Cardiovascular Sequelae and Genetics of Familial Mediterranean Fever: A Literature Review

Jahanzeb Malik Asma Shabbir Atif Nazir

Rawalpindi Institute of Cardiology, Rawalpindi, Pakistan

Keywords

Familial Mediterranean fever · Recurrent peritonitis · Periodic peritonitis · Amyloidosis

Abstract

Introduction: Familial Mediterranean fever (FMF) is an auto-inflammatory fever syndrome distinguished by recurrent attacks of spontaneous peritonitis, pleuritis, fever, and arthritis. It is specifically seen in the ethnic groups of Mediterranean origin, but sporadic cases have been reported in Eastern Europe and America due to migrations. There is a number of cardiac manifestations associated with FMF.

Methods: Using PubMed as the search engine, the literature search was done for articles published between 1958 and 2020. To summarize the body of available evidence, a scoping review was carried out to find relevant articles and case reports in patients of FMF with cardiovascular manifestations. **Results:** In the literature, there is a number of mechanisms explaining the cause of cardiac involvement in FMF, including the subclinical inflammation and secondary (AA) amyloid deposition in the vessels and the myocardium. There is a variable and often spurious course of these manifestations and it can be associated with a poor prognosis such as an acute myocardial infarction. In FMF patients, polyarteritis nodosa and Henoch-Schönlein purpura are seen more significantly as compared to the general population with increased frequency of mutations in Mediterranean fe-

ver (MEFV) gene. Through unclear mechanisms, Behçet's disease is associated with MEFV gene mutations and shares vascular manifestations with FMF. There is an interplay of IL-1 and MEFV gene, which impart an important role in inflammatory attacks of FMF. There is an intima-media thickening of blood vessels AA to persistent inflammation which can lead to atherosclerotic plaque formation resulting in atherosclerotic cardiovascular disease. **Conclusion:** FMF and its associated cardiovascular diseases are interlinked to 2 main mechanisms: subclinical atherosclerosis and amyloid deposition, and colchicine is the primary treatment of patients with FMF which shows the regression of amyloid deposits and prevents cardiovascular sequelae.

© 2021 S. Karger AG, Basel

Introduction

Familial Mediterranean fever (FMF) is a frequently seen fever syndrome due to hereditary autoinflammatory disease. It was first described by Janeway and Mosenthal [1] in 1908, while its definition as a disease was reported by the name “benign paroxysmal peritonitis” by Siegal [1, 2]. Since then, various names have been used for this disorder, including familial periodic peritonitis, paroxysmal polyserositis, recurrent polyserositis, periodic fever, Seigal-Cattan-Mamou-disease, and Wolff periodic fever [3–5].

Table 1. Most frequently observed mutations in the MEFV gene, by various ethnic groups [49]

Mutations in different ethnicities (MEFV)	
Arabs	M680I, M694V, M694I
Armenians	M680I, M694V, V726A
Turks	M680I, M694V, V726A
Jews	
Mizrahi	E148Q, M694V
Ashkenazi	E148Q, V726A
Sephardic	E148Q, V726A, M680I, M694V
MEFV, Mediterranean fever.	

It can affect all ethnic groups but the people of Mediterranean origin are more susceptible to FMF, including the Ashkenazi Jews, Turks, Kurds, Armenians, and Arabs [6]. Geographically, the disease is more frequently seen in Turkey with a prevalence of 1:150–1:10,000 [7]. Armenians are the second most affected ethnic group. Studies show a prevalence of 1:500 in Armenia [8]. Other populations like Arabs and Jews are distributed as 1:1,000 on average. The latest studies show that the disease has increased in prevalence than previously believed in Italy and Greece as well [9, 10].

FMF is transferred as an autosomal recessive trait, occurring as a consequence of point mutations in the Mediterranean Fever (MEFV) gene at chromosome 16 [11]. This gene codes for pyrin protein, which takes part in the regulation of inflammation, cell apoptosis, and is mainly expressed in white blood cells and fibroblasts. Most frequently observed mutations in different ethnic groups are shown in Table 1. As yet, no physiological use has been defined for this protein but the main hypothesis states that pyrin has a role in suppressing unregulated inflammatory response in the body. In a normal state, it activates the pro-proteins nuclear factor kappa beta and procaspase-1, while suppressing interleukin-1 (IL-1). It is believed that the mutation in pyrin leads to an unregulated cascade of pro-protein complex and thus the inflammatory response develops [12].

The disease is mostly a diagnosis of exclusion and certain characteristics can be used in a step-wise fashion to suspect FMF. Diagnostic criteria for diagnosing FMF are differentiated in Table 2. They include a history of typical attacks, mainly in the susceptible ethnic category in which FMF is prevalent. A surge in acute phase reactants and other inflammatory markers is observed during the attacks. There is almost a definite response to colchicine therapy [13].

Table 2. Detailed criteria for the diagnosis of FMF

<i>Major criteria</i>
Typical attacks
Peritonitis (generalized)
Pleuritic (unilateral) or pericarditis
Monoarthritis (hip, knee, and ankle)
Fever alone
<i>Minor criteria</i>
Incomplete attacks involving one or more of the following
Abdomen
Chest
Joint
Exertional leg pain
Favorable response to colchicine
<i>Supportive criteria</i>
Family history of FMF
Appropriate ethnic origin
Age <20 years at disease onset
Features of attacks
Severe, requiring bed rest
Spontaneous remission
Symptom-free interval
Transient inflammatory response, with one or more abnormal test results for the white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
Episodic proteinuria/hematuria
Negative laparotomy or removal of normal appendix
Consanguinity of parents

Adapted from: Livneh A, Langevitz P, Zemer D, et al. Arthritis Rheum. 1997;40:1879 (reference: [64]). FMF, familial Mediterranean fever (diagnosed if ≥ 1 major criteria, ≥ 2 minor criteria, 1 minor plus 5 supportive criteria, and 1 minor plus ≥ 4 of the first 5 criteria).

Although sensitive, these features make up the triad for other fever syndromes and there is an absolute overlap of the symptoms of FMF. Hence, a certain diagnosis is confirmed upon genetic analysis of the patients. This can recognize mutations in MEFV gene encoding exons 2, 3, 5, and 10 which makes up 97% of all known mutations [13]. A metaraminol provocative test can also differentiate between FMF and other fever syndromes. Administration of metaraminol can induce a mild form of FMF attack within 48 h, although it is more specific than sensitive, it cannot identify all FMF patients. However, a positive test has a high positive predictive value [14].

With an average of 20 h of the onset of the attack, various constitutional symptoms and physical signs including restlessness, anxiety, alterations in taste, and irritability are evoked as a prodromal phase [15]. High-grade fe-

ver is the most important clinical symptom in the diagnosis of FMF. It typically lasts for 1–3 days and emerges spontaneously, rapidly increases, touches a plateau phase followed by a rapid decline touching the baseline [16]. FMF has an insidious involvement of multiple organ systems, including the renal, gastrointestinal, hematologic, and musculoskeletal systems. However, cardiovascular involvement is less commonly reported and it is important to diagnose these manifestations as they can mislead to another diagnosis, and certain conditions have increased morbidity and/or mortality. In this review, various cardiovascular manifestations of FMF and their genetic pathophysiology are discussed.

Methods

Using PubMed as the search engine, the literature search was done for articles published between 1958 and 2020. To summarize the body of available evidence, a scoping review was carried out to find relevant articles and case reports in patients of FMF with cardiovascular manifestations. In our search, we used the terms “Familial Mediterranean fever” or “FMF” in combination with keywords “cardiovascular diseases,” “pericardial diseases,” “atherosclerotic coronary and peripheral arterial disease,” “vasculitis,” “pulmonary hypertension,” “valvular heart disease,” and “cardiomyopathies.” Relevant English full texts were selected most relevant to this discussion and incorporated in a narrative fashion. We included observational studies, case series, and case reports, while excluding duplicates.

Cardiovascular Manifestations

Pericardial Diseases

When compared with other types of serositis, pericarditis is rare in FMF. It tends to occur at a later stage of FMF in patients with recurrent attacks of polyserositis and has an incidence of <1% of the patients [17]. There is no feasible explanation for the early sparing of the pericardium. However, there may be a propensity to underdiagnose pericarditis by the concurrent attacks at other sites and there remains a dubious association of pleuritic and pericarditis, which can account for infrequent diagnosis of pericarditis.

Sohar et al. [18] did not report any pericardial attack in 470 FMF patients [18]. They considered the association of pericarditis with FMF unclear. Other large case series were unable to report an attack of pericarditis in their subjects. Likewise, Zemer et al. [19] suggested the patient with constrictive pericarditis in FMF was fortuitous [19]. However, many studies have reported that FMF has a

higher incidence of pericardial attacks as compared with healthy individuals. In some retrospective studies, the prevalence of pericarditis was reported between 0.5 and 1.5% [20, 21]. Incidence of pericardial disease was increased when using echocardiography as a diagnostic modality in FMF patients, as suggested by Dabestani et al. [22]. In children, pericardial involvement was reported to be 11% with FMF and acute presentation of chest pain. A certain M694V and E148Q mutations are implicated in causing pericardial attacks in FMF [23].

While most of the pericardial symptoms occur in conjunction with other FMF manifestations, solitary pericardial involvement has been described in the literature [24–26]. A diagnosis of FMF should be suspected in patients with recurrent episodes of pericarditis refractory to treatment, requiring further genetic analysis for the accurate diagnosis.

Vascular Manifestations

In FMF patients, polyarteritis nodosa (PAN) and Henoch-Schönlein purpura (HSP) are seen significantly more as compared to the general population [21]. Although Behçet’s disease (BD) was found to have increased frequency of mutations in MEFV gene, a clear association between FMF and BD is not clear [27].

PAN is an inflammatory necrotizing disease of small and medium arteries and it is characterized by fever, malaise, body aches, and a number of other constitutional symptoms. There is a frequent co-occurrence of FMF with PAN and FMF-associated vasculitis, including PAN has an established link with mutations in MEFV gene [28]. It is present in 1% of patients with FMF, while in general population, its prevalence is 4/100,000 [28]. PAN is primarily diagnosed in the second and third decade of life, particularly in patients with FMF. Many presentations of the disease, including arthralgias, visceral necrosis, and cutaneous vasculitis, occur more commonly in FMF-associated PAN as compared to classical PAN [29]. Investigations have demonstrated a high level (38%) of MEFV gene mutations in PAN without symptoms of FMF, reflecting a causative relationship between MEFV gene and vascular manifestations of PAN [30].

Like PAN, HSP is another common vasculitides among young FMF patients. It is an IgA-mediated immune complex disease of small vessels in children that classically presents with arthritis, palpable purpura, and colicky abdominal pain [31]. One study from Turkey demonstrated mutations in MEFV gene in 34% of pediatric HSP patients [32]. Another study from Israel found 9.6% chance of heterozygous mutations in MEFV gene in HSP pa-

tients, irrespective of FMF symptoms [33]. Its prevalence in FMF varies from 3 to 7%, while 0.8% cases are diagnosed in general pediatric cohort [28].

BD is a genetic multisystem disease consisting of oral and genital ulcers, erythematous lesions, central nervous system involvement, and vascular manifestations like arterial aneurysms, arteritis, and venous thrombosis [34]. Evidence regarding association of FMF with BD is not clear. However, many investigators have found an increased frequency of MEFV gene mutations with BD (44%). Atagunduz et al. [35] associated BD with MEFV mutations to have higher vascular manifestations as compared to noncarriers. On the other hand, Ben-Chetrit et al. [36] found that none of the 353 patients with FMF had concomitant BD. Despite contrasting results, these findings support an association of MEFV gene in BD. Apart from vasculitides, coronary vasculitis leading to myocardial infarction, vasculitis, and Raynaud's have also been reported in 2 various case reports [37, 38].

Atherosclerotic Coronary Artery Disease

There is a propensity for inflammatory attacks in FMF. They mostly consist of peritonitis, pleuritic, or arthritis presenting as abdominal pain, chest pain, and arthralgias. Although FMF is implicated as a novel risk enhancer in atherosclerotic cardiovascular disease, the mechanism is still not clear. There is an interplay of IL-1 and MEFV gene, which imparts an important role in inflammatory attacks of FMF [39].

Studies have compared markers of early arterial wall thickness in the general population with FMF patient cohort. Akdogan et al. [40] suggested an increased carotid intima-media thickness (CIMT) in patients with FMF as compared to healthy controls. Another study by Ugurlu et al. [41] showed an increased carotid and femoral artery IMT in both FMF and systemic lupus erythematosus. There are studies showing an increased IMT in pediatric FMF patients demonstrating that inflammatory process starts at an early age [41]. Therefore, a possible relationship between atherosclerosis and FMF exist as CIMT is reported as an early predictor of atherosclerosis in children and young adults [42]. In addition, there is an increased carotid and femoral pulse wave velocity in FMF, which is considered as an adjunct to atherosclerosis due to intimal damage leading to migration of smooth muscle cells in the intima of the vessels. This can promote the cascade of lipid accumulation in the vessels [43]. A proposed hypothesis is persistent inflammation even between the attacks which causes rapid proliferation of LDL-C and cholesterol in the intima of arterial lumen and lipid plaque

formation. Since a systemic inflammatory state can induce the progression of atherosclerosis, it is hypothesized that patients with FMF are at an increased risk of developing coronary artery disease (CAD) as compared with healthy patients [44]. However, 2 fair-sized studies failed to show any relationship between CIMT and atherosclerotic cardiovascular disease [45, 46]. This conflict of evidence may suggest that patients with FMF can be at a slightly higher risk of developing CAD but the progression of the preclinical atherosclerosis is not very aggressive. Hence, most of the patients are free from significant plaques. To add, colchicine with its antiatherosclerotic properties may be the slowing factor of this process, but clinical trials are needed to confirm this hypothesis.

There is a positive relationship between FMF and CAD as suggested by Kisacik et al. [47]. They compared the prevalence of MEFV mutation in patients with and without CAD which showed higher MEFV mutation in early CAD. However, there are only 2 case reports of acute coronary syndrome in FMF patients [48, 49]. Both of the patients were young and had a fatal MI. One of them had an acute myocardial infarction after stopping colchicine and the other one had a history of FMF and amyloidosis. In one autopsy analysis, 2 pathophysiological processes of both accelerated atherosclerosis and intravascular amyloidosis deposition were implicated [50]. As colchicine can alter both of these processes, this can explain the lower numbers of CAD in patients with FMF.

Cardiomyopathy

The prevalence of secondary (AA) amyloidosis varies in autoinflammatory disorders and it most commonly affects the patients with FMF. Before colchicine, it was reported in 50% of FMF patients [51]. Its frequency has decreased to 13% after appropriate treatment with colchicine prophylaxis as suggested by a large study in Turkey [21].

Deposition of amyloid in the myocardium can present as a progressive biventricular failure from systolic and diastolic dysfunction. A case report describes a chance diagnosis of a patient with complaints of systolic ventricular dysfunction after endomyocardial biopsy [52]. The biopsy revealed amyloid deposition around the myocytes, and a genetic mutation of M694V was positive which confirmed the diagnosis. Nowadays, an 18 F-FDG-PET/CT can confirm the diagnosis of FMF after initial diagnostic workup fails to show any characteristic finding [53]. The gold standard test for diagnosis of FMF is a cardiac magnetic resonance imaging [54].

Color version available online

Fig. 1. Pathophysiology and cardiovascular effects of inflammation during acute attacks of FMF. FMF, familial Mediterranean fever.

Table 3. Cardiac manifestations and their treatment in FMF

Disease states	Treatment
ASCVD Stable CAD ACSs	Antiplatelet agents, statins, beta-blockers, and RAAS blockers
Amyloidosis Heart failure Arrhythmias Hyper-coagulant state	Colchicine, IL-1/IL-6 inhibitors, RAAS blockers, ARNI, beta-blockers, and implantable cardioverter-defibrillators
Pericarditis Constrictive pericarditis Cardiac tamponade	Colchicine and NSAIDS
Vasculitis HSP PAN Isolated coronary vasculitis	Corticosteroids, azathioprine, and immunosuppressants

RAAS, renin-angiotensin-aldosterone; NSAIDS, nonsteroidal anti-inflammatory drugs; ARNI, angiotensin receptor neprilysin inhibitor; FMF, familial Mediterranean fever; PAN, polyarteritis nodosa; HSP, Henoch-Schönlein purpura; ASCVD, atherosclerotic cardiovascular disease; IL, interleukin; CAD, coronary artery disease; ACSs, acute coronary syndromes.

Rare Cardiac Manifestations

Some data associated with FMF have suggested an autonomic dysfunction with or without clinical symptoms. A study observed heart rate variability, QT dispersion, cardiac repolarization dynamics, and risk factors for re-entrant arrhythmias. It showed no difference in repolarization or QT dispersion in patients with or without amyloidotic FMF [55, 56]. Various systemic inflammatory syndromes like inflammatory bowel disease, ankylosing spondylitis, multiple sclerosis, and vasculitides can coexist with FMF. Any FMF patient with signs of right heart failure should be evaluated for pulmonary hypertension. Some researchers believe that pulmonary hypertension in FMF is due to AA amyloidosis but a study has demonstrated that pulmonary hypertension can present without amyloidosis [57].

Deposition of amyloid on heart valves with FMF affects around half of the patients with aortic valve involved in 21.8% and mitral valve in 16% [58]. Tricuspid and pulmonary valves are also affected in one study [57]. Rheumatic fever is implicated for valvular lesions in FMF because they increase the propensity of bacterial nidus on the valve endothelium [59]. Various cardiovascular manifestations and its treatment is summarized in Table 3.

Schematic mechanism of inflammation and cardiovascular manifestations is shown in Figure 1.

Treatment Modalities

The mainstay of treatment for FMF is colchicine. It is an anti-inflammatory drug that inhibits tubulin polymerization and inhibits mitosis, leading to inhibition of neutrophil migration to inflammatory sites and stops the production of superoxide anion [60]. Colchicine is metabolized in cytochrome P450 and it is actively metabolized via enterohepatic circulation. There is a robust emerging evidence of colchicine in acute coronary syndrome [61]. When used in such patients, it shows an exponential decrease in C-reactive protein levels and due to its antimitotic effects on platelets and endothelial cells, it decreases the incidence of MI and pericarditis [62, 63]. The effect of subclinical inflammation is the inciting cause for augmented atherosclerotic process in FMF. Colchicine can alter this mechanism of inflammation in FMF, exerting a cardioprotective effect on the patients. Apart from IHD, a lifelong prophylaxis of colchicine can prevent inflammatory attacks, pericarditis, and cardiac amyloidosis [64].

The patients who are resistant to colchicine have been known to respond to IL-1 receptor antagonists like anakinra and canakinumab. These agents have been studied in clinical studies and they exert a positive effect on FMF-associated amyloidosis. In patients with AA amyloidosis, IL-1 antagonists have shown a reversal of the disease. For FMF-associated vasculitis, corticosteroids and immunosuppressive agents are used with positive results. However, a paucity of literature demands more trials in these FMF subsets. Inhibition of systemic inflammation with colchicine and biologic agents has decreased cardiovascular complications in FMF patients but further large clinical trials are needed for efficacy and safety of these agents [63].

Conclusion

Several cardiovascular manifestations have been reported in the literature regarding FMF, including pericarditis, effusive-constrictive cardiomyopathy, biventricular failure, subclinical atherosclerosis, and CAD. Two main mechanisms lead to the pathophysiology: the underway inflammation and the amyloid deposition in the myocardium and the coronaries. Colchicine, by its anti-inflammatory mechanism, has shown a pivotal role in the treatment of FMF. Cardiovascular morbidity and mortality associated with FMF have not been well studied. Hence, there is a need for powerful multicenter trials to accurately describe the real burden of the disease in the susceptible regions and its impact on a global scale.

Statement of Ethics

The article is exempt from Ethical Committee approval because it does not involve human or animal subjects as a part.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

J.M.: concept, literature search, first draft, final draft, and critical review. A.S.: literature search, first draft, final draft, and critical review. A.N.: supervision and critical review.

References

- 1 Janeway TC, Mosenthal HO. An unusual paroxysmal syndrome, probably allied to recurrent vomiting. *Arch Intern Med*. 1908;II(3): 214–25.
- 2 Siegal S. Benign paroxysmal peritonitis. *Ann Intern Med*. 1945;23:1–21.
- 3 Cattani R, Mamou H. (14 Cases of periodic disease, 8 of which are complicated by kidney diseases). *Bull Mem Soc Med Hop Paris*. 1951; 67(25–26):1104–7.
- 4 Reimann HA. Periodic disease; a probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia. *J Am Med Assoc*. 1948;136(4):239–44.
- 5 Reimann HA. Perplexities of a periodic entity. *JAMA*. 1964;190(3):241.
- 6 Onen F. Familial mediterranean fever. *Rheumatol Int*. 2006;26(6):489–96.
- 7 Cakir N, Pamuk ON, Dervis E, Imeryuz N, Uslu H, Benian O, et al. The prevalences of some rheumatic diseases in western Turkey: havsa study. *Rheumatol Int*. 2012;32:895–908.
- 8 Sarkisian T, Ajrapetian H, Beglarian A, Shamsuvarian G, Egiastian A. Familial mediterranean fever in armenian population. *Georgian Med News*. 2008;156:105–11.
- 9 Ben-Chetrit E, Touitou I. Familial mediterranean fever in the world. *Arthritis Rheum*. 2009;61(10):1447–53.
- 10 Deltas CC, Mean R, Rossou E, Costi C, Koupepidou P, Hadjiyanni I, et al. Familial mediterranean fever (FMF) mutations occur frequently in the Greek-cypriot population of cyprus. *Genet Test*. 2002;6(1):15–21.

- 11 Gershoni-Baruch R, Shinawi M, Leah K, Badarnah K, Brik R. Familial mediterranean fever: prevalence, penetrance and genetic drift. *Eur J Hum Genet*. 2001;9(8):634–7.
- 12 Manukyan G, Aminov R. Update on pyrin functions and mechanisms of familial mediterranean fever. *Front Microbiol*. 2016;7:456.
- 13 Livneh A, Langevitz P. Diagnostic and treatment concerns in familial mediterranean fever. *Baillieres Best Pract Res Clin Rheumatol*. 2000;14(3):477–98.
- 14 Barakat MH, El-Khawad AO, Gumaa KA, El-Sobki NI, Fenech FF. Metaraminol provocative test: a specific diagnostic test for familial mediterranean fever. *Lancet*. 1984;1(8378):656–7.
- 15 Sönmez HE, Batu ED, Özen S. Familial Mediterranean fever: current perspectives. *J Inflamm Res*. 2016;9:13–20.
- 16 Livneh A, Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, et al. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum*. 1996;26:612–27.
- 17 Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF). *QJM*. 1997;90(10):643–7.
- 18 Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med*. 1967;43:227–53.
- 19 Zemer D, Cabili S, Revach M, Shahin N. Constrictive pericarditis in familial Mediterranean fever. *Isr J Med Sci*. 1977;13:55–8.
- 20 Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A, et al. Attacks of pericarditis as a manifestation of familial mediterranean fever (FMF). *QJM*. 1997;90:643–7.
- 21 Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine*. 2005;84:1–11.
- 22 Dabestani A, Noble LM, Child JS, Krivokapich J, Schwabe AD. Pericardial disease in familial Mediterranean fever: an echocardiographic study. *Chest*. 1982;81:592–5.
- 23 Kilic A, Varkal MA, Durmus MS, Yildiz I, Yildirim ZN, Turunc G, et al. Relationship between clinical findings and genetic mutations in patients with familial Mediterranean fever. *Pediatr Rheumatol Online J*. 2015;13:59.
- 24 Okutur K, Seber S, Oztekin E, Bes C, Borlu F. Recurrent pericarditis as the initial manifestation of familial Mediterranean fever. *Med Sci Monit*. 2008;14(12):CS139–41.
- 25 Gökçe I, Gökçe S, Kılıç A, Bozlar U, Kocaoglu M, Ongürü O, et al. Familial Mediterranean fever with protein-losing enteropathy due to constrictive pericarditis. *World J Pediatr*. 2011;7:365–7.
- 26 Yoshioka K, Furumitsu Y, Sano T, Miyamoto T, Agematsu K. Acute pericarditis as the first manifestation of familial Mediterranean fever: a possible relationship with idiopathic recurrent pericarditis. *Intern Med*. 2014;53:1659–63.
- 27 Tóitou I, Magne X, Molinari N, Navarro A, Quéllec AL, Picco P, et al. MEFV mutations in Behçet's disease. *Hum Mutat*. 2000;16:271–2.
- 28 Özdoğan H, Arısoy N, Kasapcopur Ö, Sever L, Calışkan S, Tuzuner N, et al. Vasculitis in familial Mediterranean fever. *J Rheumatol*. 1997;24:323–7.
- 29 Akar S, Göktaş Y, Akıncı B, Tekis D, Biberoglu K, Birlık M, et al. A case of familial Mediterranean fever and polyarteritis nodosa complicated by spontaneous perirenal and subcapsular hepatic hemorrhage requiring multiple arterial embolizations. *Rheumatol Int*. 2005;25:60–4.
- 30 Yalcinkaya F, Özçakar ZB, Kasapcopur Ö, Öztürk A, Akar N, Bakkağlu A, et al. Prevalence of MEFV gene mutations in childhood polyarteritis nodosa. *J Pediatr*. 2007;151:675–8.
- 31 Dedeoğlu F, Sundel RP. Vasculitis in children. *Pediatr Clin North Am*. 2005;52:547–vii.
- 32 Özcakar ZB, Yalcinkaya F, Cakar N, Acar B, Kasapcopur O, Uğüten D, et al. MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. *J Rheumatol*. 2008;35:2427–9.
- 33 Gershoni-Baruch R, Broza Y, Brik R. Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schönlein purpura. *J Pediatr*. 2003;143:658–61.
- 34 Cocco G, Gasparyan AY. Behçet's disease: an insight from a cardiologist's point of view. *Open Cardiovasc Med J*. 2010;23:63–70.
- 35 Atağündüz P, Ergun T, Direskeneli H. MEFV mutations are increased in Behçet's disease (BD) and are associated with vascular involvement. *Clin Exp Rheumatol*. 2003;21(4 Suppl 30):35–7.
- 36 Ben-Chetrit E, Cohen R, Chajek-Shaul T. Familial mediterranean fever and Behçet's disease—are they associated? *J Rheumatol*. 2002;29:530–4.
- 37 Serrano R, Martínez MA, Andrés A, Morales JM, Samartin R. Familial Mediterranean fever and acute myocardial infarction secondary to coronary vasculitis. *Histopathology*. 1998;33:163–7.
- 38 Cocco G. Vasculitis, left bundle branch block, and Raynaud's phenomenon as a manifestation of familial mediterranean fever. *Arch Med Sci*. 2008;4:460–4.
- 39 Gang N, Drenth JP, Langevitz P, Zemer D, Breznik N, Pras M, et al. Activation of the cytokine network in familial Mediterranean fever. *J Rheumatol*. 1999;26(4):890–7.
- 40 Akdoğan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L, et al. Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. *J Am Coll Cardiol*. 2006;48(11):2351–3.
- 41 Ugurlu S, Karaca S, Demirel Y, Seyahi E. P01-014 – subclinical atherosclerosis in FMF. *Pediatr Rheumatol*. 2013;11(Suppl 1):A18.
- 42 Peru H, Altun B, Dogan M, Kara F, Elmacı A, Oran B. The evaluation of carotid intima-media thickness in children with familial Mediterranean fever. *Clin Rheumatol*. 2008;27:689–94.
- 43 Bilginer Y, Özalpın F, Basaran C, Duzova A, Besbas N, Topaloglu R, et al. Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis. *Rheumatol Int*. 2008;28:1211–6.
- 44 Bilginer Y, Özalpın F, Basaran C, Duzova A, Besbas N, Topaloglu R, et al. Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis. *Rheumatol Int*. 2008;28(12):1211–6.
- 45 Caliskan M, Gullu H, Yilmaz S, Erdogan D, Unler GK, Ciftci O, et al. Impaired coronary microvascular function in familial Mediterranean fever. *Atherosclerosis*. 2007;195(2):e161–7.
- 46 Sari I, Karaoglu O, Can G, Akar S, Gulcu A, Birlık M, et al. Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. *Clin Rheumatol*. 2007;26:1467–73.
- 47 Kisacik B, Basar N, Ercan S, Pehlivan Y, Yilmaz S, Simsek I, et al. Familial Mediterranean fever (FMF) gene mutations (MEFV): are they a risk factor for coronary artery disease? *Ann Rheum Dis*. 2013;71:637.
- 48 Uyarel H, Karabulut A, Okmen E, Cam N. Familial Mediterranean fever and acute anterior myocardial infarction in a young patient. *Anadolu Kardiyol Derg*. 2006;6:272–4.
- 49 Ambartsymin SV. Myocardial infarction in patients with familial Mediterranean fever and cardiac lesions. *Georgian Med News*. 2012;204:62–6.
- 50 Obici L, Merlini G. Amyloidosis in autoimmune syndromes. *Autoimmun Rev*. 2012;12(1):14–7.
- 51 Nir-Paz R, Ben-Chetrit E, Pikarsky E, Hassin D, Hasin Y, Chajek-Shaul T, et al. Unusual presentation of familial Mediterranean fever: role of genetic diagnosis. *Ann Rheum Dis*. 2000;59:836–8.
- 52 Yamashita K, Mizugishi K, Takaori-Kondo A. Familial Mediterranean fever mutations in a patient with periodic episodes of systemic pain deriving from cancer bone metastases. *Intern Med*. 2018;57(19):2901–4.
- 53 Turan A, Mercan R, Bitik B, Kucuk H, Ozturk M, Tufan A. Magnetic resonance imaging features of familial mediterranean fever associated spondyloarthritis. *Pediatr Rheumatol*. 2015;13(Suppl 1):P114.
- 54 Nussinovitch U, Livneh A, Volovitz B, Nussinovitch M, Ben-Zvi I, Lidar M, et al. Normal QT dispersion in colchicine-resistant familial Mediterranean fever (FMF). *Clin Rheumatol*. 2012;31(7):1093–6.

- 55 Abbara S, Grateau G, Ducharme-Bénard S, Saadoun D, Georgin-Lavialle S. Association of vasculitis and familial mediterranean fever. [Front Immunol](#). 2019;10:763.
- 56 Sargsyan A, Narimanyan M. Pulmonary hypertension in familial Mediterranean fever: consequence or coincidence? [Pediatr Rheumatol](#). 2015;13(S1):O41.
- 57 Salah S, Hegazy R, Ammar R, Sheba H, Abdelrahman L. MEFV gene mutations and cardiac phenotype in children with familial mediterranean fever: a cohort study. [Pediatr Rheumatol Online J](#). 2014;12:5.
- 58 Leung YY, Yao Hui LL, Kraus VB. Colchicine—update on mechanisms of action and therapeutic uses. [Semin Arthritis Rheum](#). 2015;45(3):341–50.
- 59 Gasparyan AY, Ayyvazyan L, Yessirkepov M, Kitas GD. Colchicine as an anti-inflammatory and cardioprotective agent. [Expert Opin Drug Metab Toxicol](#). 2015;11(11):1781–94.
- 60 Grattagliano I, Bonfrate L, Ruggiero V, Scaccianoce G, Palasciano G, Portincasa P. Novel therapeutics for the treatment of familial Mediterranean fever: from colchicine to biologics. [Clin Pharmacol Ther](#). 2014;95(1):89–97.
- 61 Ben-Chetrit E, Touitou I. Familial mediterranean fever in the world. [Arthritis Rheum](#). 2009;61:1447–53.
- 62 Malik J, Javed N, Ishaq U, Khan U, Laique T. Is there a role for colchicine in acute coronary syndromes? A literature review. [Cureus](#). 2020;12(5):e8166.
- 63 Portincasa P. Colchicine, biologic agents and more for the treatment of familial mediterranean fever. The old, the new, and the rare. [Curr Med Chem](#). 2016;23(1):60–86.
- 64 Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. [Arthritis Rheum](#). 1997;40(10):1879–85.