Do all Familial Mediterranean Fever (FMF) patients with recurrent chest pain have cardiac problems?

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Original Article

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ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive autoinflammatory genetic disorder. One of the importing complication of the FMF is the cardiac disorders. We aimed to research the evaluation of cardiological parameters in FMF cases who had chest pain and MEFV gene variant.

Design: Experimental study

Setting: This study was conducted at Department of Cardiology and Medical Genetics of Duzce University, Turkey

Subject: Totaly thirty-four individuals with recurrent sharp retrosternal chest pain that exacerbate with deep inspiration and clinically diagnosed as FMF and at least one variant on MEFV gene were included in the study.

Interventions: Physical and cardiological evaluation was performed and MEFV gene sequenced for each cases.

Main outcome measures: To show whether the chest pain caused from any cardiac problem or it is derived by other problem such as tendonitis, myalgia etc. in cases with FMF

Result: Seven cases (20.5%) had previous history of pericarditis. Two of these cases had small pericardial effusion and one had pericardial thickness. All three were adults. Also one case (2.9%) had aortic regurgitation, eight cases (23.5%) had mitral regurgitation, thirteen cases (38.2) had tricuspid regurgitation, one case (2.9%) had pulmonary regurgitation. Valvular disease is seen in over half of the cases.

Conclusions: We concluded that cases with FMF who had chest pain and at least one MEFV gene variant have increased risk for the cardiac problems. So these cases should be routinely followed up life long for cardiac problems

KEY WORDS: Cardiac problem, FMF, MEFV gene, recurrent chest pain

INTRODUCTION

Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive autoinflammatory genetic disorder characterized by short and self-resolving recurrent attacks of inflammation of serosal membranes. In this manner, FMF results in acute fever, abdominal pain, joint pain, chest pain, synovitis, myalgia and erythema [1]. MEFV gene mutations are responsible for the disease. MEFV genes are located on chromosome 16p13.3 and encodes pyrin including10 exons. The disease is genarally seen in eastern Mediterranean populations including Armenians, non-Ashkenazi Jews, Turks, and Arabs[2].

FMF affects different organs and systems such as the musculoskeletal, renal, gastrointestinal systems etc. Although the relation between FMF and cardiovascular risk is rarely reported, the cardiac complications increase morbidities and/or mortality in FMF[3].

The most significant complication of the FMF that may cause the cardiac disease is secondary systemic AA amyloidosis[4]. Cardiac deposition of amyloid, which cause increased morbidity and mortality in FMF patients, may lead to cardiovascular mortality[5]. Cardiac manifestations related to FMF may genarally be associated with secondary AA amyloidosis. The most commonly reported cardiac manifestations in FMF are pericarditis, idiopathic recurrent pericarditis, cardiac tamponade and abnormal cardiovascular reactivity[6].

One of the most important symptoms of FMF is chest pain. While the chest pain may be caused by cardiac problem, it may be also caused by non-cardiac reasons such as tendonitis, myalgia etc. To the best of our knowledge, there is no study about the evaluation of cardiological parameters in FMF cases with different variants of MEFV gene who had chest pain in the literature. It was not clear whether the chest pain resulted from any cardiac problem or the chest pain is derived from other problem such as tendonitis, myalgia etc. in cases with FMF. For this reason, we performed the current study.

Aim of our study;

1. To evaluate of cardiological parameters in FMF cases with different variants of MEFV gene who had recurrent chest pain
2. To assess whether the chest pain in FMF is caused by any cardiac problem or it is derived from other problem such as muscle pain etc.

SUBJECTS AND METHODS

Genetic and Routine Biochemical Analysis

Thirty four individuals who had recurrent sharp retrosternal chest pain that exacerbated with deep inspiration and diagnosed clinically as FMF and at least one variant on MEFV gene (20 male and 14 female) (age ranged between 6-47 years old) were included in the current study. Physical examinations were performed and demographical features were obtained. For MEFV gene mutation analaysis, 2 cc peripheral blood samples were collected in tubes containing Ethylenediaminetetraacetic Acid (EDTA) for DNA isolation from the cases. Genomic DNA was isolated. All exons of MEFV gene (1-10) were amplified using PCR technic and whole exome sequencing analysis of the gene was performed. Duzce University Human Research Ethics Committee approved the study. Written informed consent was obtained from participants. Also, routine serum and urine biochemical analysis were carried out for each cases. All patient clinically diagnosed as FMF and at least one variant on MEFV gene underwent detailed cardiac examination.

Cardiological Examination

Electrocardiogram (ECG)

12-lead Electrocardiogram (ECG) (NIHON KOHDEN Cardiofax ECG 1250K model) was done for each cases at rest. Routine evaluations were done.

Echocardiography

All of the patient in the study were evaluated with transthoracic echocardiography (Siemens Acuson SC 2000). Transthoracic two dimensional (2D), (M. mode),and color Doppler echocardiogram were performed with suitable probes according to age. Cardiac anatomy, ventricular function, and valve competence were assessed using standard projections and measurements were done according to the recommendations of the American Society of Echocardiography[7].

Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences (SPSS version 15.0). The descriptional statistics were done for all data. The data are given as mean ± SD or frequency values. The

relation between the mutation and clinical parameters was evaluated with Pearson's χ 2 test depending on the type of variables.

RESULTS

Total of 34 individuals (20 male and 14 female) (age ranged between 6-47 years old) were divided into two groups <18 years old (n=17) and ≥18 years old (n=17). The demographical features of cases were given in table 1 (table 1) and clinical features of the cases were given in table 2 (table 2). According to mutation analysis results of cases; 12 cases had heterozygous R202Q (35.3%), 1 case had homozygous R202Q (2.9%), 3 cases had heterozygous M694V (8.8%), 3 cases had heterozygous E148Q (8.8%), 5 cases had compound heterozygous R202Q/M694V (14.7%), 1 case had complex genotype R202Q/M694V/M680I (2.9%), 3 cases had homozygous R202Q/M694V (8.8%), 5 cases had heterozygous V726A (14.7%) and 1 case had heterozygous P369S mutation (2.9%) (table 3).

Cardiac assessment of FMF patients

All patients had chest pain. The systolic and diastolic blood pressures were within normal range. 12-lead ECG was done and no anomaly was detected in any case. Echocardiographic testing revealed pericardial thickening in one patient and mild pericardial effusions in 2 patients. These three cases had recurrent pericarditis history. None of the cases had cardiac tamponade. One case had aortic regurgitation, which was grade I. Eight had mitral regurgitation and six of them had grade I, 2 of them had grade II. Thirteen cases had tricuspid regurgitation grade I. One case had pulmonary regurgitation, which was grade I. Left ventricular functions of all patients were normal (table 4). Also serum and biochemical analaysis results of all cases are within normal range (table 1).

The cardiac findings according to the mutation type are given in table 5 and figure 1.

DISCUSSION

FMF is an autoinflammatory disease occured by inflammatory attacks of peritonitis, pleuritis, pericarditis accompanied by fever and arthritis. Increased proinflammatory cytokines and acute phase reactants are seen throughout inflammatory attacks of FMF. Chronic inflammation may also be associated with the cardiovascular risk in cases with FMF[8].

The variability of abnormal heart rate with AA amyloidosis was reported in FMF cases[9]. Morphological analysis of cardiac tissues from the patients who died of congestive heart failure revealed amyloid deposits in the endocardium, stroma of the myocardium as well as the vascular walls. It was reported that the backlog of amyloid was less obvious in lung and liver than spleen, kidneys, endocrine and digestive organs of cases with FMF. Morphological analysis of cardiac tissues from the cases who died due to congestive heart failure revealed amyloid accumulation in the vascular walls, endocardium and stroma of the myocardium[10]. It was reported that cardiac amyloidosis can lead to heart failure and death in FMF even before renal failure and uremia. Heart failure can occur by amyloid deposits in heart valves and myocardium. Amyloid angiopathies and coronary vasculitis are important risk factors for myocardial infarction in cases with FMF[10]. According to our results, two cases had amyloidosis. One of them with M694V variant had tricuspit regurgitation.

Many studies showed higher incidence of pericarditis in FMF patients than the general population. The prevalence of pericarditis was 0.7%–1.4% in some research studies [11,2]. It was reported that acute pericarditis, constrictive pericarditis and pericardial tamponade may even be the initial symptoms of FMF[12,13]. Turkish FMF study group reported that 60 (2.4%) FMF cases among 2468 had at least one episode of pericarditis during the course of their disease[2]. According to our results, 7 case (20.5%) (one case <18 years old and six cases ≥18 years old) had previous pericarditis history. The high rate of pericarditis in our study is due to inclusion of all cases with recurrent chest pain in the study. Also 2 of these cases had small pericardial effusion and 1 case had pericardial thickness. All of those three case were adults. Therefore it may be said that when the age increased, the cases with FMF had increased risk for pericardial diseases. Thus, the cases with FMF, especially who had chest pain, should be routinely followed up for the cardiac problem.

In a research study, different degrees of tricuspid regurgitation were reported[14]. Also in another study, it was shown that valves are affected around half of the cases-rates vary 21.8% for aortic valve, 16% for mitral valve, and 11% for the pulmonary valve[15]. In our study, one case (2.9%) had aortic regurgitation, which was grade I. Eight cases (23.5%) had mitral regurgitation and six of them had grade I, 2 of them had grade II. Thirteen cases (38.2) had tricuspid regurgitation who had grade I. One case (2.9%) had pulmonary regurgitation, which was grade I. (table 4). According to our findings, valvular disease affect over the half of the cases.

FMF is autosomal recessive autoinflammatory disease. Heterogeneous genetic basis is seen in this syndrome. More than 314 mutations and polymorphisms have been reported to date[16]. According to our results, 22 cases (64.7%) had R202Q carrier, 12 cases (35.3%) had M694V carrier, 5 cases (14.7%) had V726A carrier, 3 cases had (8.8%) E148Q carrier and 1 case (2.9%) had P369S carrier (table 3). When the cardiac findings are taken into consideration with mutation type of cases, the number of the cardiac disordes are 19 in cases with R202Q carrier, 11 in cases with M694V carrier, 5 in cases with E148Q carrier, 5 in cases with V726A carrier and 1 in cases with P369S carrier (table 5). So it may be said that cases with FMF variant (especially R202Q and M694V etc.) who had recurrent chest pain, have increasing risk for the cardiac problems. Thus these cases should be routinely followed up life long for cardiac problems.

CONCLUSION

We conclude that patients with FMF and recurrent chest pain have increasing risk for cardiac problems. Therefore those cases should be routinely followed up life long for cardiac problems.

Compliance with Ethical Standards:

Funding: There is no funding

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Duzce University Human Research Ethics Committee approved the study. Written informed consent was obtained from participants.

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All the authors have equally participated in the study.

Conflict of interest : The authors declare that there is no conflict of interest.

Disclosure - The authors have no financial or competing interests in relation to this work.

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Table 1: Demographical and Biochemical features of the cases with children and adults

Cases Features	Cases with <18 years old (n)	Cases with ≥18 years old (n)
Sex(M ;F)	M=8(47.1%);F=9 (52.9%)	M=12(70.6%); F=5 (29.4%)
Age (mean±SD)	12.824±3.644	38.118±8.710
BMI (mean±SD)	19.457±4.407	24.604±2.525
Cases with family history	13 (76.5%)	11 (64.7%)
Cases withouth family history	4 (23.5%)	6 (35.3%)
Age onset of symptom	5.103±3.517	21.544±12.149
Recurrancy of attacks	a=9(52.9%);b=3(17.6%);c=5(29.4%)	a=6(35.3%);b=4(23.5%);c=6(35.3%); d=1(5.9%)
ESR (mmHg)	12.177±9.174	10.412±9.612
Creatinin (mg/dl)	0.514±0.167	0.699±0.155
HB (g/dl)	13.277±1.736	14.235±2.019
WBC	7205.882±2947.556	7500±1390.593
Platelet (10^3/uL)	307.471±59.835	268.118±30.864
C-Reactive Protein (mg/dL)	0.236±0.178	0.418±0.350

N: individuals number; M: Male; F: Female; SD: Standard Deviation; BMI: Body Mass Index

a: more than one in a month; b: one in a month; c: one in three months; d: one in six months; ESR: Erythrocyte sedimentation rate; HB: Hemoglobin; WBC: White blood cell

Table 2: Clinical features of the cases

Clinical Features	Cases with<18 years old (n)	Cases with≥18 years old (n)
Cases with chest Pain, n (%)	17 (100%)	17 (100%)
Cases with abdominal Pain, n (%)	16 (94.1%)	14 (82.4%)
Cases with arthritis, n (%)	11 (64.7%)	12 (70.6%)
Cases with fever, n (%)	11 (64.7%)	7 (41.2%)
Cases with pericarditis, n (%)	1 (5.8%)	6 (35.3%)
Cases with amyloidosis, n (%)	0 (0%)	2 (11.8%)
Cases with appendicectomy, n (%)	0(0%)	2 (11.8%)
Cases with erythema, n (%)	3 (17.6%)	6 (35.3%)
Dsypnea	5 (29.4%)	5 (29.4%)
Palpitation	1 (5.9%)	6 (35.3%)
Oedema	0 (0%)	0 (0%)
Syncop	0 (0%)	0 (0%)

n: Number of the cases

Table 3: Variant type of the cases

Variant type	Cases with<18 years old (n)	Cases with≥18 years old (n)
Heterozygous R202Q	6 (35.3%)	6 (35.3%)
Homozygous R202Q	1 (5.9%)	0 (0%)
Heterozygous M694V	1 (5.9%)	2 (11.8%)
Heterozygous E148Q	2 (11.8)	1 (5.9%)
Compound Heterozygous R202Q/M694V	2 (11.8%)	3 (17.6%)
Compound Heterozygous R202Q/M694V/M680I	1 (5.9%)	0 (0 %)
Homozygous R202Q/M694V	1 (5.9%)	2 (11.8%)
Heterozygous V726A	3 (17.6%)	2 (11.8%)
Heterozygous P369S	0 (0%)	1 (5.9%)

n: Number of the cases

Table 4: Echocardiographical findings of the cases

Cardiac findings	Cases with<18 years old (n)	Cases with≥18 years old (n)
Aortic	0 (0%)	1 (5.9%)
Mitral	4 (23.5%)	4 (23.5%)
Tricuspit	5 (29.4)	8 (52.9%)
Pulmonary	0 (0%)	1 (5.9%)
Pericardial effusion	0 (0%)	2 (11.8%)
Pericardial thickness	0 (0%)	1 (5.9%)

n: Number of the cases

Table 5: Cardiac findings according to variant type

Variant type	Aortic	Mitral	Tricuspit	Pulmonary	Pericarditis	Pericardial effusion	Pericardial thickness
Heterozygous R202Q	-	-	5	-	2	-	-
Homozygous R202Q	-	3	-	-	-	-	-
Heterozygous M694V	-	-	1	-	1	-	-
Heterozygous E148Q	-	1	1	-	2	1	-
Compound Heterozygous R202Q/M694V	-	2	2	-	1	-	1
Compound Heterozygous R202Q/M694V/M680I	-	-	-	-	-	-	-
Homozygous R202Q/M694V	-	-	1	1	1	-	-
Heterozygous V726A	-	2	2	-	-	1	-
Heterozygous P369S	1	-	1	-	-		-

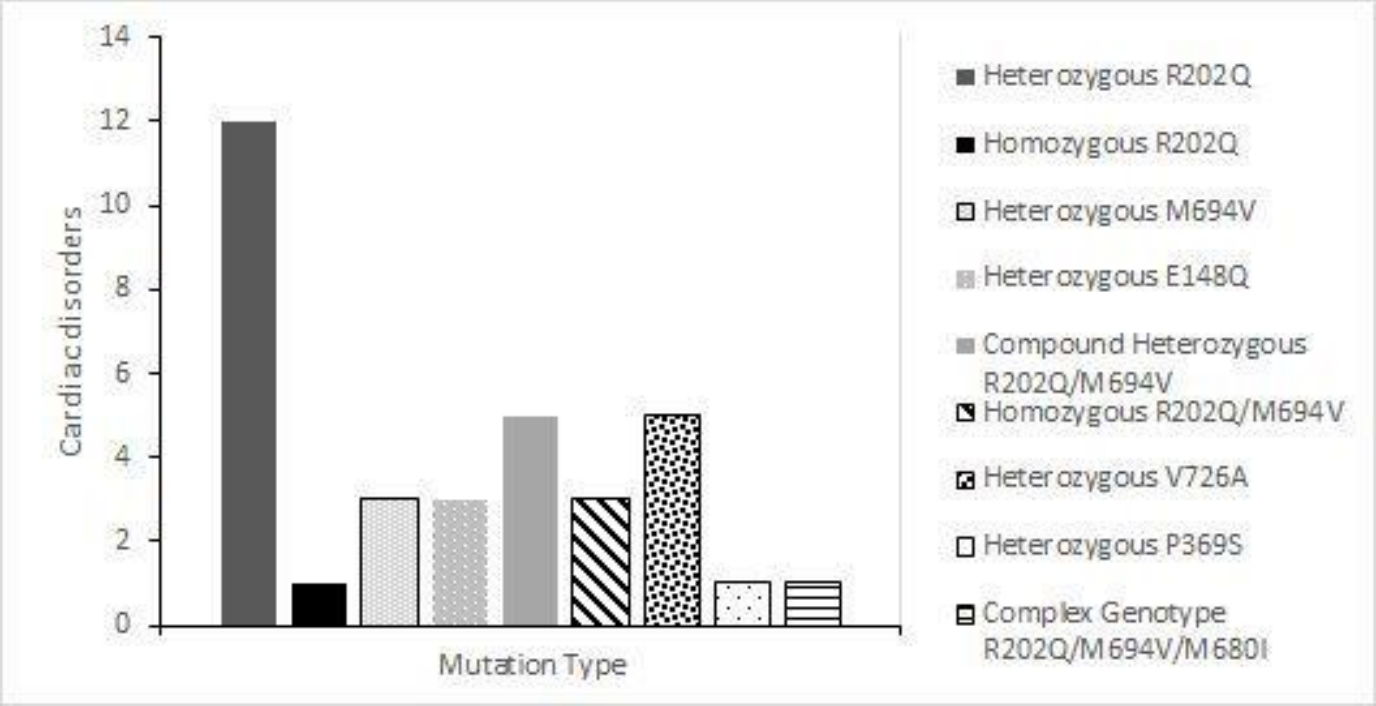

Figure 1: Cardiac disorders according to variant type