Article published online: 2021-08-09

REVIEW ARTICLE

Cardiac manifestations of Familial Mediterranean fever

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Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/ajm.AJM_78_17

Quick Response Code:

ABSTRACT

Familial Mediterranean fever (FMF) is autoinflammatory disorder characterized by sporadic attacks of fever, peritonitis, pleuritis, and arthritis. It is mainly seen in patients from Mediterranean origins, but it is now reported more frequently in Europe and North America due to immigration. To analyze the data on the cardiovascular manifestations in FMF patients, we searched PubMed using the terms "Familial Mediterranean Fever" or "FMF" in combination with other key words including "cardiovascular diseases" "pericardial diseases" "atherosclerosis" "coronary artery diseases" "cardiomyopathy" "pulmonary hypertension" or "valvular diseases." suggested several mechanisms to explain the cardiac involvements in FMF including the ongoing inflammation and the amyloid deposits in the heart and vessels' walls at the advanced stages of FMF. The course of these manifestations varies widely, but it can associate with poor prognosis in some cases such as with pulmonary hypertension. Interestingly, Colchicine, which is the cornerstone therapy of FMF, plays a vital role in treating and preventing some of these disorders. In this article, In this article, we will discuss the incidence, pathophysiology, and prognosis of the various cardiac manifestations affecting FMF patients.

Key words: Atherosclerosis, cardiomyopathy, coronary artery disease, familial mediterranean fever, pericarditis

INTRODUCTION

Familial Mediterranean fever (FMF) is autoinflammatory disease characterized by periodic episodes of fever, peritonitis, pleuritis, and arthritis. It is mostly inherited as autosomal recessive disorder among people from specific ethnicities such as Turks, Arabs, Armenians, and nonAshkenazi Jews.[1] In those patients, MEFV gene which is responsible for the production of Pyrin protein, an important regulator of inflammation and immune response, is mutated.[2] Patients with defective Pyrin tend to develop an inappropriate inflammatory response leading to the typical symptoms of FMF[2]. While the diagnosis of FMF can be highly suspected depending on the clinical picture, family history, ethnicity, and response to colchicine therapy, the definite diagnosis of this disorder can only be confirmed by genetic analysis.

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Several organs and systems affected by FMF, including the renal, gastrointestinal, and musculoskeletal systems. While cardiovascular involvements are less commonly reported, it is important to recognize those complications as some of them are associated with an increased morbidities and/or mortality. In this article, we will review the available literature and discuss the various cardiac manifestations of FMF, their incidence, pathophysiology, and prognosis.

METHODS

A comprehensive review of the literature is conducted to analyze the data on the cardiovascular manifestations in

Cite this article as: Alsarah A, Alsara O, Laird-Fick HS. Cardiac manifestations of Familial Mediterranean fever. Avicenna J Med 2017;7:158-63.

FMF patients. Using PubMed as the database, the literature search was carried out for English articles published between 1960 and 2016. We used in our search the terms "Familial Mediterranean Fever" or "FMF" in combination with other key words including "cardiovascular diseases," "pericardial diseases," "atherosclerosis," "coronary artery diseases," "cardiomyopathy," "pulmonary hypertension," or "valvular diseases." We selected the papers of most relevance to this review for discussion including observational studies, case series, and case reports. We excluded the articles that were duplicates. We also performed a manual search of the references of the selected articles for any relevant articles that we might have missed.

PERICARDIAL DISEASES

Several studies and case reports have described the pericardial involvement in FMF patients including acute and recurrent pericarditis, constrictive pericarditis, pericardial effusion, and tamponade. These articles reviewed and summarized in [Table 1].

Pericarditis is commonly seen with FMF, presenting usually as chest pain that lasts for about 4 days and then resolves spontaneously without further complications.[8] Yet, massive pericardial effusions and cardiac tamponade have been reported requiring pericardiocentesis.[6,11,12,16]

Although Sohar *et al*. did not find any case of pericarditis when they retrospectively reviewed the symptoms of 470 FMF patients,[18] many studies have found that the incidence of pericarditis in FMF patients is higher than the general population. The prevalence of pericarditis varied from 0.7%–1.4% in some retrospective studies[8,11] to 3.6% in one prospective study that used echocardiogram for diagnosis.[10] Using M-mode echocardiography, Dabestani *et al*. reported pericardial changes (effusion or thickening) in about quarter of their group.[5] In a recent study, Kilic *et al*. diagnosed pericarditis in about 11% of children with FMF presenting with chest pain and showed that pericarditis was especially seen in those with M694V and E148Q mutations.[17]

While pericarditis typically presents simultaneously with other FMF symptoms,[8] it has been reported as the only manifestation of the attack.[,6,7,11,13-15] In those cases, recurrent pericarditis which are refractory to the typical treatments raised the suspicion of FMF requiring further genetic studies to confirm the diagnosis.

Table 1: Pericardial diseases in patients with Familial Mediterranean fever

Author, year	Study type	*n*	Diagnostic study	Important reported findings
Eliakim and Ehrenfeld, 1961[3]	Prospective study	3/30	ECG	ECG was abnormal during attacks but back to normal in the intervals between attacks
Zemer *et al*., 1977[4]	Case report	1	Chest X-ray	Fibrosing pericarditis and constrictive pericarditis
Dabestani *et al*., 1982[5]	Prospective study	8/30	M-mode echocardiogram	Pericardial effusions and or pericardial thickening
Zimand *et al*., 1994[6]	Case report	1	N/A	Life-threatening cardiac tamponade
Tauber *et al*., 1995[7]	Case report	2	N/A	Recurrent pericarditis as the initial symptom of FMF
Kees *et al*., 1997[8]	Retrospective study	27/1553	Symptoms, ECG, echocardiogram and chest X-ray	Pericarditis accompanied by symptoms of FMF attack at another site
Tutar *et al*., 2001[9]	Case report	1	Symptoms and echocardiogram	Recurrent pericarditis was the initial symptom of FMF. Patient also had cardiac tamponade
Tutar *et al*., 2003[10]	Prospective study	2/55	Two-dimensional, M-mode, and Doppler echocardiogram	Small pericardial effusion
Tunca *et al*., 2005[11]	Cohort study	60/2468	Clinical and laboratory findings in 34 patients and clinical findings only in 26 patients	Recurrent pericarditis was the initial and only manifestation of FMF in 2 patients In one patient, pericardiocentesis was performed due to pericardial tamponade The other patient had constrictive pericarditis requiring pericardiectomy
Ishak *et al*., 2006[12]	Retrospective study	2/38	Echocardiogram	One patient had cardiac tamponade
Okutur *et al*., 2008[13]	Case report	1	Symptoms and echocardiogram	Idiopathic recurrent pericarditis was the initial manifestation of FMF
Gökçe *et al*., 2011[14]	Case report	1	Cardiac magnetic resonance imaging	Constrictive pericarditis resulted in protein losing enteropathy and resolved with colchicine therapy
Yoshioka *et al*., 2014[15]	Case report	1	Symptoms, ECG, echocardiogram	Recurrent pericarditis was the initial symptom of FMF
Sánchez Ferrer *et al*., 2015[16]	Case report	1	N/A	Recurrent pericarditis and cardiac tamponade. The genetic confirmation showed an autosomal dominant inheritance
Kilic *et al*., 2015[17]	Retrospective cross-sectional study	25/229	Echocardiogram	Pericarditis was seen in patients with M694V and E148Q mutations

FMF: Familial Mediterranean fever, ECG: Electrocardiogram, N/A: Not mentioned, *n*: Number of patients with pericardial disorders out of total number of FMF cases

Constrictive pericarditis, a rare pericardial complication, has also been diagnosed in FMF patients using chest X-ray and echocardiogram.[4,14] Although pericardiectomy is the main treatment of this disorder,[4] conservative management has been used by Gökçe *et al*., who showed a complete disappearance of constrictive pericarditis after 6 months of regular colchicine therapy.[14]

ATHEROSCLEROSIS AND CORONARY ARTERY DISEASES

Even though FMF patients are symptoms free between the attacks, C-reactive protein was detected in the attack free periods indicating a continuous subclinical inflammation between the clinical episodes.[19] Since systemic inflammation stimulates the development and progression of atherosclerosis,[20] many researchers are now questioning whether FMF patients are at a higher risk of atherosclerosis and coronary artery diseases (CAD) than other patients.

While atherosclerotic plaques are rarely seen in FMF patients,[21-24] intima media of the carotid and femoral arteries were found to be thick in various studies, suggesting of preclinical atherosclerosis.[21,22,25] Furthermore, this thickness associated with endothelial dysfunction and correlated with increased in inflammatory markers.[25] Two studies though failed to show any significant difference in intima-media thickening between FMF patients and other patients.[23,24] This conflict between the studies may suggest that FMF patients are at a slightly higher risk of developing subclinical atherosclerosis and that its progression is not aggressive enough to result in a significant plaque. In addition, colchicine therapy with its antiatherosclerotic characteristics may be the slowing factor of this process, but we still need more trials to clarify this point Table 2. Reviews the studies of intima-media thickness in FMF patients.

The relationship between FMF and CAD has been suggested in two genetic studies. Grimaldi *et al*. evaluated the prevalence of three of the mutations causing FMF in a group of Sicilian patients with acute myocardial infarction (AMI).[29] The authors found that M694V mutation is over-represented in AMI patients and it predicted a significant risk to develop AMI even after adjustment for other cardiac risk factors. Similarly, Kisacik *et al*. studied the prevalence of MEFV mutations in 197 CAD patients (91 with early CAD and 106 patients with typical CAD) and compared them to 119 healthy controls.[30] In this study, MEFV mutations in patients with early CAD were significantly higher compared to both older CAD patients and healthy controls.[30] Yet, only three cases of acute coronary syndrome have been reported in FMF patients; all of them were young, and at least, two of them had fatal myocardial infarction. The first case was reported by Puricel *et al*. when they reviewed the data on patients suffering acute coronary syndrome at age <30 years old.[31] Uyarel *et al*. described another case of a 22-year-old FMF patient who deceased due to myocardial infarction after stopping colchicine therapy.[32] The third case was reported by Serrano *et al*. of a 29-year-old female with a history of FMF and amyloidosis who experienced a fatal AMI due to coronary vasculitis.[33] CAD in FMF patients seems to be a consequence of either the augmented atherosclerosis or amyloid depositions in the vascular walls as was demonstrated in autopsy analysis.[34] Since colchicine suppresses the progression of these two factors, it may play an important protective role against CAD in those patients. This can explain the lower frequency of ischemic heart disease in colchicine-treated FMF patients compared to the general population.[35]

CARDIOMYOPATHY

Cardiac amyloidosis is a late complication reported in about 13% of FMF patients.[11] It presents mainly as progressive

Table 2: Review of studies that evaluated Intima-Media Thickening in patients with Familial Mediterranean fever

Author, year	Study type	*n* (FMF vs. control)	The evaluated arteries	Mean intima-media thickness in FMF patients versus control group (mm)	*P*
Akdogan, 2006[21]	Case–control study	43 versus 29	Right and left carotid arteries	Right: 0.62 versus 0.53 Left: 0.61 versus 0.53	0.001 0.001
Sari, 2007[23]	Case–control study	61 versus 31	Right and left common carotid arteries	Right: 0.49 versus 0.5 Left: 0.51 versus 0.52	>0.05
Peru *et al*., 2008[26]	Case–control study	49 versus 26	Common carotid arteries	0.038 versus 0.032	<0.05
Bilginer, 2008[25]	Case–control study	70 versus 50	Common and internal carotid arteries	Common: 0.37 versus 0.28 Internal: 0.25 versus 0.22	<0.001 <0.001
Ugurlu, 2009[22]	Case–control study	100 versus 103	Carotid and femoral arteries	Carotid: 0.57 versus 0.48 Femoral: 0.57 versus 0.49	<0.001 0.001
Ugurlu *et al*., 2013[27]	Case–control study	44 versus 44	The common carotid arteries	0.52 versus 0.53	0.709
Kucuk *et al*., 2016[28]	Case–control study	58 versus 38	The common carotid arteries	1.12 versus 0.74	<0.0001

n: Number of patients in each group, FMF: Familial Mediterranean fever

cardiomyopathy due to amyloid deposit in the myocardium. Both sides of the heart can be effected[36,37] resulting in either systolic or diastolic dysfunction.[34,38] Nir-Paz *et al*. reported a very interesting case of a 50-year-old woman who had several admissions of fever, cough, and fatigue presented with the left heart failure and left bundle branch block. An echocardiography revealed a mildly dilated left ventricle with mild-to-moderate left ventricular systolic dysfunction. A myocardial biopsy revealed amyloid deposition around myocytes, and a genetic test showed M694V mutation confirming the diagnosis of FMF.[39] Interestingly, early subclinical changes in myocardial tissues can now be detected by strain and strain rate echocardiography techniques even in asymptomatic FMF patients who used to have normal heart function by the conventional echocardiography.[40] Although the prognosis of amyloidosis induced cardiomyopathy in FMF patients is not well defined, at least one case of mortality has been reported in this population due to advanced heart failure.[41]

PULMONARY HYPERTENSION

Pulmonary hypertension should be suspected in patients at advanced stages of FMF presenting with shortness of breath, fatigue, recurrent fever, and symptoms of the right ventricular failure. Although most researchers believe pulmonary hypertension in FMF is a result of pulmonary amyloidosis,[42] Sargsyan and Narimanyan have diagnosed elevated pulmonary pressure in 6% of FMF patients without any evidence of amyloidosis.[36] In general, those patients seem to have very poor prognosis. Johnson and Lie reported a case of 48-year-old FMF patient who was diagnosed with pulmonary hypertension and then developed hypoxia, hypotension, and terminal cardiac arrhythmias that were the immediate cause of her death.[42] Likewise, in a retrospective study at the Mayo Clinic of patients with pulmonary hypertension due to amyloidosis, the authors reported a case of FMF patient who died 61 days after her diagnosis with pulmonary hypertension as a result of advanced heart failure.[43]

VALVULAR DISEASES

In a cohort study of a group of children who were diagnosed with FMF, Salah *et al*. showed that valvular diseases affect about half of the patients in rates vary from 21.8% for aortic valve, 16% for mitral valve, and 11% for the pulmonary valve.[44] Different degrees of tricuspid regurgitation were reported as well in another study.[36] These findings are attributed to amyloid deposition on heart valves during the course of FMF or they may be related to rheumatic heart disease which is believed to affect FMF patients more than others.[45]

COLCHICINE AND CARDIOVASCULAR DISEASES IN FAMILIAL MEDITERRANEAN FEVER

Colchicine has been the core treatment of FMF being so effective not only in suppressing the acute inflammatory attacks but also reducing the recurrence rate and subsequently preventing the development of amyloidosis. These benefits are believed to be related to its ability to suppress some of the functions of neutrophils, T-cells, and endothelial cells.[46] At the same time, colchicine inhibits vascular hyperplasia and fibrosis and hence plays an important role in preventing atherosclerosis and myocardial infarction.[46] The use of colchicine in cardiovascular medicine has been mainly restricted to the management of acute and recurrent pericarditis in patients who failed to respond to conventional treatment.[47] Despite the limited articles discussing the effect of colchicine on other cardiac manifestations of FMF, some data suggest a cardioprotective role. For instance, Sari *et al*. showed that the regular treatment with colchicine may prevent atherosclerosis and endothelial dysfunction in FMF patients.[23] Similarly, Langevitz *et al*. found that the frequency of ischemic heart disease was lower in colchicine-treated FMF patients compared to the general population.[35]

CONCLUSION

Various cardiovascular manifestations have been described in patients with FMF, including pericarditis, valvular diseases, CAD, cardiomyopathies, subclinical atherosclerosis, and pulmonary hypertension. Two main mechanisms, at least, are suggested: The ongoing inflammation and the amyloid deposition in the heart and vessels. By reducing these factors, colchicine, the cornerstone therapy of FMF, has been shown as an important agent in treating and preventing some of these disorders. The prognosis of cardiac complications of FMF is not well studied. However, mortality has been particularly reported in patients developing pulmonary hypertension, AMI, and cardiomyopathy. While this article presented the available data on the prevalence, pathophysiology, and prognosis of cardiac diseases in FMF patients, more studies with larger number of patients are needed to explore the relationship between cardiovascular diseases and FMF to provide better understanding of these disorders.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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