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REVIEW ARTICLE

Cardiovascular manifestations of monogenic periodic fever syndromes

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Abstract

Periodic fever syndromes (PFS) are a group of autoinflammatory diseases characterized by repeated febrile episodes and systemic inflammation. The most common monogenic periodic fever syndromes are familial Mediterranean fever, mevalonate kinase deficiency/hyper immunoglobulin D syndrome, cryopyrin-associated periodic syndrome, and tumor necrosis factor receptor-associated periodic syndrome. Although fever is the predominant feature of PFS, other systems, including the cardiovascular system, may be involved in the disease process. This review focuses on cardiovascular risks and issues in monogenic PFS. Cardiovascular involvement may occur as a disease manifestation, association, or result of complications or a drug's adverse effects in monogenic PFS. Pericarditis seems to be a feature of PFS. Patients with recurrent pericarditis or pericarditis resistant to conventional treatment should be evaluated for PFS. Amyloidosis is the most severe complication of PFS, increasing the risk of cardiac morbidity. Furthermore, ongoing inflammation may result in early atherosclerosis. Therefore, assessing cardiovascular risks in PFS patients should be considered a part of routine care.

Key points

- *Pericarditis is the most common cardiac involvement of monogenic periodic fever syndromes (PFS), while some forms may present with myocarditis.*
- *Amyloidosis, the most significant complication of PFS, may lead to deterioration in cardiac functions.*
- *Ongoing inflammation in PFS may result in endothelial dysfunction and atherosclerosis.*
- *Effective control of inflammation and reducing concomitant risk factors such as obesity, diabetes mellitus, and hypertension could improve cardiovascular outcomes in PFS patients.*

Keywords Cardiac involvement · Cardiovascular disease · Pericarditis · Periodic fever syndromes

Abbreviations

ADMA	Asymmetric dimethyl arginine
ANS	Autonomic nervous system
BD	Behçet's disease
CAPS	Cryopyrin-associated periodic syndrome
CIMT	Carotid intima-media thickness
EMPs	Endothelial microparticles
FCAS	Familial cold autoinflammatory syndrome
FMF	Familial Mediterranean fever
HIDS	Hyper immunoglobulin D syndrome
HDL	High-density lipoprotein
HRV	Heart rate variability
IgAV	Immunoglobulin-A vasculitis
IL	Interleukin
IRAP	Idiopathic recurrent acute pericarditis
LDL	Low-density lipoprotein
MEFV	Mediterranean fever
MKD	Mevalonate kinase deficiency
MVK	Mevalonate kinase
MWS	Muckle-Wells syndrome
NLRP3-AIDs	NLRP3-associated autoinflammatory diseases
NOMID/CINCA	Neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome

Part of the Topical Collection entitled '*Cardiovascular Issues in Rheumatic Diseases*'

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PAN	Polyarteritis nodosa
PFS	Periodic fever syndromes
SAA	Serum amyloid A
TG	Triglyceride
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome

Introduction

Periodic fever syndromes (PFS) are a group of autoinflammatory disorders that are mediated by the overactivation of the innate immune system without the presence of autoreactive antibodies or antigen-specific T cells [1]. Periodic fever syndromes are a diagnostic spectrum that includes illnesses with Mendelian inheritance and diseases with complex modes of inheritance [1]. The clinical manifestations of PFS consist mainly of repeated febrile episodes lasting for a few days to a few weeks, accompanied by systemic inflammation.

The most common monogenic PFS is familial Mediterranean fever (FMF) [2]. The other relatively more common ones are mevalonate kinase deficiency (MKD)/hyper immunoglobulin D syndrome (HIDS), cryopyrin-associated periodic syndrome (CAPS), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Clinical features of these syndromes differ; however, genetic analysis is generally required to verify the ultimate diagnosis.

Cardiovascular findings are commonly present in PFS. However, there are limited data on cardiovascular issues in PFS. Therefore, this review aims to provide an overview of cardiovascular involvement and cardiovascular risk factors in monogenic PFS. We will focus on the more common PFS such as FMF, MKD/HIDS, CAPS, and TRAPS.

Search strategy

A review of the literature was retrieved from Web of Science, Scopus, and MEDLINE/PubMed databases until December 2022, according to the published guidance on narrative reviews [3], by using the following keywords: "familial Mediterranean fever," "mevalonate kinase deficiency," "hyper immunoglobulin D syndrome," "cryopyrin-associated periodic syndrome," "tumor necrosis factor receptor-associated periodic syndrome," "cardiac involvement," and "cardiovascular disease." The search was restricted to English-language articles. The publications that provided data about cardiovascular issues in monogenic PFS were included. The reference lists of the included articles were also examined in detail. Priority was frequently given to the papers published within the last decade.

Familial Mediterranean fever

Familial Mediterranean fever (FMF), which is due to gain-of-function mutations of the *MEditerranean FeVer* (*MEFV*) gene, is the prototype of PFS [4]. The pyrin protein encoded by the *MEFV* gene is involved in the activation of the caspase-1 enzyme and the production of interleukin (IL)-1-β [4]. Pyrin is expressed in monocytes, granulocytes, and dendritic cells in the serosal membranes, such as peritoneal, pleural, and pericardial. Pyrin plays a role in converting pro-IL-1β molecule into its active form IL-1β, which is a significant mediator of fever and inflammation. Despite being categorized as an autosomal recessive condition, the FMF phenotype can be present in people carrying just one mutation [5].

Colchicine forms the mainstay of FMF treatment [6]. It prevents febrile episodes, subclinical inflammation, and secondary amyloidosis. Most of the patients with FMF demonstrate a complete response, while 5–10% are unresponsive or intolerant to colchicine therapy. Colchicine resistance is generally defined as perpetuating disease activity as frequent attacks (≥1 attack per month) or subclinical inflammation despite a maximum tolerated dose of colchicine for 3–6 months [7]. Since interleukin-1 (IL-1) is the main cytokine responsible for the inflammation in FMF, anti-IL-1 agents emerge as a potential therapeutic alternative in colchicine-resistant FMF cases [7].

Patients with FMF usually manifest with recurrent, unprovoked, and self-limiting episodes of fever and serositis [8]. Cardiovascular issues in FMF include cardiac involvement of FMF as pericardial disease, increased frequency of comorbid vascular disorders (mainly vasculitis), cardiovascular effects secondary to inflammation such as atherosclerosis, cardiovascular effects due to secondary amyloidosis, and side effects of FMF treatment (Fig. 1) (Table 1).

Cardiac involvement of FMF

Pericardial disease

Pericarditis is the inflammation of the pericardium. In the presence of pericarditis, patients present with sudden onset of sharp chest pain worsening by lying down or deep breathing. The diagnosis of pericarditis is based on symptoms. In case of pericarditis, the pain is characteristically retrosternal, which is different from unilateral chest pain due to pleuritis in FMF attacks [9]. The electrocardiogram reveals elevated ST, and a chest X-ray or echocardiography may confirm the evidence of pericardial fluid accumulation.

Compared with other serositis types, recurrent pericarditis is infrequent in FMF [10]. Usually, pericarditis is seen in the late course of FMF [10]. A study including children and adults showed that the mean age at the first pericardial attack and the first FMF attack was 30 ± 10.8 years and 13 ± 7.96

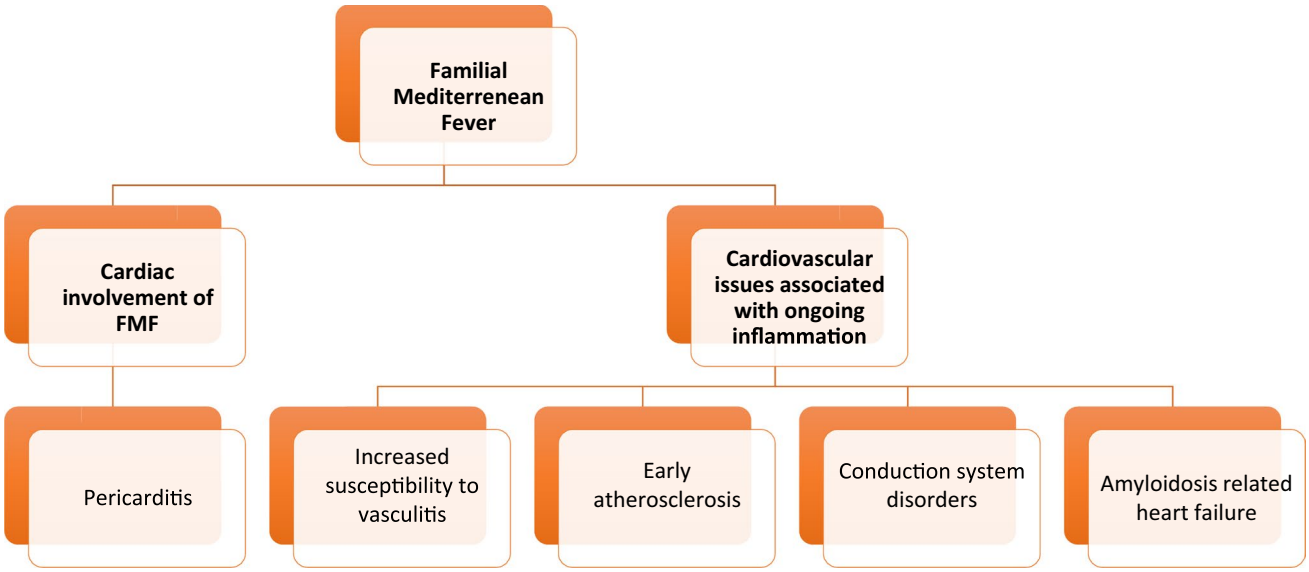

Fig. 1 Cardiovascular risks and issues in familial Mediterranean fever

years, respectively [10]. However, recurrent pericarditis may be FMF's initial or sole manifestation [11]. FMF has even been reported in pediatric cases who had cardiac tamponade at disease onset [12–14].

Many studies have confirmed that pericarditis is more common in FMF patients than in healthy individuals [15]. A nationwide multicenter study from Turkey evaluating 2468 pediatric and adult FMF patients reported 60 (2.4%) cases, presenting with at least one episode of pericarditis during their disease course. Among these 60 patients, 34 had definite, and 26 had probable pericarditis [16]. In another study including pediatric and adult FMF patients (n=4000) from Israel, the rate of pericarditis was reported as 0.6% [10]. Kilic et al. [17] evaluated the association between clinical findings and genetic variants in pediatric FMF patients. They showed an increased frequency of chest pain among patients carrying homozygous M694V and heterozygous E148Q variants. Pericardial effusion was detected by using echocardiography in 10.9% of patients suffering from chest pain. Another pediatric study by Salah et al. [18] reported an association between pericardial effusions and the presence of E148Q, P369S, and V726A variants. Tutar et al. [19] found that the frequency of pericardial effusion during the FMF attacks was 3.6% in their study including adult and pediatric patients. With the increase in the usage of echocardiography as a diagnostic tool in clinical practice, pericardial disease may be more frequently diagnosed. Most recently, the rate of pericarditis in FMF patients was 0.6% in a large pediatric cohort, and an increased frequency of chest pain among children with homozygous or compound heterozygous mutations in exon 10 was observed [20]. In patients with recurrent attacks of pericarditis or pericarditis refractory to standard treatment, FMF should be sought for, especially in endemic regions.

Increased frequency of comorbid vascular diseases

Vasculitides

Increased susceptibility to various systemic inflammatory diseases has been reported in FMF patients [21]. The high prevalence of vasculitides, such as polyarteritis nodosa (PAN) and immunoglobulin-A vasculitis (IgAV), was demonstrated in pediatric and adult FMF patients [21]. A systematic review showed that the most prevalent vasculitis in FMF patients was IgAV (prevalence: 2.7–7%), followed by PAN (prevalence: 0.9–1.4%) [22]. Patients with IgAV and FMF share the same phenotype with isolated IgAV except for intussusception. Increased frequency of intussusception in patients with IgAV and FMF (8.7%) was reported compared to the patients with isolated IgAV [22]. Also, recurrent IgAV suggests FMF comorbidity [23]. Polyarteritis nodosa is a necrotizing vasculitis, predominantly affecting medium-sized vessels. Patients with FMF-associated PAN and patients with isolated PAN express some distinctive features. FMF-associated PAN is associated with a younger age at disease onset, increased frequency of central nervous system involvement, and perirenal hematoma [22]. Cardiac involvement, including coronary vasculitis, is a significant feature of PAN. However, cardiac involvement is less common in patients with FMF-associated PAN than in patients with PAN alone (6.6% vs. 20.4%) [22, 24]. Behçet's disease (BD) is a vasculitis affecting arteries and veins of any size. The association between FMF and BD is not clear. Ben-Chetrit et al. [25] suggested that BD and FMF were two distinct diseases with a mildly high trend that cannot be verified to have a definite relationship. However, interestingly, carriage

Table 1 Summary of relevant publications addressing cardiovascular issues in familial Mediterranean fever (FMF)

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Kees et al. [10]	Observational study	Adults and children	4000	Frequency of pericarditis	27/4000 (0.6%)
Turkish FMF Study Group [16]	Observational study	Adults and children	2468	Frequency of pericarditis	60/2468 (2.4%)
Okutur et al. [11]	Case report	Adult	1	Association between recurrent pericarditis and FMF	A 25-year-old woman presenting with recurrent pericarditis as an initial manifestation of FMF
Zimand et al. [13]	Case report	Child	1	Cardiac tamponade	One child presented with cardiac tamponade and was finally diagnosed with FMF
Yoldas et al. [12]	Case report	Children	2	Cardiac tamponade	Two children presented with cardiac tamponade and were finally diagnosed with FMF
Malek A et al. [14]	Case report	Child	1	Cardiac tamponade	One child presented with cardiac tamponade and was finally diagnosed with FMF
Salah et al. [18]	Observational study	Children	55	Association between genotype and phenotype	Increased frequency of pericardial effusion among patients carrying E148Q, P369S, and V726A *MEFV* variants
Kılıç et al. [17]	Observational study	Children	562	Association between genotype and phenotype	Increased frequency of chest pain among patients who were homozygous for M694V and heterozygous for E148Q
Tutar et al. [19]	Observational study	Adults and children	42	The frequency of pericardial effusion diagnosed by echocardiography during the FMF attacks	3.6%
Ozturk et al. [20]	Observational study	Children	3454	The frequency of pericardial effusion	0.6%
Ben-Chetrit et al. [25]	Observational study	Adults and children	353	The association between FMF and Behçet's disease	No definite relationship
Kirino et al. [26]	Genome-wide association studies	Adults	2461	The association between FMF and Behçet's disease	Increased 2.5-fold risk in the Turkish population
Abbara et al. [22]	Systematic review and meta-analysis	Adults and children	58 articles	The co-occurrence of FMF and vasculitis	Immunoglobulin-A vasculitis (2.7–7%) Polyarteritis nodosa (0.9–1.4%)
Karadag et al. [23]	Observational study	Children	265	Demographic features of patients with immunoglobulin-A vasculitis	Recurrent immunoglobulin-A vasculitis suggests FMF comorbidity
Acay et al. [30]	Observational study	Adults	60	The atherogenic index of FMF patients	Increased atherogenic index
Keles et al. [28]	Observational study	Adults	58	The atherogenic index of FMF patients	Increased atherogenic index
Icli et al. [29]	Observational study	Adults	162	The atherogenic index of FMF patients	Increased atherogenic index

Table 1 (continued)

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Terekeci et al. [33]	Observational study	Adults	38	Marker of endothelial dysfunction (asymmetric dimethylarginine (ADMA))	Increased ADMA levels in the attack
Yılmaz et al. [64]	Observational study	Adults	98	Markers of endothelial dysfunction (ADMA, pentraxin 3) in patients with FMF-related amyloidosis	Increased ADMA levels
Ozalper et al. [34]	Observational study	Adults	57	Markers of endothelial dysfunction (ADMA, endocan)	Endocan may be a favorable biomarker for endothelial dysfunction
Yel et al. [32]	Observational study	Children	65	Markers of endothelial dysfunction (endothelial microparticles)	Increased endothelial microparticles in the attack
Akdogan et al. [35]	Observational study	Adults	43	Flow-mediated dilation (FMD) of the brachial artery and intima-media thickness (IMT) of carotid arteries	Impaired FMD and increased IMT of the carotid arteries
Sari et al. [38]	Observational study	Adults	61	IMT of the carotid arteries	Similar IMT of the carotid arteries compared to healthy controls
Bilginer et al. [36]	Observational study	Children	70	IMT of the carotid arteries	Increased IMT of the carotid arteries
Peru et al. [37]	Observational study	Children	49	IMT of the carotid arteries	Increased IMT of the carotid arteries
Yildiz et al. [40]	Observational study	Adults	23	PWV	Increased PWV
Uluca et al. [31]	Observational study	Children	45	Epicardial adipose tissue thickness (EAT) and the mean platelet volume (MPV)	Increased EAT and MPV indicate an increased risk of atherosclerosis
Kozan et al. [39]	Observational study	Adults	65	EAT and pulse wave velocity (PWV)	Increased EAT and PWV
Motawea et al. [41]	Systematic review and meta-analysis	Adults and children	256	EAT	Elevated risk of increased EAT and atherosclerosis
Uyarel et al. [45]	Case report	Adult	1	Acute myocardium infarction (MI)	A young FMF case presented with acute MI
Ambartsymian [44]	Observational study	Autopsy	68	Effect of FMF on MI	Amyloidosis of the vessels and myocardium stroma were related to MI
Langevitz et al. [46]	Observational study	Adults	290	Frequency of ischemic heart disease (IHD)	Lower prevalence of IHD in FMF (15.5%) compared to control group (30.2%)
Gendelman et al. [47]	Observational study	Adults	7670	Frequency of IHD	A higher prevalence of IHD in FMF
Basar et al. [42]	Observational study	Adults	197	Prevalence of *MEFV* mutations in patients with coronary heart disease (CHD)	Carrying *MEFV* mutations increases the risk of early CHD
Calıskan et al. [43]	Observational study	Adults	33	Investigate coronary flow reserve (CFR) and left ventricular (LV) diastolic function	Impaired CFR and LV diastolic function
Rozenbaum et al. [50]	Observational study	Adults	40	Presence of dysautonomia	Autonomic dysfunction without clinical symptoms

Table 1 (continued)

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Rozenbaum et al. [49]	Observational study	Adults	55	Presence of dysautonomia	Autonomic dysfunction without clinical symptoms
Ardic et al. [52]	Observational study	Adults	38	Heart rate recovery (HRR)	Abnormal HRR
Canpolat et al. [51]	Observational study	Adults	38	HRR	Abnormal HRR
Evrengul et al. [53]	Observational study	Children	50	HRR	Abnormal HRR
Nussinovitch et al. [57]	Observational study	Adults	40	Heart rate variability (HRV)	Abnormal HRV parameters in FMF patients complicated with amyloidosis
Nussinovitch et al. [55]	Observational study	Adults	34	HRV	Normal HRV parameters colchicine-responsive FMF patients without amyloidosis
Nussinovitch et al. [56]	Observational study	Adults	24	HRV	Normal HRV parameters in colchicine-resistant FMF patients without amyloidosis
Sahin et al. [54]	Observational study	Children	35	HRV	Similar HRV to controls
Nussinovitch et al. [58]	Observational study	Adults	53	QT dispersion	Cardiac repolarization indices were similar regardless of colchicine response between FMF patients and healthy controls
Nussinovitch et al. [59]	Observational study	Adults	22	QT dispersion	Similar cardiac repolarization indices in colchicine-resistant patients compared to controls
Giese et al. [60]	Observational study	Adults	30	Indices P and QT dispersion	No increased risk of atrial or ventricular arrhythmias
Ahbap et al. [61]	Observational study	Adults	77	Ventricular repolarization indices (QT dispersion, peak to end interval of T wave (Tpe), Tpe/QT, and Tpe/QTc ratios)	Abnormal ventricular repolarization indices
Farag et al. [62]	Observational study	Children	60	Ventricular repolarization indices	Increased risk of arrhythmia
Bozaci and Tatar [65]	Observational study	Adults	52	The role of serum azurocidin levels in patients with FMF- and FMF-related amyloidosis	Higher azurocidin levels related to inflammatory state and cardiovascular risk
Sahin et al. [66]	Observational study	Adults	169	The genotype-phenotype association exists in terms of endothelial dysfunction in patients with FMF-related amyloidosis	The presence of M694V homozygosity is associated with an increased cardiovascular disease risk
Ceylan et al. [67]	Observational study	Children	45	Evaluating subclinical changes by Doppler and strain echocardiography	Impaired measurements of strain echocardiography
Celik et al. [69]	Observational study	Adults	80	Evaluating subclinical changes by Doppler echocardiography	Impaired Doppler-derived diastolic index

Table 1 (continued)

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Erken Pamukcu et al. [68]	Observational study	Adults	60	Evaluating subclinical changes by speckle echocardiography	Subclinical right ventricular deterioration
Frommeyer et al. [73]	Animal study	Rabbit	10	Evaluating the pro-arrhythmic or toxic effect of colchicine	Increased ventricular fibrillation inducibility
Ocal et al. [74]	Observational study	Adults	28	Evaluating the arrhythmogenic effect of colchicine	Impaired ventricular repolarization indices
Nussinovitch et al. [75]	Observational study	Adults	56	Evaluating the arrhythmogenic effect of colchicine	Normal total cosine R to T (TCRT) analysis (a repolarization marker)

of *MEFV* mutation was found to cause a 2.5-fold increase in BD risk in the Turkish population [26].

Cardiovascular effects of inflammation in FMF

Endothelial dysfunction and atherosclerosis

Inflammatory diseases may display predisposition factors for early atherosclerosis [15]. Atherosclerosis is a form of chronic inflammation caused by the interaction between macrophages, T cells, modified lipoproteins, and the cellular elements of the arterial wall [27]. Ongoing low-grade inflammation in FMF may result in endothelial dysfunction and vascular damage. The atherogenic index is calculated by dividing plasma high-density lipoprotein (HDL) to triglyceride (TG) levels, and some studies showed an increased atherogenic index in adult FMF patients [28–30]. Furthermore, elevated mean platelet volume, a risk marker for atherosclerosis, was also observed in pediatric and adult FMF patients [31]. A pediatric study by Yel et al. [32] showed increased endothelial microparticles (EMPs) as a marker of endothelial dysfunction in FMF attacks, while EMPs were similar to healthy controls in the attack-free period. They concluded that uncontrolled disease might be the source of endothelial dysfunction and early atherosclerosis [32]. Correspondingly, previous adult studies showed elevated endothelial dysfunction markers such as asymmetric dimethyl arginine (ADMA) and endocan in patients with FMF [33, 34].

Akdogan et al. [35] reported impaired flow-mediated dilation of the brachial artery and increased carotid intima-media thickness (CIMT) in FMF patients compared with healthy controls. They noticed an increased atherosclerosis risk in FMF patients [35]. Similarly, increased CIMT was demonstrated in several studies, including children with FMF [36, 37]. It is hypothesized that persistent inflammation results in a rapid proliferation of low-density lipoprotein (LDL) and cholesterol in the intima of arterial lumen and lipid plaque formation. Increased CIMT levels were positively correlated with serum amyloid A (SAA), the most sensitive laboratory test for detecting subclinical inflammation in FMF patients [36, 37]. However, some conflicting results have also been published. Sari et al. [38] showed that CIMT measurements in adult FMF patients did not differ from healthy controls. Different results could be due to the diversity in disease severity among study participants.

Arterial stiffness is the rigidity of the arterial wall, which may be the early sign of atherosclerosis. Pulse wave velocity is a technique that evaluates arterial elasticity. Pulse wave velocity measurement may help the detection of impaired arterial elasticity. Some studies concluded that patients with FMF showed increased pulse wave velocity compared to the control group [39, 40]. Evaluation of epicardial adipose thickness is another sensitive method for detecting

subclinical atherosclerosis. The myocardium is surrounded by epicardial adipose tissue, which positively correlates with cholesterol and TG levels. The thickness of this tissue increases in many diseases, such as obesity, metabolic syndrome, and diabetes mellitus. A recent meta-analysis by Motawea et al. [41] showed that epicardial adipose tissue thickening and atherosclerosis risks were elevated in patients with FMF. Basar et al. [42] suggested that carrying *MEFV* mutations may predispose to early coronary heart disease. Caliskan et al. [43] reported impaired coronary microvascular function and left ventricular diastolic function in adult patients with FMF. However, data on the acute coronary syndrome in FMF patients have been restricted to case reports and autopsy studies [44, 45].

Colchicine, the mainstay treatment of FMF, has an antiatherosclerotic effect that may be attributed to slowing vascular damage down. Correspondingly, a study from Israel [46] showed that ischemic heart disease prevalence in adult FMF patients was lower compared to the age-matched general population. In this study, the authors highlighted the cardioprotective effect of colchicine. In contrast to this study, Gendelman et al. [47] showed an elevated risk for ischemic heart disease and mortality in FMF patients.

Conduction system disorders

In healthy individuals, the autonomic nervous system (ANS) has a significant role in regulating the cardiovascular system by ensuring optimal function during various activities. Several non-invasive methods are used to assess ANS, such as heart rate turbulence, heart rate variability (HRV), heart rate recovery index, and QT dynamics. Systemic inflammation may cause dysautonomia [48]. Since FMF is an inflammatory disorder, evaluating the ANS in FMF patients has become an area of interest. Autonomic dysfunction without clinical symptoms has been reported in adult FMF patients [49, 50]. However, the association between FMF and ANS is controversial. Rozenbaum et al. [50] evaluated the autonomic responses of adult patients with FMF by tilt table testing. Patients with FMF showed significantly different heart rate and blood pressure responses to postural challenges compared to healthy individuals. Another study by the same group showed an increased cardiovascular reactivity score among adult FMF patients related to abnormal ANS [49].

Furthermore, deterioration in the heart rate recovery index in both children and adults with FMF has been reported [51–53]. In contrast to these studies, Sahin et al. [54] did not find any difference in heart rate recovery between pediatric FMF patients and healthy controls. Nussinovitch et al. [55, 56] demonstrated normal HRV parameters in both colchicine-resistant and colchicine-responsive adult FMF patients without amyloidosis, while they detected HRV abnormalities in adult FMF patients complicated with amyloidosis [57]. The discrepancy between studies on ANS function in FMF may be related to the different characteristics of patients and the degree of inflammation.

Researchers also evaluated the conduction system abnormalities in FMF patients. The QT dispersion is a value measurement to predict the risk for ventricular arrhythmia. However, studies focusing on QT dispersion in FMF patients showed debatable results. Some studies revealed that cardiac repolarization indices were similar regardless of colchicine response between adult FMF patients and healthy controls [58–60]. In contrast, some others demonstrated that QT interval was longer in both pediatric and adult FMF patients than healthy subjects [61, 62]. In a recent study, Farag et al. [62] have demonstrated that FMF patients had an increased risk of arrhythmia [62]. In their study, some cardiac repolarization abnormalities were associated with FMF disease severity markers, suggesting that better inflammation control may help prevent arrhythmia in these patients [62]. Despite these findings, current knowledge does not lead to conclusion on a definite interaction between the FMF and the conduction system.

Cardiovascular effects due to FMF-associated secondary (AA) amyloidosis

Secondary AA amyloidosis, which could cause chronic renal failure, is the most severe consequence of FMF. With increased awareness and better medical care, the frequency of secondary amyloidosis has gradually decreased during the last two decades [63]. A recent pediatric study from Turkey reported the amyloidosis rate as 0.3% in a large FMF cohort [20]. FMF-related AA amyloidosis also increases the prevalence of cardiac complications and mortality. Patients with AA amyloidosis may have cardiomyopathy due to amyloid deposition in the myocardium.

Furthermore, renal failure due to amyloidosis may also assist the progression of cardiovascular involvement. Amyloid deposition in the myocardium and heart valves may lead to heart failure, while accumulation in coronary arteries may result in myocardial infarction [44]. Yılmaz et al. [64] showed elevated ADMA levels and impaired brachial flow-mediated dilatation in adult patients with FMF-related amyloidosis. They concluded that amyloidosis related to FMF resulted in endothelial dysfunction and increased the cardiovascular disease event risk [64]. In a study by Ambartsymian [44], 68 FMF patients aged 15–65 years who died from amyloid-induced congestive heart failure were included, and the autopsy materials were investigated. They suggested that cardiac failure might have developed before renal amyloidosis and uremia. Therefore, early detection of subclinical changes in myocardial tissue is quite essential. Bozaci and Tatar [65] proposed that azurocidin might be a predictor of

both inflammatory state and risk of cardiovascular disease in adult FMF patients with amyloidosis. Recently, M694V homozygosity has been related to cardiovascular disease risk elevation in FMF patients with amyloidosis [66].

Doppler imaging or strain echocardiography studies may be more sensitive than conventional echocardiography studies while evaluating cardiac functions. For instance, Ceylan et al. [67] confirmed that Doppler and strain echocardiography might detect subclinical changes when conventional echocardiography was normal. Erken Pamukcu et al. [68] also assessed ventricular systolic and diastolic functions with speckle-tracking echocardiography in adult FMF patients. They reported lower values of right ventricular global longitudinal strain and higher myocardial performance index in FMF patients suggesting subclinical right ventricular deterioration. A study by Celik et al. [69] also showed impaired Doppler-derived diastolic index in FMF patients aged 29 ±12 years. However, all these studies are limited by a small sample size.

Side effects of FMF treatment on the cardiovascular system

Colchicine, which prevents inflammatory flares and the development of amyloidosis, is the primary drug in the treatment of FMF. It is metabolized by cytochrome P450. In addition to its use in rheumatology, colchicine has been used in the treatment of many cardiovascular diseases, such as recurrent pericarditis, coronary artery disease, atherosclerosis, vascular restenosis, myocardial infarction, and heart failure [70, 71]. Furthermore, a definite benefit of colchicine has been demonstrated in the cardiovascular outcomes of adults who had a myocardial infarction during the last 30 days in the COLCOT (Colchicine Cardiovascular Outcomes Trial) [72]. However, colchicine itself may also lead to an increased occurrence of ventricular tachyarrhythmias [73]. Frommeyer et al. [73] showed the pro-arrhythmic effect of colchicine in rabbits. They found that colchicine treatment increased ventricular fibrillation inducibility in a dose-dependent way. Interestingly, unlike the animal models, Ocal et al. [74] showed that colchicine treatment had a favorable effect on ventricular repolarization, while another study by Nussinovitch et al. [75] reported that FMF patients receiving colchicine showed normal total cosine R to T (TCRT) (a repolarization marker) analysis.

In patients with a resistance or intolerance to colchicine, anti-IL-1 drugs are used in the management [6]. To date, there is no relevant data on side effects of anti-IL-1 drugs on cardiac system. In systemic juvenile idiopathic arthritis patients treated with anti-IL-1 drugs, fatal lung disease and pulmonary hypertension were reported [76]. A recent study has shown that this could be the result of a severe delayed hypersensitivity reaction named "drug reaction with eosinophilia and systemic symptoms" (DRESS), due to exposure to anti-IL-1 or anti-IL-6 drugs [77]. Furthermore, a specific HLA haplotype, HLA-DRB1*15, is associated with an increased risk of this reaction in case of biologic exposure. Checking for the mentioned haplotype could be considered in PFS patients before initiating anti-IL-1 therapies.

Other monogenic periodic fever syndromes and cardiovascular involvement

Mevalonate kinase deficiency/hyper immunoglobulin D syndrome (MKD/HIDS)

Mevalonate kinase deficiency (MKD) is an autosomal recessive disease caused by mutations in the *MVK* gene. This gene encodes mevalonate kinase (MVK), which takes a role in isoprenoid and cholesterol synthesis. Residual enzyme activity determines the phenotype [78, 79]. The milder phenotype of HIDS/MKD is usually characterized by febrile attacks lasting for 3–7 days. Infections, vaccination, or stress could trigger attacks. The signs and symptoms include aphthous stomatitis, cervical lymphadenopathy, abdominal pain, nausea/vomiting, diarrhea, and maculopapular or urticarial skin rash. On the other hand, mevalonate kinase is deficient in mevalonic aciduria, which forms the severe phenotype. Patients with mevalonic aciduria usually have severe cognitive impairment along with complications such as macrophage activation syndrome due to hyperinflammation. The elevated urinary mevalonic acid level is an important clue for diagnosis [80].

Pericarditis has also been described in the setting of MKD/HIDS, although it is not part of the typical disease features [81]. In a cohort of 1910 individuals with monogenic autoinflammatory diseases, acute pericarditis was observed in 3.7% of MKD/HIDS patients [82]. Prominent systemic involvement was observed in all patients at diagnosis, but pericardial chest pain was not indicated as a first symptom by any of these patients. Only one patient with MKD/HIDS needed pericardiocentesis due to cardiac tamponade, and no case with myocardial complication was recorded [82].

Thors et al. [78] reported a case of a young female patient with fever of unknown origin, who was diagnosed with and treated for incomplete Kawasaki disease. However, observation of recurrent febrile attacks leads to the correct diagnosis as MKD/HIDS. With cardiac ultrasonography on the tenth day of fever, mild dilation of the right and left coronary arteries was detected. The dilation of the proximal coronary arteries had resolved spontaneously within five months. Coronary artery dilation was thought to be a part of the systemic inflammatory response [78].

In 2008, Willer et al. [83] performed a genome-wide association study in European populations to analyze genetic variants affecting plasma lipid concentrations. They discovered

Table 2 Summary of relevant publications addressing cardiovascular issues in monogenic autoinflammatory syndromes other than familial Mediterranean fever

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Breda et al. [81]	Case report	Child	1	Association between recurrent pericarditis and mevalonate kinase deficiency (MKD)/hyper-IgD syndrome (HIDS)	A 12-year-old girl presented with recurrent pericarditis and was diagnosed with MKD/HIDS
Cantarini et al. [95]	Observational study	Adults and children	30	Presence of *TNFRSF1A* mutations in patients with idiopathic recurrent pericarditis who were refractory to colchicine treatment	4/30 (13.3%)
Kuemmerle-Deschner et al. [88]	Family study	Adults and children	13	Frequency of pericarditis	3 patients (23%) presented with a single episode of pericarditis
Cantarini et al. [96]	Observational study	Adults and children	131	Presence of *TNFRSF1A* mutations in patients with idiopathic recurrent pericarditis	8/131 (6.1%)
Peet et al. [82]	Observational study	NA	1910	Frequency of pericarditis in autoinflammatory diseases	MKD/HIDS (3.7%) Cryopyrin-associated periodic fever syndrome (CAPS) (1.3%) TNF receptor-associated periodic fever syndrome (TRAPS) (0.7%)
Willer et al. [84]	Genome-wide association scans study	Adults	188,777	Risk locus factors for coronary heart disease	The *mevalonate kinase (MVK)* gene may be a candidate as a susceptibility gene modulating HDL concentrations
Sun et al. [85]	Genome-wide association scan study	Adults	1561	Risk locus for coronary heart disease	No relation between *MVK* gene and dyslipidemia
Thors et al. [78]	Case report	Child	1	Coronary artery dilatation resembling Kawasaki disease	An 8-week-old girl presented with fever and coronary artery dilatation and was finally diagnosed with MKD/HIDS
Li et al. [90]	Observational study	Children	15	Clinical manifestations and genetic mutations in Chinese CAPS patients	Coronary artery ectasia in two
Endo et al. [91]	Case report	Adult	1	A 39-year-old woman with CAPS presented with sudden cardiac arrest due to cardiac amyloidosis	Coronary angiography showed no signs of cardiac vessel stenosis, but cardiac biopsy confirmed amyloidosis
Yamamura et al. [92]	Observational study	Children	3	Intima-media thickness (IMT) of carotid arteries, stiffness parameter b, ankle-brachial index (ABI), and pressure wave velocity (PWV)	Higher carotid IMT, stiffness parameter b, and PWV in CAPS compared to healthy control
Trost et al. [98]	Case report	Child	1	Association between myocarditis and TRAPS	A 9-year-old boy presented with myocarditis

Table 2 (continued)

Reference	Study design	Patient cohort	Number of patients	Evaluating parameters	Results
Roubille et al. [99]	Case report	Adult	1	Association between myocarditis and TRAPS	A 38-year-old woman presented with myocarditis
Poirier et al. [100]	Observational study	Adults	95	Association between the *TNFRSF1A* polymorphisms and premature myocardial infarction	The R121Q variant was found to be associated with myocardial infarction
Stojanov et al. [101]	Family study	Adults and children	4 family	Association between the *TNFRSF1A* mutations and myocardial infarction	The *TNFRSF1A* V173D cleavage site mutation may be associated with an increased risk for cardiovascular complications
Amoura et al. [102]	Observational study	Adults	112	Association between the R121Q *TNFRSF1A* variant and deep vein thrombosis in Behçet's disease	Increased risk of venous thrombosis

a novel loci at chromosome 12q24, which includes the *MVK* gene influencing HDL concentrations. Epidemiological and clinical studies have demonstrated that low levels of HDL in plasma increase the risk of coronary heart disease [83, 84]. Therefore, the *MVK* gene may be a candidate as a susceptibility gene modulating HDL concentrations affecting dyslipidemia and coronary heart disease risk. However, different ethnic backgrounds and lifestyle changes across populations could affect the influences of single-nucleotide polymorphisms on dyslipidemia [85]. For instance, no significant associations between dyslipidemia and polymorphisms in *MVK* gene were shown in the Chinese population [85] (Table 2).

Cryopyrin-associated periodic syndromes (CAPS)

Cryopyrin-associated periodic syndromes (CAPS) or NLRP3-associated autoinflammatory diseases (NLRP3-AIDs) are rare autosomal dominant autoinflammatory diseases associated with gain-of-function mutations in *NLRP3*. CAPS is a spectrum including mild to severe NLRP3-AID phenotypes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA) [86]. In FCAS, attacks of fever, urticarial, and arthralgia occur, usually triggered by a generalized exposure to cold [87]. Patients with MWS usually have progressive sensorineural hearing loss. The febrile attacks are more severe than FCAS attacks, and arthritis and severe fatigue could also be observed [88]. Patients with NOMID/CINCA, the most severe phenotype, usually have disease onset during the first years of life, and the clinical picture is characterized by inflammatory central nervous system involvement among many severe organ manifestations.

Cardiovascular involvement may also occur in CAPS patients [89]. In a family study including 13 MWS patients with heterozygous E311K mutation in *NLRP3*, a single pericarditis attack was seen long before the diagnosis of MWS in three patients (23%). Pericarditis was presented with typical symptoms like shortness of breath and chest pain, and patients were treated with nonsteroidal anti-inflammatory drugs and corticosteroids. Recurrence of pericarditis was not seen with or without IL-1 inhibition [88]. In a study from China investigating 15 Chinese children with CAPS, two patients with coronary artery ectasia were diagnosed with Kawasaki disease before admission [90]. Endo et al. [91] reported sudden cardiac death in a 39-year-old woman with CAPS. In coronary angiography, there was no stenosis in cardiac vessels, and amyloidosis was detected in cardiac biopsy [91].

Severe CAPS may be associated with premature atherosclerosis even during childhood. Yamamura et al. [92]

Table 3 Cardiovascular involvement in periodic fever syndromes (PFS)

	FMF	MKD/HIDS	CAPS	TRAPS
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant
Gene (chromosome)	*MEFV* (16p13.3)	*MVK* (12q24)	*NLRP3* (1q44)	*TNFRSF1A* (12p13)
Protein	Pyrin/marenostrin	Mevalonate kinase	Cryopyrin	TNFRSF1A
Cardiac involvement of the PFS (disease-related involvements)	Pericarditis	Pericarditis	Pericarditis	Pericarditis Myocarditis
Cardiovascular manifestations due to ongoing inflammation	Endothelial dysfunction Autonomic dysfunction Conduction system disorders Atherosclerosis Secondary (AA) amyloidosis	Endothelial dysfunction Atherosclerosis Secondary (AA) amyloidosis	Endothelial dysfunction Atherosclerosis Secondary (AA) amyloidosis	Endothelial dysfunction Atherosclerosis Secondary (AA) amyloidosis
Management strategies for cardiovascular issues in PFS	-Effective control of disease activity -Considering PFS in the differential diagnosis in case of recurrent or refractory pericarditis -Controlling concomitant cardiovascular risk factors such as obesity and hypertension			

CAPS, cryopyrin-associated periodic syndromes; *FMF*, familial Mediterranean fever; *MKD/HIDS*, mevalonate kinase deficiency/hyper immunoglobulin D syndrome; *TRAPS*, tumor necrosis factor receptor-associated periodic syndrome

examined three young NOMID patients (aged 5, 7, and 15 years) and age-matched healthy controls. Early signs of atherosclerosis were observed in NOMID patients after ultrasonographic evaluations, including CIMT, ankle-brachial index, the stiffness parameter β, and pressure wave velocity [92] (Table 2).

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominantly inherited periodic fever syndrome associated with *TNFRSF1A* mutations [93]. Clinical symptoms of TRAPS include recurrent fever, arthralgia or arthritis, severe myalgia, muscle tenderness, migratory rash, conjunctivitis, periorbital edema, and serositis. Like other chronic inflammatory diseases, some patients may experience systemic amyloidosis, a potentially fatal condition that typically manifests with nephropathy [94].

Cardiac involvement can mainly occur as pericarditis in TRAPS [93]. Pericarditis during attacks, often as a component of polyserositis, is common in TRAPS. Furthermore, there have been reports of patients who present with recurrent pericardial involvement as a distinct clinical symptom of inflammatory attacks [95]. Therefore, some idiopathic recurrent acute pericarditis (IRAP) cases may eventually be diagnosed with TRAPS. In a study by Cantarini et al. [96], *TNFRSF1A* gene mutations were examined in 131 Caucasian IRAP patients. Eight (6.1%) of them had a mutation in this gene. Six of these eight patients were heterozygous for the R121Q variant. The R121Q variant (previously known as R92Q) is classified as a variant of unknown significance [97]. In a study by Peet et al. [82] in a cohort of non-Finnish European ancestry, the allele frequency of R121Q was 2.5% (5/200), which was not significantly different from ancestry-matched healthy controls. This result argues against the pathogenic role of R121Q in IRAP, but this issue is an area of debate currently. *TNFRSF1A* mutations should be sought in patients with recurrent pericarditis if they have a positive family history of pericarditis or PFS, a poor response to colchicine, recurrences in a year after the initial attack, or while taking colchicine, steroid dependency, or if they require immunosuppressive medications.

Patients with TRAPS may also manifest with myocarditis [98]. Myocarditis was reported in two patients with TRAPS, accompanied by an acute dilated cardiomyopathy in one [98, 99].

Although TRAPS is an inflammatory disease with attacks usually longer than other PFS, no studies evaluate the incidence of atherosclerosis in TRAPS patients compared to the healthy controls.

The R121Q variant has been associated with myocardial infarction in a cohort of 95 individuals with premature myocardial infarction and familiarity with myocardial infarction [100]. Stojanov et al. [101] reported the novel V173D *TNFRSF1A* mutation (involving the receptor cleavage site) in an Austrian family. Two members of this family developed an arterial thrombosis and a myocardial infarction caused by the hypothetical atherogenic effect of the mutation [101]. Stojanov et al. [101] also postulated that patients with the *TNFRSF1A* V173D cleavage site mutation responded well to etanercept which may be a good therapeutic option for cardiovascular complications of TRAPS [101]. The atherogenic effect of V173D *TNFRSF1A* mutation may be due to prolonged inflammation. *TNFRSF1A* mutations may increase the risk of atherosclerosis by

impairing the endothelial TNF receptor-mediated stimulation of nitric oxide synthetase [102]. Thus, young patients who present with heart attacks could be screened for *TNFRSF1A* mutations [103] (Table 2).

Conclusion

This review summarized cardiovascular issues in PFS. Cardiovascular involvement in PFS may occur as a disease manifestation, association, or result of complications or a drug's adverse effects (Table 3). Cardiac involvement, especially pericarditis, may be a feature of PFS. In the presence of recurrent attacks of pericarditis or pericarditis refractory to conventional treatment, PFS should be considered in the differential diagnosis. Furthermore, uncontrolled inflammation may result in early endothelial damage and increase the risk of early atherosclerosis. Also, PFS complications such as amyloidosis and drugs used in the treatment could cause cardiovascular problems. Since long-term survival is provided in PFS with the improvement of therapeutic options, secondary complications such as endothelial dysfunction and atherosclerosis may be increasingly encountered in clinical practice. Therefore, screening for cardiovascular diseases in patients with PFS appears reasonable, and assessment of cardiovascular risk in these patients should be a part of routine care. Controlling the disease activity and subclinical inflammation may prevent early atherosclerosis and amyloidosis. Also, a further focus on reducing concomitant factors increasing the risk of atherosclerosis, such as obesity, diabetes mellitus, dyslipidemia, and hypertension could provide better control for cardiovascular risk in patients with PFS. Clinicians should be alert about cardiovascular issues during the follow-up of patients with PFS. Increasing knowledge will guide physicians to better care for cardiovascular problems in PFS patients. However, prospective and well-planned studies are required to increase the evidence-based data.

Compliance with ethical standards

Disclosures None.

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