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Subclinical Cardiac Affection in Children with FMF

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ABSTRACT

Background: Globally, the most prevalent hereditary autoinflammatory illness is Familial Mediterranean fever (FMF). It results in polyserositis, feverish periods of inflammation, and in rare cases, erysipelas-like erythema or non-erosive monoarthritis. Because of their chronic and recurring inflammatory condition, patients with FMF are at risk for cardiovascular disease. Endothelial dysfunction caused by persistent chronic inflammation is a major factor in the development of atherosclerosis.

Objective: To detect early cardiac affection and subclinical atherosclerosis in FMF patients.

Patients and Method: This study included 30 children with FMF and 30 apparently healthy children as control group. Patients with thyroid, hepatic, renal diseases, history of heart failure, any valve disorders or ischemic heart disease or any other autoimmune diseases were excluded from the study. Demographic data was collected and clinical disease severity was assessed by FMF severity index. Subclinical atherosclerosis was detected by carotid intima-media thickness (cIMT) and cardiovascular assessment using Echo and ECG was done.

Results: cIMT was significantly higher in FMF patients (0.75 ± 0.08 mm) than controls (0.64 ± 0.037) and there was a significant positive correlation between cIMT and duration of the disease, triglycerides, LDL, cholesterol and HDL.

Conclusions: FMF patients may be associated with cardiovascular and early subclinical atherosclerosis. Furthermore, cIMT can be regarded a viable noninvasive approach for detecting early atherosclerosis.

Keywords: FMF, Subclinical atherosclerosis, cIMT.

INTRODUCTION

The most prevalent hereditary autoinflammatory illness in the world, FMF mostly affects groups of Turkish, Armenian, Italian, and Arabic origin in the eastern Mediterranean [1]. An autosomal recessive mutation in the Mediterranean fever (MEFV) gene results in intermittent flare-ups of inflammation accompanied by fever, polyserositis, and in rare cases, recurrent non-erosive monoarthritis or erysipelas like erythema [2]. Mutations in the MEFV gene, which is found on chromosome 16's short arm, are the cause of FMF [3]. This gene encodes a protein called pyrin, which is connected to the interleukin-1 inflammatory cascade [4]. Amyloidosis, which results in end-stage renal failure and other organ issues, is the most hazardous side effect of FMF [5]. Even in the absence of established cardiovascular risk factors, these individuals may nonetheless develop cardiovascular issues [6]. A variety of cardiovascular symptoms, including pericarditis, cardiomyopathy, valvular disease, arrhythmia, and conduction abnormalities, have been documented in FMF [7].

Because of their chronic and recurring inflammatory condition, patients with FMF are at risk for CVD. Chronic inflammation that persists increases nitric oxide production and vascular permeability, which leads to endothelial dysfunction. The development of atherosclerosis is significantly influenced by endothelial dysfunction [8]. Subclinical atherosclerotic alterations impact the arterial wall through vascular flexibility and intima-media thickness [9]. A trustworthy and non-invasive technique for identifying patients with subclinical atherosclerosis is CIMT assessment [10]. In the light of this background, this study aimed to detect early cardiac affection and subclinical atherosclerosis in FMF patients.

MATERIALS AND METHODS

This is a case control research performed at a single center.

Setting: Patients were gathered from Tanta University Hospitals' Outpatient clinic for the Rheumatology and Rehabilitation Department, study duration 6 months (From June 2024 to November 2024).

Patients: The study included 30 children with FMF diagnosed according to the new pediatric FMF criteria [11] and 30 apparently healthy children matched for age and gender as control group. Patients with thyroid, hepatic, renal diseases, history of heart failure, any valve disorders or ischemic heart disease or any other autoimmune diseases were excluded from the study.

Ethics approval: This study complies with the ethical standards of Tanta Faculty of Medicine and the Declaration of Helsinki's ethical principles, having been authorized by the institution's ethics board under license number 36264PR536/2/24. Every patient gave their informed permission according to the local ethics committee. To ensure the protection of all patient data, each patient file had a code number that included the findings of all investigations.

Clinical assessment: Complete history was taken of each patient, with special attention to the family history of FMF, clinical manifestations, demographic information, consanguinity, age at onset, and physical examination. The FMF severity score was used to evaluate the severity of the disease [12].

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Laboratory assessment: Including complete blood count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), serum creatinine, Albumin/ Creatinine ratio and serum amyloid A. Total lipid profile with emphasis on LDL and triglycerides as predictors for atherosclerosis. The MEFV mutation analysis was obtained from files of patients, patients were compound heterozygotes or homozygotes.

Cardiovascular assessment:

- Analysis of any **cardiac complaints such** as palpitation, chest pain, syncope or dyspnea.
- **Electrocardiogram ECG:** For detection of any conduction defects.
- **Echocardiography:** Performed using a GE vivid seven Cardiac ultrasound phased array system with tissue Doppler imaging using M4S transducer 4 M.HZ).

Two-dimensional echocardiographic assessment by M-mode for measuring LV systolic function (Ejection fraction EF %), measuring E/A ratio for detection of diastolic dysfunction, which may be an early sign of arterial stiffness, assessment of valvular lesions by color Doppler & continuous wave Doppler, also detection of different types cardiomyopathies, pericardial diseases or pericardial effusion [13].

Assessment of carotid atherosclerosis by cIMT:

A high-resolution linear transducer (frequency from 7.5-10MHz, Vivid 7- GE Ultrasound, Korea) is used to measure carotid IMT as a marker of subclinical atherosclerosis and to evaluate structural changes in the vascular wall. Patients were placed supine with their necks extended and slightly turned to the contralateral side. Both carotids were scanned in both transverse and longitudinal scans to measure the IMT in the far wall of the artery. IMT was obtained at three locations on each side: The internal carotid artery (10 mm after the flow divider), the common carotid artery (10 mm before the bulb), and the bulb (5–10 mm cranially to the commencement of the bulb). The greatest IMT value among the six segments under study, known as the maximum IMT (M-IMT), was evaluated. The current sonographic criterion figure states that IMT was normal if M-IMT was less than 0.9 mm, thickened intima if M-IMT was greater than 0.9 mm, and atherosclerotic plaque if M-IMT value was greater than 1.3 mm. Two ultrasonography operators analyzed the recorded scans of the patients and controls independently [14].

Statistical analysis

The data were statistically analyzed using SPSS version 20.0. The qualitative data were described using numbers and percentages. The quantitative data were described using mean ± SD. The X^2 test was used to compare the category data. For normally distributed quantitative variables, two groups were compared using the Student t-test. Pearson's correlation coefficient was used to determine the variables' connection with one another. Statistical significance was defined as $P \leq 0.05$.

RESULTS

Thirty FMF patients and 30 healthy volunteers completed this study. There were no significant differences between our patients and control groups as regard age, gender and BMI (p=0.6,0.64 and 0.845 respectively) (Table 1).

Table (1): Demographic data of the two groups

Parameter		FMF group (N=30)	Control (N=30)	P value
Age		9.97 ± 3.47	9.5 ± 3.06	0.6
Gender	Male	15 (50%)	13(43.33%)	
	Female	15 (50%)	17(56.67%	0.604
Body Mass Index		25.05±2.458	25.2 ± 2.818	0.845

*Significant, FMF: Familial Mediterranean fever.

14 of our patients had family history of FMF and half of them are homozygous. The laboratory investigations of the two groups (Table 2).

Table (2): Laboratory investigations of the two groups

Parameter (Mean ± SD)	FMF group (N=30)	Control (N=30)	P value
ESR (mm/hr)	30.3 ± 7.48	6.2 ± 1.3	0.0001*
CRP (mg/L)	4.57 ± 1.12	0 ± 0	0.0001*
Serum amyloid A	86.5±21.31	5.67± 1.06	0.0001*
Serum creatinine (mg/dl)	0.65± 0.15	0.66±0.159	0.793
Albumin\creatinine ratio	7.2 ± 1.79	5.1± 1.14	0.0003*
LDL level (mg/dl)	66.8± 6.61	43.37±10.64	0.0001*
TG (ng/mL)	54.6±13.04	45.24±10.53	0.008*
Cholesterol (mg/dl)	138.83±33.89	78.33±9.48	0.0001*
HDL (mg/dl)	38.0±3.48	50.13±3.6	0.0001*

*Significant. ESR: erythrocyte sedimentation rate, CRP: C reactive protein, LDL: low density lipoprotein, TG: triglycerides, HDL: high density lipoproteins.

Our patients were assessed for their severity by FMF severity score, 12 of our patients showed mild disease severity, 18 showed moderate disease severity, none of our patients had severe disease. Cardiac manifestations of our patients are demonstrated in table (3), which showed that palpitation and dyspnea being the most common manifestations in our studied patients (18 & 14 patients respectively).

Table (3): Cardiac manifestations in FMF patients.

Cardiac manifestations	FMF (N=30)
Palpitation	18(60%)
Dyspnea	14(46.67%)
Chest pain	4(13.33%)
Syncope	5(16.67%)
Rhythm	3 (10 %)
Effusion	4 (13.33%)
Valvular affection	6 (20%)

ECG and Echo findings are shown in table (4). cIMT was significantly higher in FMF patients (0.75 ± 0.08 mm) than controls (0.64 ± 0.037). 5 of our patients (16.6%) showed early subclinical atherosclerosis.

Table (4): Cardiac parameters in the two groups

Parameter (Mean ± SD)	FMF group	Control group	P value
Heart rate	94.83 ± 18.26	82.37±9.48	0.0052*
QTc	405.33± 41.21	367.83±28.18	0.0002*
LVEDD	3.42±0.66	3.07±0.248	0.0065*
LVESD	2.487±0.712	2.153±0.343	0.0286*
EF	61.77±12.24	69.03±3.88	0.0049*
CIMT	0.75±0.08	0.64±0.037	0.0001*

*Significant. QTc: corrected QT interval, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic diameter, EF: ejection fraction, CIMT: carotid intimal media thickness.

There was a significant positive correlation between cIMT and duration of the disease, triglycerides, LDL, cholesterol and HDL (Table 5).

Table (5): Correlation between cIMT and other parameters

Parameters	cIMT	
	r	p
Age (years)	0.147	0.438
Sex (r_s)	0.174	0.359
BMI (kg/m^2)	-0.181	0.340
Duration of disease	0.688	<0.001*
ESR (mm/hr)	0.121	0.525
CRP (mg/L)	-0.050	0.792
Serum amyloid	-0.072	0.705
HDL (mg/dl)	-0.579	<0.001*
LDL (mg/dl)	0.832	<0.001*
Cholesterol (mg/dl)	0.511	0.004*
Triglycerides (ng/mL)	0.451	0.012*
FMF severity (r_s)	0.053	0.780
Rhythm (r_s)	0.046	0.809
ECG Parameters HR (r_s)	-0.189	0.316
Qtc (ms) (r_s)	0.012	0.951
LVEDD(mm)	-0.048	0.802
LVESD(mm)	-0.027	0.886
Effusion (r_s)	-0.308	0.098
Valvular affection (r_s)	-0.094	0.622
EF	0.079	0.678

*Significant.

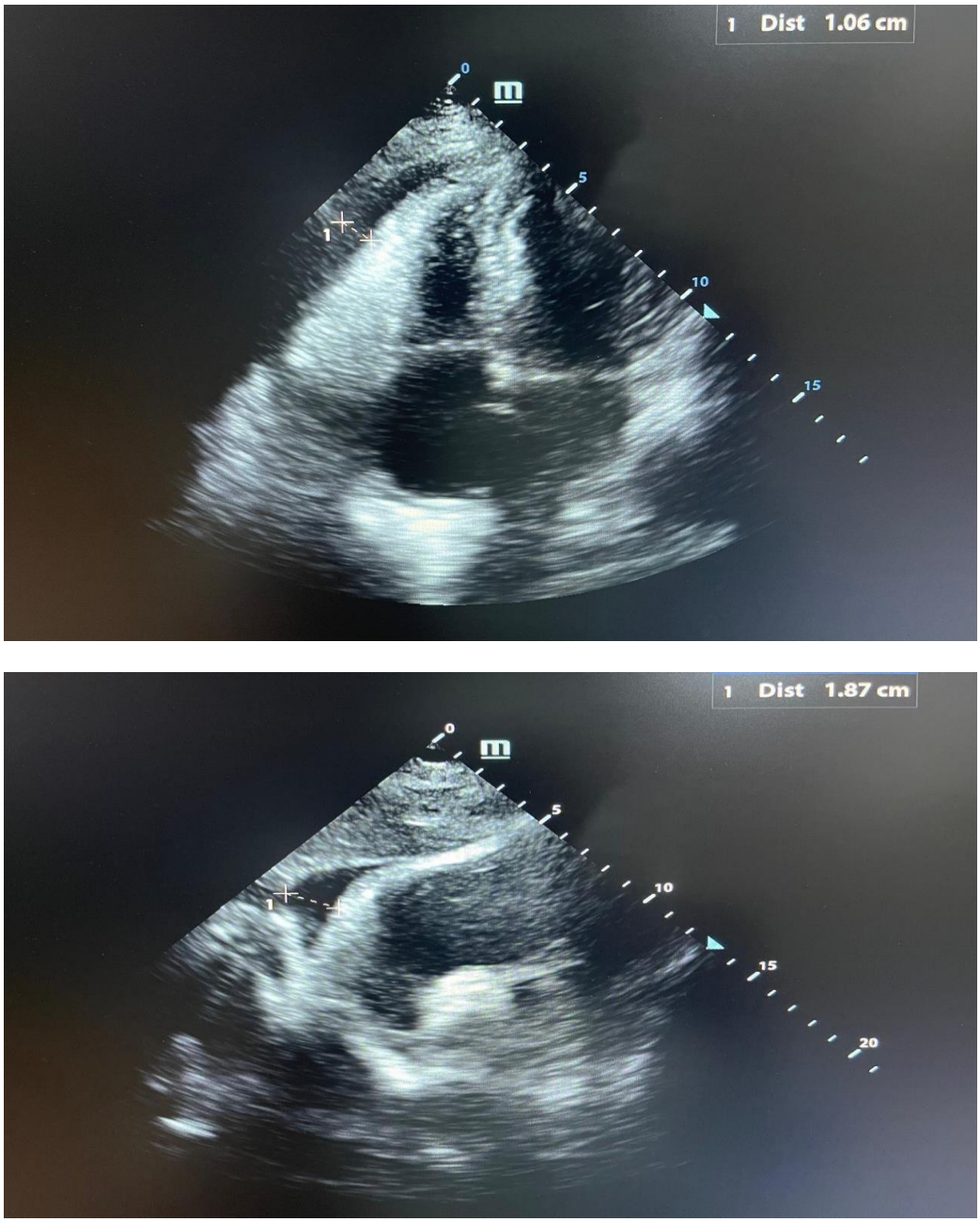

Figure (1): Male patient aged 14 years old with FMF since 4 years ago. Echo showed glistening pericardium with mild pericardial effusion about 1 cm anterior (Around RV and RA), A picture suggestive of pericarditis.

DISCUSSION

FMF is characterized by severe serositis attacks. Even during periods without attacks, there can be persistent inflammation, and symptoms might manifest subtly, depending on the nature of the serositis episodes.

Our study group's male to female ratio was 1.1. (Table 1), which agreed with other studies [15-16]. In our research, the average age of FMF patients was 9.97 ± 3.47 (6–17) years. In the **Salah *et al.*** [15] research has indicated that the average age upon diagnosis is decreasing.

FMF patients are prone to inflammatory episodes. The majority of them are pleuritic, arthritis, or peritonitis that manifest as arthralgias and chest discomfort, or abdominal pain. The mechanism behind FMF's involvement as a new risk enhancer in atherosclerotic CVD remains unclear. The interaction between the MEFV gene and IL-1 plays a significant element in the inflammatory assaults of FMF [17].

The current study found that patients with FMF had considerably lower HDL-C and significantly higher levels of LDL-C, triglycerides, and cholesterol than the control group. It has been noted that children with FMF had greater triglyceride and lower HDL-C values than children in healthy controls [18]. According to a **Turhan *et al.*** [19] study, compared to healthy participants, FMF patients showed greater blood triglyceride levels and lower HDL-C. This implies that the inflammation and increased risk of atherosclerosis in FMF participants may be connected to variations in HDL-C and triglyceride levels.

Palpitations were the most prevalent cardiac symptom in 60% of FMF episodes. Numerous patients displayed multiple complaints. Every patient's blood pressure was within normal limits. Four patients had pericardial effusions, and 20% of patients had valve involvement (aortic and mitral) according to echocardiographic tests. In another study, palpitations were the most prevalent cardiac complaint among the 39 FMF cases (74%) that experienced them. Pericardial effusions were discovered in nine patients by echocardiographic testing. Aortic regurgitation was present in twelve patients and 9 patients with mitral regurgitation [15].

In individuals with FMF, atherosclerosis and CVD are major causes of morbidity and death. Endothelial dysfunction caused by systemic inflammation results in oxidative stress, vascular damage, and ultimately atherosclerosis [20].

Endothelial damage, foam cell development, smooth cell proliferation, and ultimately the rupture of atherosclerotic plaque are all steps in the multi-step process known as atherogenesis [21]. Chronic inflammation contributes to nearly every step by accelerating the formation of foam cells and atherosclerotic plaques, activating endothelial cells, and producing reactive oxygen species. Exaggerated inflammation is a hallmark of FMF assaults, although subclinical inflammation has also been shown to endure during attack-free intervals [22–23].

We concentrated on cIMT, a quick, simple, and affordable way to assess cardiovascular risk by calculating the total thickness of the arterial wall's medial and intima layers. It is thought to be a noninvasive indicator of premature atherosclerosis and reflects early morphological changes in the arterial wall brought on by a variety of risk factors over time [24].

In this study, a significant difference in cIMT between patients and controls, which is in agreement with other studies [25–26]. In contrast, another study revealed no significant difference between FMF patients and controls [22].

In a research, **Mahmoud *et al.*** [25] highlighted the importance of inflammation in atherogenesis and found that children with FMF had greater levels of cIMT, a visible biomarker of atherosclerosis, than the control group. Additionally, cIMT was shown to be greater in the in-patient group in a research by **Bilginer *et al.*** [27] that compared the endothelium functioning of juvenile FMF patients with healthy controls. They ascribed this outcome to elevated inflammatory markers (ESR, CRP, and serum amyloid A) throughout the time without an incident. This agrees with our study that found high inflammatory markers.

There was a substantial positive correlation between cIMT, duration of the disease, and lipid profile, which matches with a study done by **Ugurlu *et al.*** [14], who reported a positive correlation between cIMT and lipid profile, and this is contradictory with another research by **Mahmoud *et al.*** [25] who revealed no association between cIMT and lipid profile. The disparity might be attributed to various patient populations and study methodology, as well as varying ages.

Our study found no correlation between cIMT and inflammatory markers including ESR, CRP and serum amyloid, which agrees with **Bilginer *et al.*** [27] and **Ugurlu *et al.*** [14]. This might be caused by varying ethnic groups and the level of disease activity, as well as the fact that CIMT takes longer to be impacted by subclinical inflammation than the subclinical indicators.

LIMITATIONS

The patient cohort was quite small, with the majority exhibiting mild to moderate activity levels. Also, this is a single center cross sectional study, so in the future multicentric, prospective studies are important to support the data in this study.

CONCLUSION

FMF patients may be associated with cardiovascular and early subclinical atherosclerosis. Furthermore, cIMT can be regarded a viable noninvasive approach for detecting early atherosclerosis.

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