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REVIEW ARTICLE

Non-canonical manifestations of familial Mediterranean fever: a changing paradigm

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Abstract Paroxysmal crises of fever and systemic inflammation herald familial Mediterranean fever (FMF), considered as the archetype of all inherited systemic autoinflammatory diseases. Inflammatory bouts are characterized by short-term and self-limited abdominal, thoracic, and/or articular symptoms which subside spontaneously. Erysipelas-like findings, orchitis, and different patterns of myalgia may appear in a minority of patients. In recent years, many non-classical manifestations have been reported in the clinical context of FMF, such as vasculitides and thrombotic manifestations, neurologic and sensory organ abnormalities, gastrointestinal diseases, and even macrophage activation syndrome. As FMF left unrecognized and untreated is ominously complicated by the occurrence of AA-amyloidosis, it is highly desirable that diagnosis of this autoinflammatory disorder with its multiple clinical faces can be contemplated at whatever age and brought forward.

Keywords Autoinflammation · Colchicine · Familial Mediterranean fever · Interleukin-1

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Introduction

Familial Mediterranean fever (FMF, OMIM 249100) is an autosomal recessive disorder characterized by recurrent self-limited bouts of fever and sterile inflammation mostly confined to serosal membranes, joints, and/or skin [1]. Febrile attacks, sometimes induced by trivial triggers, are accompanied by a strong acute phase response, and the most ominous potential complication is secondary multi-site amyloidosis [2]. The disease occurs most commonly among people originating from the Mediterranean basin, Turks, Arabs, Armenians, and non-Ashkenazi Jews, but has been recognized in every country of the world [3]. The causative gene of FMF is named *MEFV* and was first identified by two independent groups in 1997: it is located on the chromosome 16p13.3, displays 10 exons, and encodes a 781-amino acid protein known as pyrin or also marenostrin to recall the ancient name of the Mediterranean sea, "mare nostrum" [4, 5]. Pyrin is expressed in neutrophils, eosinophils, monocytes, and to a lesser extent in skin and synovial fibroblasts, and *MEFV* mutations lead to dysfunctional pyrin with downregulation of neutrophil activation: as a result, pyrin cannot control inflammation, leading to lengthened inflammatory responses with a final overload of interleukin-1β [6, 7]. It has been proposed that pyrin regulates the inflammatory process at the level of leukocyte cytoskeletal organization, and indeed, the therapeutic effect of colchicine in FMF is dependent on this specific interaction [8]. To date, over 300 *MEFV* sequence variants have been identified, mostly in exon 10, followed by exons 2, 3, and 5. The five founder mutations, M694V, V726A, M680I, M694I, and E148Q, account for 74 % of cases living around the Mediterranean basin [9]. Four of these mutations, M694V, V726A, M680I, and M694I, are located in exon 10 (E148Q is located in exon 2), while M694V is the most common in North African Jews and V726A predominates in Arabs, Armenians, and Iraqi Jews [10]. FMF symptoms are seen by the age of 10 in 60 % of

patients and by age of 20 in 90 % [11], but diagnosis remains only clinical since there are no specific laboratory tests for a definite diagnostic confirmation (see Table 1). AA-amyloidosis is the most frequent complication of FMF left untreated or overlooked, involving a host of different organs, as kidney, heart, respiratory and gastrointestinal tracts, and even central nervous system with a host of potential variable and uncanny phenotypes [12].

A protean clinical spectrum

The majority of patients with FMF have painful episodes localized to the abdomen, which are usually the dominant clinical manifestations, but children and a minority of adults can also present unusual phenotypes with less clinical signs or symptoms, which make diagnostic identification more puzzling [13]. FMF attacks typically involve serous membranes, and the tunica vaginalis is also one of the sites involved, giving unilateral self-limited orchitis with no apparent sequelae [14], though complications characterized by testicular necrosis and requiring orchiectomy have been reported [15]. Joint manifestations are really typical in most FMF attacks, but in some cases, they may show some peculiarities. For instance, peripheral entheses, frequently involved in different rheumatologic diseases like ankylosing spondylitis and Behçet's disease, have been studied by Tufan et al., who investigated the possible relationship between FMF and enthesopathy, revealing a peculiar association with the M694V *MEFV* variant [16]. Furthermore, Erten et al. first reported the association between Gitelman syndrome and FMF (which share their genes on chromosome 16) in an adult patient with recurrent knee arthritis and heel pain, in whom laboratory investigations disclosed hypokalemia, hypomagnesemia, urinary magnesium wasting, increased plasma renin level, and the FMF-related heterozygous E148Q *MEFV* variant, all successfully managed with potassium, magnesium, spironolactone, and colchicine [17]. Cutaneous manifestations have been well described in both children and adults with FMF: the most typical lesion is the erysipelas-like dermatitis, usually localized on the lower extremities, which is self-remitting within 24–48 h. However, several skin lesions other than erysipelas-like pictures have been reported, including non-specific rashes, diffuse erythema of the face and/or trunk, angioedema, Raynaud's phenomenon, Sweet's syndrome-like lesions, chronic panniculitis, lichenified erysipelas-like plaques, and severe recurrent pyoderma, all variably responding to colchicine administration, proving that skin involvement is integral part of FMF [18]. Uncommon pigmentation patterns have also been noted, and vitiligo reported in a 24-year-old woman [19]. In these last years, there have been many reports of clinical sceneries attributed to FMF or associated with FMF, and Table 2 lists the prominent diverse heterogeneous manifestations and disorders described in young patients with FMF.

Table 1 Diagnostic criteria for familial Mediterranean fever

Tel-Hashomer criteria	
Major	Minor
Recurrent febrile episodes associated with serositis or synovitis	Recurrent febrile episodes
Amyloidosis of AA-type without any causing or predisposing disease	Erysipelas-like erythema
Favorable response to daily colchicine prophylaxis	Positive history of familial Mediterranean fever in a first degree relative

Phenotype I is diagnosed by the positivity of 2 major or 1 major and 2 minor criteria.
Phenoytype II is related to AA-amyloidosis before the clinical onset of the disease.
Phenotype III is defined by the confirmation of two *MEFV* mutations without any clinical manifestations of the disease.

Yalçinkaya-Ozen pediatric criteria	
Clinical criterion	Required description for the criterion
Fever	Axillary temperature >38 °C, 6 to 72-h duration, ≥3 attacks
Abdominal pain	6 to 72-h duration, ≥3 attacks
Chest pain	6 to 72-h duration, ≥3 attacks
Oligoarthritis	6 to 72-h duration, ≥3 attacks
Family history of familial Mediterranean fever	

The diagnosis can be established in the presence of 2 or more of the 5 clinical criteria.

Vasculitides

The association of FMF with systemic non-granulomatous vasculitides, namely Henoch-Schönlein purpura, polyarteritis nodosa, and Behçet's disease, has been intensely documented: there have been several reports of vasculitic syndromes in children with a definite diagnosis of FMF as well as in children with an ambiguous genetic diagnosis of FMF, revealing that the environment might interplay with genetic factors in the pathogenesis of vascular inflammation [20]. Ozdogan et al. evaluated the frequency of Henoch-Schönlein purpura and polyarteritis nodosa in FMF, finding that they occur with a frequency of 7 and 1 %, respectively; moreover, diagnosis of FMF was made after the onset of Henoch-Schönlein purpura in 9 and after polyarteritis nodosa in 1 patient [21]. The appearance of vasculitis can preexist or sometimes follow a typical FMF attack, suggesting primarily that FMF should be considered in the evaluation of children with recurrent Henoch-Schönlein purpura, even in the absence of FMF peculiar clinical sceneries or a negative family history, and, in fact, occult FMF cases are much more numerous than

Table 2 Heterogeneous non-canonical manifestations and associated disorders in young patients with familial Mediterranean fever (FMF)

Clinical studies			
Disorder or specific organ involvement	Number of patients	Observations	First author, year of publication
Henoch-Schönlein purpura	76	*MEFV* genotype in children with Henoch-Schönlein purpura revealed that 14.4 % of patients had 1 mutated allele and 9.2 % had 2 mutated alleles	Dogan CS et al., 2013 [23]
Polyarteritis nodosa	17	Younger age at the onset of polyarteritis, overall better prognosis, and more frequent occurrence of perirenal hematomas for patients with a concomitant FMF	Ozen S et al., 2001 [24]
Behçet's disease	24	Twenty-one (out of a cohort of 54) patients with Behçet's disease carried a single *MEFV* mutation and 3 were compound heterozygotes	Rabinovich E et al., 2007 [40]
Multiple sclerosis	12	Median age of 26.8 years at the onset of the neurologic disease (with multifocal white matter lesions and oligoclonal IgG bands in the cerebrospinal fluid) in mutated *MEFV* carriers	Akman-Demir G et al., 2006 [52]
Creutzfeldt-Jakob disease	3	Rapid progression and earlier onset of the neurologic disease in patients with a concomitant FMF	Appel SA et al., 2010 [55]
Sleep disturbance	51	Poor sleep quality associated with number of FMF attacks	Makay B et al., 2014 [63]
Depression	43	Increased depression scores negatively influenced by FMF severity score and overall number of FMF attacks	Makay B et al., 2010 [64]
Ocular manifestations	6	Posterior uveitis in 2 FMF patients, anterior uveitis in 2, posterior scleritis in 1, intermediate uveitis in 1; the course has been recurrent in 50 % of patients	Yazici A et al., 2014 [66]
Cochlear involvement	34	Increased hearing thresholds at frequencies 8000, 10,000, 12,500, and 16,000 in children with FMF	Koybasi S et al., 2012 [68]
Small bowel disease	41	Small bowel mucosal defects in half of FMF patients evaluated by capsule endoscopy	Demir A et al., 2014 [71]
Liver involvement	58	Observed in 18.9 % of FMF cases (abnormal liver enzymes in 2, acute hepatitis in 2, Budd-Chiari syndrome in 2, chronic hepatitis or cirrhosis in 5)	Unal F et al., 2012 [77]
Recurrent aphthous stomatitis	100	Significant difference of the mutated *MEFV* carrier rate in patients with recurrent aphthous stomatitis	Kalkan G et al., 2013 [72]
Case reports			
Manifestations	Age (years)	Clinical details	First author, year of publication
Gitelman syndrome	46	Recurrent arthritis of right knee, heel pain, muscle weakness, hypomagnesemia, hypokalemic metabolic alkalosis, increased plasma renin level	Erten S et al., 2012 [17]
Vitiligo	24	Generalized depigmentation patches on the skin in a 10-year period	Melikoglu MA et al., 2009 [19]
Pulmonary embolism	43	History of recurrent serositis, occurrence of right-sided pleuritic chest pain which disclosed pulmonary embolism and FMF	Ruiz XD & Gadea CM, 2011 [28]
Budd-Chiari syndrome	9 and 8	Two children with hepatic venous outflow obstruction, ascites, hepatomegaly (normal liver microanatomy in one case, inactive cirrhosis in the other)	Sari S et al., 2009 [29]
Cerebral vasculitis	10	Henoch-Schönlein purpura, behavioral changes, irritability, repeated generalized tonic-clonic seizures	Ozkaya O et al., 2007 [38]
Reversible posterior leukoencephalopathy syndrome	16	Headache, nausea, generalized tonic-clonic seizures, parieto-occipital cortical and subcortical edematous lesions on the brain magnetic resonance imaging	Ozyurek H et al., 2005 [41]
Stroke	13	Right lateral medullary syndrome (aphonia, dysarthria, nystagmus, diplopia, hypoesthesia over the left side of the body and right side of the face, ataxia, right-sided Horner's sign)	Aoun EG et al., 2009 [42]
Acute infarction of the right dorsolateral medulla oblongata	34	Right-sided Horner's sign, gaze nystagmus, right-sided glossopharyngeal paresis, left-sided hypoesthesia	Luger S et al., 2013 [43]
Recurrent aseptic meningitis	33	Six episodes of aseptic meningitis improving within 24 h after spinal tap, leukocytic pleocytosis	Collard M et al., 1991 [45]
Right peripheral facial palsy	14	Three episodes in a 9-month period	Yilmaz U et al., 2013 [50]
Macrophage activation syndrome	11	Association with Crohn's disease treated with immunosuppressants	Uslu N et al., 2010 [79]

expected among children with Henoch-Schönlein purpura. Such children should be closely monitored for renal complications, and treatment with colchicine considered [22]. Dogan et al. investigated the prevalence of *MEFV* mutations in children with Henoch-Schönlein purpura but without FMF to define whether FMF-related mutations might have any effect on the disease course and on the risk of potential complications: a total of 76 children with Henoch-Schönlein purpura

who had no classic symptoms of FMF were screened for *MEFV* mutations in exons 2 and 10, and 14.4 % were heterozygous, 6.6 % homozygous, and 2.6 % compound heterozygous; no significant differences in joint, gastrointestinal, renal involvement, subcutaneous edema, and also abnormalities of acute phase reactants, including leukocyte count, erythrocyte sedimentation rate, and C-reactive protein, were noted in both groups. The prevalence of the two allele-*MEFV* mutations in children with Henoch-Schönlein purpura was higher (9.2 %) than in the general Turkish population (1 %): however, it seemed that *MEFV* mutations did not exert significant effects on the clinical expression of vasculitis [23]. The relationship between FMF and polyarteritis nodosa was explored by Ozen et al. in 2001 through a questionnaire sent to 7 referral centers for FMF from Turkey and Israel: 17 patients with an age ranging from 3.5 to 37 years who were diagnosed with FMF and who developed polyarteritis nodosa were included; diagnosis of polyarteritis nodosa was indeed confirmed by renal angiography in 8 patients, renal biopsy in 6, and muscle and/or nodule biopsies in 6. When compared with other patients with polyarteritis nodosa, those with FMF tended to have a younger onset age of the vasculitic process and an overall better prognosis [24]. Furthermore, a large Turkish study by Tasliyurt et al. found that the frequency of *MEFV* mutations was significantly higher in patients with Behçet's disease, an enigmatic syndrome marked by idiopathic inflammation of blood vessels, in comparison with the healthy control group originating from an area of Turkey where both diseases are frequently encountered [25].

Thrombotic manifestations

An increased inflammatory milieu in patients with FMF may predispose to develop abnormal coagulation tests as a result of subclinical chronic inflammation. Aksu et al. reported decreased prothrombin time and protein C activity, and increased levels of factor I and II in a cohort of FMF patients without other factors predisposing to thrombosis [26]. Demirel et al. found prolongation of prothrombin time and differences in tissue plasminogen activator and P-selectin levels in 34 FMF patients who were classified as attack-free patients (aged 3–19 years, all on colchicine prophylaxis) and 30 newly diagnosed patients (aged 3–21 years) during a febrile attack, suggesting that increased cytokine levels may signify an ongoing subclinic inflammation between the attack periods, and that hypercoagulability may have a role in the clinical progression and severity of attacks [27]. Heterozygosity for the M694V *MEFV* mutation was found in an adult Turkish patient who suffered from recurrent serositis and presented pulmonary embolism, which led to the identification of FMF [28]. FMF has been also regarded as a possible additional thrombotic risk after the observation of two pediatric cases of hepatic venous outflow obstruction, framed in the context of Budd-Chiari syndrome [29]. Although a tendency to hypercoagulability has been observed in different cohorts of patients with FMF, only anecdotal reports of thrombotic manifestations in the absence of amyloidosis and nephrotic syndrome have been reported. Different studies have suggested that FMF can be even associated with an increased risk of atherosclerosis [30]. However, the evaluation of carotid intima-media thickness, which is a parameter used to define preclinical atherosclerosis, has revealed conflicting results in FMF patients [31]. Sari et al. showed non-significant differences regarding markers of early-onset atherosclerosis between adult FMF patients and healthy controls [32]. Mean platelet volumes, a marker of platelet activation, considered a crucial determinant of atherosclerosis, and platelet counts have been found significantly higher in FMF patients both during febrile attacks and attack-free periods than in healthy people, though with no statistically significant difference, and this phenomenon has been also reported in children [33, 34]. A size increase of platelet volume occurs also when the platelets are incubated with 1–10 mM colchicine, following changes in the orientation of the marginal bundle of microtubules, producing platelet disc-sphere transformations [35]. Low-grade chronic inflammation and hypercytokinemia are believed to increase platelet reactivity, thrombocytosis, and long-term cardiovascular risk in any case [36].

Neurologic manifestations

A wide range of neurologic manifestations has been described in patients with FMF, some of which directly related to FMF, others to complications or treatment adverse effects, though they might represent incidental comorbidities [37]. Diagnosis of FMF was established in a 10-year-old girl following Henoch-Schönlein purpura with severe central nervous system involvement [38]. Behçet's disease is classically associated with heterogeneous neurologic manifestations, which were encountered in 28.1 % of cases from a large cohort of 430 Turkish patients [39]: *MEFV* analysis in Behçet patients for the three most common mutations (M694V, V726A, and E148Q) has revealed that mutated *MEFV* may act as a susceptibility gene in Behçet's disease irrespective of gender, frequency of HLA B51 antigen, and clinical severity score, and that carriers experience thrombotic events more often and uveitis less often [40]. A reversible leukoencephalopathy syndrome, characterized by headache, altered mental functioning, behavioral changes, seizures, and visual loss during an FMF attack, has been reported in a 16-year-old girl [41]: the pathogenesis may result from cerebral blood flow disruption and endothelial dysfunction, driven by interleukin-1β upregulation, which led to localized brain edema. The association between FMF and cerebral stroke has not yet been studied

thoroughly and is limited to few reports in pediatric patients. Aoun et al. described a child with FMF presenting a stroke-related lateral medullary syndrome, in whom an extensive work-up revealed many inherited and acquired risk factors of thrombophilia, suggesting that early screening for concurrent thrombotic risk factors should be warranted in areas with high prevalence of prothrombotic mutations in children born from consanguineous marriages [42]. Luger et al. reported a young patient with a genetically proven FMF who presented a brain stem infarction during a typical FMF attack: after a careful diagnostic work-up including cerebrospinal fluid analysis, intra-arterial angiography, and even leptomeningeal biopsy, an FMF-associated central nervous system vasculitis was identified as the cause of the stroke [43].

A mild form of headache is generally considered constitutional in FMF attacks, requiring that colchicine be started to control frequency and severity of pain episodes [44]. Recurrent aseptic meningitis with self-limited bouts lasting 3–5 days, whose cause is undetermined, has been firstly described by Collard et al. in a patient with FMF, who distinguished this picture from Mollaret's meningitis, a sporadic and ubiquitous transient disorder, in which the cerebrospinal fluid might contain specific large mononuclear cells [45]. However, the possibility of aseptic meningitis due to FMF is still unproven, as further evidence convincingly supporting a causal relationship is poor [46]. There are also reports of electroencephalogram abnormalities in patients with FMF, but these sparse data do not represent a strong-enough basis to establish a relationship with FMF [47, 48]. Multiple cranial nerve lesions and abnormal visually evoked potentials can occur in FMF as expression of either cerebral vasculitis or amyloidosis [49]. Three episodes of right-sided peripheral facial palsy during a 9-month interval have been reported in a 14-year-old child with FMF who had been receiving colchicine for 8 years [50]. The autonomic nervous system is considered to be clinically intact in FMF, but conflicting data have been accumulated over the last decade with respect to its subclinical involvement, even in uncomplicated FMF, but mostly in inveterate forms of FMF inadequately treated with colchicine, in which amyloidosis could explain different autonomic dysfunctions, such as abnormal cardiovascular reactivity [51].

Several studies support the association between FMF and demyelinating diseases, and both disorders share episodic bouts of inflammation. The rate of FMF in a Turkish cohort of patients with multiple sclerosis was almost 4 times the expected prevalence in the general population (0.43 vs. 0.10 %) [52]. It was found a significantly increased rate of *MEFV* mutation carriers among patients with multiple sclerosis compared to healthy subjects (38 vs. 11 %) [53], making *MEFV* a susceptibility gene predisposing to the development of a demyelinating disease even in young patients. The mechanism of this effect, however, is unknown, though a relationship with interleukin-1 might be suggested by the correlation of disease activity in multiple sclerosis and caspase-1 dependent interleukin-1β release from peripheral blood mononuclear cells of these patients [54]. Creutzfeldt-Jakob disease can be exacerbated by the coexistence of FMF, as shown by patients with a concomitant FMF who had a significantly shorter disease duration and earlier age of onset than those without FMF. Both Creutzfeldt-Jakob disease and FMF are encountered with increased frequency in patients of North-African descent, especially from Libya and Tunisia, and FMF might modify the course and outcome of this prion-related degenerative disorder, suggesting a role for inflammation in the pathologic process ruthlessly progressing to severe neurologic disability [55].

Myalgia is a frequent finding in FMF, firstly described by Schwabe and Peters [56], recurring in up to 25 % of patients, who report spontaneous, exercise-induced, or protracted (with a duration of 4–12 weeks) muscle pains [57]. In particular, protracted febrile myalgia is a rare severe form of FMF-related leukocytoclastic vasculitis, characterized by severe paralyzing muscle pain, high fever, abdominal complaint, joint symptoms, and transient vasculitic rashes mimicking Henoch-Schönlein purpura: this debilitating disorder may even recur in the course of colchicine prophylaxis but effectively responds to corticosteroids [58]. The intriguing observations of a potential link between streptococcal infections and FMF-protracted febrile myalgia could be explained by the recently reported ability of streptococci to activate the *NLPR3* inflammasome, suggesting a synergism between *Streptococcus*-induced interleukin-1β production and an already malfunctioning inflammasome in FMF, resulting in an "interleukin-1 burst" with subsequent development of vasculitis [59, 60]. Moreover, patients with FMF have an exaggerated response to streptococcal antigens in comparison with healthy children, becoming prone to post-streptococcal non-suppurative complications, such as acute rheumatic fever [61].

Sleep disturbances are much more prevalent among ill children and adolescents when compared with the general population, and the presence of comorbidities may adversely affect medical outcomes or quality of lives of these patients. The prevalence and impact of sleep problems have been described in several chronic rheumatologic disorders, but much less is known in patients with FMF [62]. Sleep quality is negatively affected by the number of attacks, while the association between pain and sleep disturbance may be bi-directional, as pain contributes to disrupted sleep and sleep disturbance itself can likewise enhance pain perception. Makay et al. showed that children with FMF had more sleep problems than their healthy peers, with higher scores of sleep onset delay, sleep anxiety, night wakings, and sleep-disordered breathing [63]. Furthermore, the impact of depressive disorders and anxiety is unknown in FMF: recurrent chronic pains have a negative role on everyday activities of children, both physical and social. Makay et al. investigated depression and anxiety in children

and adolescents with FMF, finding that young patients are considerably more depressed than their healthy peers, while there was no difference for anxiety scores. In addition, their study showed that depression of FMF pediatric patients is negatively affected by disease severity score and number of febrile attacks, suggesting that psychosocial assessment of children with FMF has relevant implications for the overall health care needs and highlighting the necessity of individualized counseling and interventions [64].

Sensory organ involvement

In 1959, Michaelson et al. published the first report of eye manifestations in FMF: these were retinal colloid-like bodies at the slit-lamp examination, with varying colors from porcelain-like white to yellowish, in 56 % of Jewish patients, compared to 11 % of the non-Jewish ones. Subsequent studies from the same center in a larger group of patients yielded a lower prevalence (20 %), and a later review of 50 Armenian and Arab patients with FMF revealed colloid-like bodies in only 4 [65]. However, although some single FMF case reports of recurrent episcleritis and panuveitis, even complicated with symblepharon, pseudopterygium, cystoid macular edema, cataract, glaucoma, and band keratopathy have been reported, sometimes in association with Behçet's disease, there are not sufficient data to consider ocular signs as specifically associated with FMF [66].

Cochlear involvement has been shown to be rarely present in vasculitic syndromes, and subclinical inflammation in FMF is considered to play a role for amyloid fibril deposition in any organ, cochlea included, mostly in the case of M694V homozygosity [67]. Koybasi et al. studied cochlear damage for the first time in children with FMF, finding increased hearing thresholds at higher frequencies in audiometry [68]. Yalçinkaya et al. reported that FMF patients with earlier clinical onset have a more severe disease course, which might also include hearing impairment [69]. Continuous prophylaxis with colchicine may produce significant differences in improving audiological findings, though more studies are required to explain the exact mechanisms of a potential cochlear involvement in FMF [70].

Bowel and liver involvement

Small bowel mucosal damage has been studied by capsule endoscopy screening in 41 adult patients with FMF, showing erosions in 26.8 %, ulcers in 17.1 %, and edema in 29.3 %, with most of the ulcers and erosions localized in jejunum, and only 24 % in ileum [71]. Recurrent oral aphthae may be easily encountered in childhood, and Kalkan et al. studied the frequency and clinical significance of *MEFV* mutations in a cohort of 100 unrelated Turkish patients with a clinical diagnosis of recurrent aphthous stomatitis: a statistically significant increased prevalence of *MEFV* variants, mostly the E148Q allele, was found [72]. In 2010, Uslu et al. reported that inflammatory bowel disease is more frequent and severe in patients with FMF: colitis might be the only presenting finding at the time of diagnosis, and gastrointestinal involvement can be heralded by constipation or diarrhea, only partially controlled by colchicine administration. In addition, disease-causing *MEFV* mutations and FMF rate were increased among patients with inflammatory bowel diseases: the increase was prominent among patients with Crohn's disease, whereas the rate was similar to the Turkish healthy control population for ulcerative colitis [73]. Yildirim et al. found that patients undergoing colectomy showed the highest rate of FMF-associated mutations, which might predict the severity of colitis [74]. Possible modifying effects of *MEFV* variants on the susceptibility to inflammatory bowel disease have been discussed by several research groups, finding that similar cytokine pathways controlling caspase-1 activation and interleukin-1β processing are involved in FMF as well as in inflammatory bowel disease [75, 76].

Different proinflammatory cytokines contribute also to the pathogenesis of acute liver injury, but the relationship between FMF and chronic liver disease remains obscure. Persistent cytokine overproduction may cause non-amyloid chronic hepatitis and even cryptogenic cirrhosis, as shown by Unal et al. in 58 FMF patients with a mean age of 10.8±4.2 years, who found that the M694V allele was more common in those with liver involvement, concluding that pediatric hepatologists should keep in mind FMF as a potential cause of non-infectious hepatitis and cirrhosis [77]. A macrophage activation syndrome, characterized by overwhelming inflammation with uncontrolled expansion of highly activated T lymphocytes and macrophages secreting high amounts of proinflammatory mediators, mostly occurring in patients with systemic juvenile idiopathic arthritis and systemic lupus erythematosus [78], has been reported in an 11-year-old boy with a diagnosis of both Crohn's disease, treated with immunosuppressive therapy, and FMF, who presented unexplained unremitting fever, severe cytopenia, and significant hepatomegaly [79].

In the end, Ardalan et al. reported a young man with end-stage renal disease, FMF and amyloidosis secondary to FMF, with no history of biliary stone diseases or alcohol consumption, who developed a fatal necrotizing pancreatitis following 10 months of continuous ambulatory peritoneal dialysis: there are few reports indicating that patients on peritoneal dialysis have a higher risk of developing acute pancreatitis than those on hemodialysis, but systemic generalized amyloidosis might act as an additional risk factor for pancreatic diseases [80].

The future

In conclusion, recurrent self-limited attacks of fever, serositis, and/or synovitis characterize FMF, the most common monogenic autoinflammatory disorder, considered as the archetype of all inherited systemic autoinflammatory diseases. Findings presented in this review suggest that the clinical features within the FMF spectrum are broader than previously thought: we have attempted to sketch the phenotypic diversity of FMF and define the impact of non-canonical manifestations into access to timely diagnosis and colchicine prophylaxis, with the final aim of building a common knowledge basis rather than a compartmentalized view of FMF, with its nuanced and even severe phenotypes throughout different organs and systems. During the last decade, the management of FMF and outlook for affected patients has undergone a remarkable transformation, giving a significant exemplar of personalized medicine. Further exciting progress is expected to overcome some of the unmet needs of these patients by the more profound knowledge of this extremely heterogeneous disease.

Disclosure None.

References

1. Sohar E, Gafni J, Pras M, Heller H (1967) Familial Mediterranean fever: a survey of 470 cases and review of the literature. Am J Med 43:227–253
2. The International FMF Consortium (1997) Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 90:797–807
3. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 10:1879–1885
4. The French International FMF consortium (1997) A candidate gene for familial Mediterranean fever. Nat Genet 17:25–31
5. Centola M, Wood G, Frucht DM, Galon J, Aringer M, Farrell C, Kingma DW, Horwitz ME, Mansfield E, Holland SM, O'Shea JJ, Rosenberg HF, Malech HL, Kastner DL (2000) The gene for familial Mediterranean fever, *MEFV*, is expressed in early leukocyte development and is regulated in response to inflammatory mediators. Blood 95:3223–3231
6. Diaz A, Hu C, Kastner DL, Schaner P, Reginato AM, Richards N, Gumucio DL (2004) Lipopolysaccharide-induced expression of multiple alternatively spliced *MEFV* transcripts in human synovial fibroblasts: a prominent splice isoform lacks the C-terminal domain that is highly mutated in familial Mediterranean fever. Arthritis Rheum 50: 3679–3689
7. Taskiran EZ, Cetinkaya A, Balci-Peynircioglu B, Akkaya YZ, Yilmaz E (2012) The effect of colchicine on pyrin and pyrin interacting proteins. J Cell Biochem 113:3536–3546
8. Rigante D, La Torraca I, Avallone L, Pugliese AL, Gaspari S, Stabile A (2006) The pharmacological basis of treatment with colchicine in children with familial Mediterranean fever. Eur Rev Med Pharmacol Sci 10:173–178
9. Milhavet F, Cuisset L, Hoffman HM, Slim R, El-Shanti H, Aksentijevich I, Lesage S, Waterham H, Wise C, Sarrauste de Menthiere C, Touitou I (2008) The infevers autoinflammatory mutation online registry: update with new genes and functions. Hum Mutat 29:803–808
10. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, Saatci U, Bakkaloglu A, Ozguc M (2001) Mutation frequency of familial Mediterranean fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 9:553–555
11. Shohat M, Halpern GJ (2011) Familial Mediterranean fever—a review. Genet Med 13:487–498
12. Rigante D, Frediani B, Galeazzi M, Cantarini L (2013) From the Mediterranean to the sea of Japan: the transcontinental odyssey of autoinflammatory diseases. Biomed Res Int 2013:485103
13. Moradian MM, Sarkisian T, Amaryan G, Hayrapetyan H, Yeghiazaryan A, Davidian N, Avanesian N (2014) Patient management and the association of less common familial Mediterranean fever symptoms with other disorders. Genet Med 16:258–263
14. Eshel G, Zemer D, Bar-Yochai A (1988) Acute orchitis in familial Mediterranean fever. Ann Intern Med 109:164–165
15. Livneh A, Madgar I, Langevitz P, Zemer D (1994) Recurrent episodes of acute scrotum with ischemic testicular necrosis in a patient with familial Mediterranean fever. J Urol 151:431–432
16. Tufan A, Mercan R, Tezcan ME, Kaya A, Bitik B, Ozturk MA, Haznedaroglu S, Goker B (2013) Enthesopathy in patients with familial Mediterranean fever: increased prevalence in M694V variant. Rheumatol Int 33:1933–1937
17. Erten S, Ceylan GG, Altunoğlu A (2012) Concomitance of Gitelman syndrome and familial Mediterranean fever: a rare case presentation. Ren Fail 34:1333–1334
18. Majeed HA, Quabazard Z, Hijazi Z, Farwana S, Harshani F (1990) The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six year study. Q J Med 75:607–616
19. Melikoglu MA, Melikoglu M (2009) A coincidence of FMF and vitiligo: a case report. Acta Reumatol Port 34:442–443
20. Tekin M, Yalçinkaya F, Tümer N, Akar N, Misirlioğlu M, Cakar N (2000) Clinical, laboratory and molecular characteristics of children with familial Mediterranean fever-associated vasculitis. Acta Paediatr 89:177–182
21. Ozdogan H, Arisoy N, Kasapçapur O, Sever L, Calişkan S, Tuzuner N, Mat C, Yazici H (1997) Vasculitis in familial Mediterranean fever. J Rheumatol 24:323–327
22. Gershoni-Baruch R, Broza Y, Brik R (2003) Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schönlein purpura. J Pediatr 143:658–661
23. Dogan CS, Akman S, Koyun M, Bilgen T, Comak E, Gokceoglu AU (2013) Prevalence and significance of the *MEFV* gene mutations in childhood Henoch-Schönlein purpura without FMF symptoms. Rheumatol Int 33:377–380
24. Ozen S, Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T (2001) Polyarteritis nodosa in patients with familial Mediterranean fever (FMF): a concomitant disease or a feature of FMF? Semin Arthritis Rheum 30:281–287
25. Tasliyurt T, Yigit S, Rustemoglu A, Gul U, Ates O (2013) Common *MEFV* gene mutations in Turkish patients with Behcet's disease. Gene 530:100–103
26. Aksu G, Ozturk C, Kavakli K, Genel F, Kutukculer N (2007) Hypercoagulability: interaction between inflammation and coagulation in familial Mediterranean fever. Clin Rheumatol 26:366–370
27. Demirel A, Celkan T, Kasapcopur O, Bilgen H, Ozkan A, Apak H, Arisoy N, Yildiz I (2008) Is familial Mediterranean fever a thrombotic disease or not? Eur J Pediatr 167:279–285
28. Ruiz XD, Gadea CM (2011) Familial Mediterranean fever presenting with pulmonary embolism. Conn Med 75:17–19

29. Sari S, Egritas O, Bukulmez A, Dalgic B, Soylemezoglu O (2009) Case report: is familial Mediterranean fever a possible cofactor for Budd-Chiari syndrome? J Pediatr Gastroenterol Nutr 49:481–484
30. Caliskan M, Gullu H, Yilmaz S, Erdogan D, Unler GK, Ciftci O, Topcu S, Kayhan Z, Yucel E, Muderrisoglu H (2007) Impaired coronary microvascular function in familial Mediterranean fever. Atherosclerosis 195:e161–e167
31. Peru H, Altun B, Doğan M, Kara F, Elmaci AM, Oran B (2008) The evaluation of carotid intima-media thickness in children with familial Mediterranean fever. Clin Rheumatol 27:689–694
32. Sari I, Karaoglu O, Can G, Sari I, Karaoglu O, Can G (2007) Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 26:1467–1473
33. Çoban E, Adanir H (2008) Platelet activation in patients with familial Mediterranean fever. Platelets 19:405–408
34. Arica S, Ozer C, Arica V, Arica S, Ozer C, Arica V (2012) Evaluation of the mean platelet volume in children with familial Mediterranean fever. Rheumatol Int 32:3559–3563
35. Laufer N, Grover NB, Ben-Sasson S, Freund H (1979) Effects of adenosine diphosphate, colchicine and temperature on size of human platelets. Thromb Haemost 41:491–497
36. Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, Theurl I, Widder W, Molnar C, Ludwiczek O, Atkins MB, Mier JW, Tilg H (2001) Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood 98: 2720–2725
37. Feld O, Yahalom G, Livneh A (2012) Neurologic and other systemic manifestations in FMF: published and own experience. Best Pract Res Clin Rheumatol 26:119–133
38. Ozkaya O, Bek K, Alaca N, Ceyhan M, Açikgöz Y, Taşdemir HA (2007) Cerebral vasculitis in a child with Henoch-Schönlein purpura and familial Mediterranean fever. Clin Rheumatol 26:1729–1732
39. Houman MH, Bellakhal S, Ben Salem T, Hamzaoui A, Braham A, Lamloum M, Monia SK, Ben Ghorbel I (2013) Characteristics of neurological manifestations of Behçet's disease: a retrospective monocentric study in Tunisia. Clin Neurol Neurosurg 115:2015–2018
40. Rabinovich E, Shinar Y, Leiba M, Ehrenfeld M, Langevitz P, Livneh A (2007) Common FMF alleles may predispose to development of Behçet's disease with increased risk for venous thrombosis. J Rheumatol 36:48–52
41. Ozyurek H, Oguz G, Ozen S, Akyuz C, Karli Oguz K, Anlar B, Aysun S (2005) Reversible posterior leukoencephalopathy syndrome: report of three cases. J Child Neurol 12:990–993
42. Aoun EG, Musallam KM, Uthman I, Beydoun A, El-Hajj T, Taher AT (2009) Childhood stroke in a child with familial Mediterranean fever carrying several prothrombotic risk factors. Lupus 18:845–847
43. Luger S, Harter PN, Mittelbronn M, Wagner M, Foerch C (2013) Brain stem infarction associated with familial Mediterranean fever and central nervous system vasculitis. Clin Exp Rheumatol 31(3 Suppl 77):93–95
44. Gedalia A, Zamir S (1993) Neurologic manifestations in familial Mediterranean fever. Pediatr Neurol 9:301–302
45. Collard M, Sellal F, Hirsch E, Mutschler V, Marescaux C (1991) Recurrent aseptic meningitis in periodic disease or Mollaret's meningitis? Rev Neurol (Paris) 147:403–405
46. Capron J, Grateau G, Steichen O (2013) Is recurrent aseptic meningitis a manifestation of familial Mediterranean fever? A systematic review. Clin Exp Rheumatol 31(3 Suppl 77):127–132
47. Gentiloni N, Gabrielli N, Caradonna P, Schiavino D, Anti M, David M, Segni G, Gambassi G (1992) Familial Mediterranean fever and electroencephalographic changes. A clinical case. Minerva Med 83: 307–310
48. Karachaliou I, Karachalios G, Charalabopoulos A, Charalabopoulos K (2005) Meningitis associated with familial Mediterranean fever. Int J Clin Pract Suppl 147:60–61
49. Finsterer J, Stollberger C, Shinar Y (2002) Cranial nerve lesions and abnormal visually evoked potentials associated with the M694V mutation in familial Mediterranean fever. Clin Rheumatol 21:317–321
50. Yilmaz U, Gülez N, Cubukçu D, Güzel O, Akinci G, Oztürk A (2013) Recurrent peripheral facial palsy in a child with familial Mediterranean fever. Pediatr Neurol 49:289–291
51. Nussinovitch U, Livneh A, Kaminer K, Langevitz P, Feld O, Nussinovitch M, Volovitz B, Lidar M, Nussinovitch N (2011) Normal autonomic nervous system responses in uncomplicated familial Mediterranean fever: a comparative case–control study. Clin Rheumatol 30:1347–1351
52. Akman-Demir G, Gul A, Gurol E, Ozdogan H, Bahar S, Oge AE, Gurvit H, Saruhan-Direskeneli G, Yazici H, Eraksoy M (2006) Inflammatory/demyelinating central nervous system involvement in familial Mediterranean fever (FMF): coincidence or association? J Neurol 253:928–934
53. Unal A, Dursun A, Emre U, Tascilar NF, Ankarali H (2010) Evaluation of common mutations in the Mediterranean fever gene in multiple sclerosis patients: is it a susceptibility gene? J Neurol Sci 294:38–42
54. Furlan R, Filippi M, Bergami A, Rocca MA, Martinelli V, Poliani PL, Grimaldi LM, Desina G, Comi G, Martino G (1999) Peripheral levels of caspase-1 mRNA correlate with disease activity in patients with multiple sclerosis: a preliminary study. J Neurol Neurosurg Psychiatry 67:785–788
55. Appel SA, Chapman J, Kahana E, Rosenmann H, Prohovnik I, Pras E, Reznik-Wolf H, Cohen OS (2010) Rapidly progressive Creutzfeldt-Jakob disease in patients with familial Mediterranean fever. Eur J Neurol 17:861–865
56. Schwabe AD, Peters RS (1974) Familial Mediterranean fever in Armenians. Analysis of 100 cases. Medicine (Baltimore) 53:453–462
57. Langevitz P, Zemer D, Livneh A, Shemer J, Pras M (1994) Protracted febrile myalgia in patients with familial Mediterranean fever. J Rheumatol 21:1708–1709
58. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM (2000) The clinical patterns of myalgia in children with familial Mediterranean fever. Semin Arthritis Rheum 30:138–143
59. Costa A, Gupta R, Signorino G, Malara A, Cardile F, Biondo C, Midiri A, Galbo R, Trieu-Cuot P, Papasergi S, Teti G, Henneke P, Mancuso G, Golenbock DT, Beninati C (2012) Activation of the *NLRP3* inflammasome by group B streptococci. J Immunol 188: 1953–1960
60. Omenetti A, Carta S, Delfino L, Martini A, Gattorno M, Rubartelli A (2014) Increased *NLRP3*-dependent interleukin-1β secretion in patients with familial Mediterranean fever: correlation with *MEFV* genotype. Ann Rheum Dis 73:462–469
61. Yalçinkaya F, Ince E, Uçar T, Ozkaya N, Tekin M, Elhan AH, Tutar E, Güriz DH, Aysev D, Gökdemir R, Doğru U, Tümer N (2002) Antistreptococcal response is exaggerated in children with familial Mediterranean fever. Clin Rheumatol 21:378–381
62. Buskila D, Zaks N, Neumann L, Livneh A, Greenberg S, Pras M, Langevitz P (1997) Quality of life of patients with familial Mediterranean fever. Clin Exp Rheumatol 15:355–360
63. Makay B, Kiliçaslan SK, Anik A, Bora E, Bozkaya O, Cankaya T, Unsal E (2014) Assessment of sleep problems in children with familial Mediterranean fever. Int J Rheum Dis. doi:10.1111/1756-185X.12339
64. Makay B, Emiroğlu N, Unsal E (2010) Depression and anxiety in children and adolescents with familial Mediterranean fever. Clin Rheumatol 29:375–379
65. Michaelson I, Eliakim M, Ehrenfeld EN, Rachmilewitz M (1959) Fundal changes resembling colloid bodies in recurrent polyserositis (periodic disease). AMA Arch Ophthalmol 62:1–4

66. Yazici A, Ozdal P, Yuksekkaya P, Elgin U, Teke MY, Sari E (2014) Ophthalmic manifestations in familial Mediterranean fever: a case series of 6 patients. Eur J Ophthalmol 24:593–598
67. Shohat M, Magal N, Shohat T, Chen X, Dagan T, Mimouni A, Danon Y, Lotan R, Ogur G, Sirin A, Schlezinger M, Halpern GJ, Schwabe A, Kastner D, Rotter JI, Fischel-Ghodsian N (1999) Phenotype-genotype correlation in familial Mediterranean fever: evidence for an association between Met694Val and amyloidosis. Eur J Hum Genet 7:287–292
68. Koybasi S, Atasoy Hİ, Bicer YO, Tug E (2012) Cochlear involvement in Familial Mediterranean Fever: a new feature of an old disease. Int J Pediatr Otorhinolaryngol 76:244–247
69. Yalçinkaya F, Ozcakar ZB, Tanyildiz M, Elhan AH (2011) Familial Mediterranean fever in small children in Turkey. Clin Exp Rheumatol 29:S87–S90
70. Ozkaya N, Yalçinkaya F (2003) Colchicine treatment in children with familial Mediterranean fever. Clin Rheumatol 22:314–317
71. Demir A, Akyüz F, Göktürk S, Evirgen S, Akyüz U, Ormeci A, Soyer O, Karaca C, Demir K, Gundogdu G, Güllüoğlu M, Erer B, Kamalı S, Kaymakoglu S, Besisik F, Gül A (2014) Small bowel mucosal damage in familial Mediterranean fever: results of capsule endoscopy screening. Scand J Gastroenterol 49:1414–1418
72. Kalkan G, Yigit S, Karakus N, Baş Y, Pancar GŞ, Balta I (2013) Association between *MEFV* gene mutations and recurrent aphthous stomatitis in a cohort of Turkish patients. J Dermatol 40:516–521
73. Uslu N, Yüce A, Demir H, Saltik-Temizel IN, Usta Y, Yilmaz E, Beşbaş N, Gürakan F, Ozen H, Ozen S (2010) The association of inflammatory bowel disease and Mediterranean fever gene (*MEFV*) mutations in Turkish children. Dig Dis Sci 55:3488–3494
74. Yildirim B, Tuncer C, Kan D, Tunc B, Demirag MD, Ferda Percin E, Haznedaroglu S, Alagozlu H (2011) *MEFV* gene mutations and its impact on the clinical course in ulcerative colitis patients. Rheumatol Int 31:859–864
75. Giaglis S, Mimidis K, Papadopoulos V, Thomopoulos K, Sidiropoulos P, Rafail S, Nikolopoulou V, Fragouli E, Kartalis G, Tzioufas A, Boumpas D, Ritis K (2006) Increased frequency of mutations in the gene responsible for familial Mediterranean fever (*MEFV*) in a cohort of patients with ulcerative colitis: evidence for a potential disease-modifying effect? Dig Dis Sci 51:687–692
76. Villani AC, Lemire M, Louis E, Silverberg MS, Collette C, Fortin G, Nimmo ER, Renaud Y, Brunet S, Libioulle C, Belaiche J, Bitton A, Gaudet D, Cohen A, Langelier D, Rioux JD, Arnott ID, Wild GE, Rutgeerts P, Satsangi J, Vermeire S, Hudson TJ, Franchimont D (2009) Genetic variation in the familial Mediterranean fever gene (*MEFV*) and risk for Crohn's disease and ulcerative colitis. PLoS One 4:e7154
77. Unal F, Cakir M, Baran M, Arıkan C, Yuksekkaya HA, Aydoğdu S (2012) Liver involvement in children with familial Mediterranean fever. Dig Liver Dis 44:689–693
78. Stabile A, Bertoni B, Ansuini V, La Torraca I, Sallì A, Rigante D (2006) The clinical spectrum and treatment options of macrophage activation syndrome in the pediatric age. Eur Rev Med Pharmacol Sci 10:53–59
79. Uslu N, Demir H, Balta G, Saltik-Temizel IN, Ozen H, Gürakan F, Yüce A (2010) Hemophagocytic syndrome in a child with severe Crohn's disease and familial Mediterranean fever. J Crohns Colitis 4:341–344
80. Ardalan MR, Shoja MM, Ghabili K, Taheri S, Shakeri A, Etemadi J, Einollahi B (2009) Fulminant acute pancreatitis in a patient with familial Mediterranean fever on CAPD: what caused the pancreatitis? Perit Dial Int 29:676–678