in patients who also experienced chest pain during an FMF attack, and this difference was found to be statistically significant ($p < 0.05$) (Table 6).

The drug dosage for the study group patients who received colchicine treatments was 0.5 to 2 mg/day since the time they were diagnosed with FMF. Our FMF patients were receiving colchicine treatment suitable to their age because they did not experience frequent

Table 6 Difference in pericardial thickness in FMF patients

	FMF no-attack period ($n = 64$)	FMF attack period ($n = 35$)	Control group ($n = 24$)	p
Pericardial thickness (mm)	0.46 (0.27–0.78)	0.61 (0.38–0.92)	0.36 (0.25–0.44)	**< 0.05**

attacks or colchicine resistance that would need a modification in colchicine treatment.

Discussion

FMF presents with debilitating serositis attacks. There may be ongoing inflammation, even during attack-free periods, and symptoms may occur, albeit asymptomatically, depending on the serositis attacks.

FMF is prevalent in communities across the Eastern Mediterranean, especially in non-Ashkenazi Jews, Armenians, Turks, and Arabs. Turkey is home to the majority of FMF patients worldwide; hence, FMF-TR was created to create a patient registry database and examine clinical, genetic, and demographic traits. The male-to-female ratio in our study group was 1.3 (56:43). Although it has been stated in the literature that both sexes are affected equally, several studies have reported that the male or the female gender is more predominantly affected. The male-to-female ratio in our study is consistent with that of the FMF-TR [11–17]. In line with previous research, the average age of FMF patients in our study was 9.6 ± 3.7 years, and their average age upon diagnosis was 6.5 ± 3.2 years [17–22]. Studies conducted in recent years have shown that the mean age at diagnosis is getting younger [23]. The most significant factor contributing to reducing the age at diagnosis for FMF is thought to be an increase in awareness of FMF among social and health workers, leading to the disease being diagnosed at an earlier age.

In our study, a genetic mutation was detected in 85% of the FMF patients, and the most common mutation was the E148Q mutation, which was detected in one or two alleles in 32 (32.32%) patients. In studies conducted in Turkey, the M694V mutation is the most common mutation in patients with FMF, and the mutation frequency varies between 41 and 70% [11, 17, 24]. These differences between genotype and phenotype are due to epigenetic factors such as environmental and regional factors. When the cardiological evaluations of the patients in our study who were not in an FMF attack period and those experiencing FMF attacks were examined, no significant difference was observed in their systolic and diastolic heart functions. In some other studies, left ventricular systolic functions were found to be at normal levels in FMF patients, while diastolic functions were affected by the disease [25, 26]. However, other studies have reported that cardiac functions remain normal in FMF patients, similar to our study's findings [20, 26].

Farag et al. found statistically higher QTc, JTc, and TPe/QTc ratios in patients than in controls in their study, and they submitted that these higher values indicated an increased risk of arrhythmia [20]. In this study, we identified a statistically significant ($P < 0.05$) difference in the QTc measurement between patients who were in an FMF attack period and those who were not. Due to the elevated risk of arrhythmia suggested by FMF patients' high QTc values during relapse, patients should be monitored.

When the participants were evaluated for pericardial involvement, neither pericarditis nor effusion was diagnosed in any of the FMF patients. However, regarding pericardial thickness, it was observed that FMF patients had thicker pericardia than participants in the control group. There are reports in the literature of cardiac findings such as smearing in FMF, with transient ST-T segment changes in the ECG, cardiac shadowing, and temporary enlargement in chest radiography. A retrospective study by Kees et al. detected pericarditis in 57 patients, 27 of whom received a definite diagnosis, while 30 received a probable diagnosis [27]. It was reported that the number of FMF patients with pericarditis detected in this Kees et al. study was 11 times higher than the average rate in the human population. In an echocardiographic study on pericardial involvement conducted by Dabestani et al. on 210 patients with FMF, 30 patients were randomly selected, and the frequency of pericardial involvement was investigated using M-mode echocardiography. They found pericardial involvement in 8 (27%) patients [15]. In their study on ventricular function and pericardial effusion in FMF patients, Sari et al. found no evidence of pericarditis and/or pericardial effusion in any of the FMF patients in their study group [26].

In a study by Peet et al. involving 136 patients with idiopathic recurrent pericarditis (IRP), 7.8% (10:128) of the patients with IRP carried a known or predicted variant of the MEFV gene, and the presence of a single MEFV mutation predisposed carriers to developing recurrent pericarditis [28]. They concluded that it might cause pericarditis. Pericardial involvement in FMF varies, with a varied clinical presentation ranging from pericardial involvement, pericardial thickening alone, and/or pericarditis coupled with pericardial tamponade.

All patients in our study group received colchicine treatment of between 0.5 and 2 mg/day from time of diagnosis. Colchicine prevents amyloidosis from developing and lessens the frequency and intensity of FMF

episodes. Nussinovich et al. revealed in their 2020 study that individuals with FMF receiving colchicine treatment may be less likely to experience a cardiac arrhythmia than patients with FMF who are just receiving a diagnosis [29]. Yomna Farag et al. observed a favorable link between the dose of colchicine medication and the JT interval. Consequently, they emphasized the importance of adherence to colchicine treatment and the consequent enhancement of FMF management by lowering the risk of arrhythmia [20].

In FMF patients, therapy with colchicine averts attacks and renal amyloidosis development. Our FMF patients did not use additional treatments (anti-IL1 medicines) since they did not develop colchicine resistance, which would have necessitated a modification in the prescription for colchicine. Medication for colchicine that was age appropriate was given to our patients. Larger studies that include more FMF patients, also have pericarditis, and explain the changes in cardiac functions in FMF patients are needed because the number of cases in our study was small and pericarditis could not be found in FMF cases, distinct dosages, and methods of treatment.

Conclusion

The fact that pericardial thickening was more common in FMF patients in our study who were in an attack period indicates pericardial involvement in FMF, due to increased inflammation during the attack period. We believe that cardiac functions, including the status of the pericardium, should be monitored as part of the long-term follow-up of FMF patients because the pericardium is affected—as are all serosae—by ongoing inflammation.

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Authors' contributions
ÖKK, MK, and MKG were involved in the design of the study, collected and interpreted the data, were responsible for the drafting of the manuscript, and critically reviewed the drafts. Statistical analysis was done by MKG and YDY, and EGA contributed to the writing of this study in the form of an article. The final version of the manuscript was approved by all authors, who had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication.

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Consent for publication
None.

Competing interests
The authors declare that they have no competing interests.

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