Clinical manifestations and diagnosis of familial Mediterranean fever

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INTRODUCTION

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever and serosal inflammation. This topic will review the clinical manifestations and diagnosis of FMF. The epidemiology, genetics, pathophysiology, and management of FMF and an overview of periodic fever syndromes and other autoinflammatory diseases can be found elsewhere. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis" and "Management of familial Mediterranean fever" and "The autoinflammatory diseases: An overview".)

CLINICAL MANIFESTATIONS

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of fever and serositis (eg, peritonitis, pleuritis, pericarditis, synovitis) or erysipelas-like erythema. Most patients with FMF experience their first attack in early childhood. The initial attack occurs before the ages of 10 and 20 years in 65 and 90 percent of cases, respectively [1]. However, in rare cases, the initial attack can occur in individuals older than 50 years of age.

The onset of fever and pain (due to serositis at one or more sites) is usually abrupt, peaking soon after onset. Some patients have a stereotypic prodrome (an aura) before their attacks [2].

This may include various constitutional and physical signs, such as restlessness at the site where the symptom is about to occur, anxiety, irritability, increased appetite, and taste alterations [2]. Episodes last for one to three days and then resolve spontaneously. Patients are asymptomatic between attacks. The frequency of attacks is highly variable, even in a given patient. The intervals between episodes are irregular, ranging from one week to several months or years. Usually, FMF patients cannot describe a consistent triggering event. Nevertheless, vigorous exercise, emotional stress, intercurrent infections, exposure to cold, surgery, and menstruation have been associated with an attack in some patients. During pregnancy, the course of FMF may worsen in about a third of the patients, improve in another third of patients, and remain unchanged in the rest [3].

Clinical manifestations of FMF vary among different populations (Middle Eastern patients versus European or Japanese patients) [4]. In the Middle East, a typical case of FMF almost always includes recurrent attacks of fever with serositis (peritonitis, pleuritis, pericarditis, or synovitis) in one or more sites in a single attack. The characteristic skin manifestation of FMF is erysipelas-like erythema (no urticaria or maculopapular rash). Among Japanese or European patients with FMF, the frequency of fever and peritonitis is relatively low, while the presence of headache is quite common. Moreover, Japanese and European patients may display various types of skin rash, posing a serious doubt about the diagnosis of FMF [4]. These differences are mainly related to genotypic differences; typical Middle Eastern FMF pattern is associated with exon 10 mutations. Atypical features of FMF (such as those seen in Japanese patients) are associated with non-exon 10 mutations [5].

Recurrent fever — Fever is one of the most constant characteristics of FMF and is present in almost all cases during attacks [6]. In the majority of FMF patients, the temperature rises from 38° to 40°C (100.4° to 104°F), although mild attacks may be accompanied by a subfebrile temperature (37.5° to 38°C or 99.5° to 100.4°F). Typically, the duration of the fever is brief, lasting between 12 hours and three days. Fever may be the first and only symptom of FMF, especially in toddlers [7]. In FMF patients who are treated with colchicine, an acute attack may occur without fever.

Abdominal pain — In Middle-Eastern populations where FMF is common, up to 95 percent of the patients with FMF have episodic abdominal pain [1]. Abdominal pain and tenderness may initially be localized and then progress to become more generalized. Since the cause of the abdominal pain is inflammation of the peritoneum, signs of peritonitis such as guarding, rebound tenderness, rigidity, and an adynamic ileus are often present. These findings can be mistaken for an acute surgical abdomen leading to diagnosis delay and sometimes even to futile operations. (See "Evaluation of the adult with abdominal pain", section on 'Urgent

evaluation and/or surgical abdomen' and "Causes of acute abdominal pain in children and adolescents" and "Emergency evaluation of the child with acute abdominal pain".)

Chest pain — Painful FMF attacks are localized to the chest in 33 to 84 percent of patients, depending on the patient's ethnic origin [6]. Armenian FMF patients are reported to have a higher rate of pleuritic involvement compared with other ethnic groups. Chest pain may be due to inflammation of the pleura or referred pain from subdiaphragmatic inflammation. Pleural inflammation typically manifests as unilateral chest pain that is worse with inspiration or coughing. Patients often have a small, transient pleural effusion. Fluid analysis is exudative, and neutrophils are dominant. In some patients, thickening and adhesion have been reported in the pleura as a result of repeated attacks. Episodes usually resolve within three days but may last up to one week. Concomitant pericarditis can also be observed in patients with pleuritis.

Joint pain — Among non-Ashkenazi Jews with FMF, approximately 75 percent experience sudden attacks of articular pain, which may be precipitated by minor trauma or effort such as prolonged walking. The joint attacks are usually monoarticular, involving one of the large joints (knee, ankle, hip). In rare cases, patients present with a migratory polyarthritis. Gradual resolution of the signs and symptoms occur after peaking in 24 to 48 hours. The synovial fluid analysis is typically sterile, with a nucleated white cell count ranging from 200 to >100,000 white blood cells/mm^3 [8]. The synovitis usually resolves completely without leading to joint destruction. However, some 5 to 10 percent of patients with FMF may experience protracted arthritis attacks affecting mainly the knees and hips, lasting more than a month, sometimes even years [9,10]. Protracted hip arthritis may exhibit destructive characteristics. In trials, it has been shown that approximately 30 percent of patients with hip involvement required a total hip replacement [9]. (See "Synovial fluid analysis" and "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women" and "Treatment of nontraumatic hip osteonecrosis (avascular necrosis of the femoral head) in adults".)

Erysipelas-like skin lesion — An erysipelas-like skin lesion is reported in 12 to 40 percent of FMF patients [11]. The lesion is typically 10 to 35 cm^2 in area, tender, raised, and erythematous and occurs on the lower leg, ankle, or dorsum of the foot, usually on one side (picture 1). Lesions may be transiently warm without associated pain or tenderness. Erysipelas-like skin lesions may be the presenting feature of FMF in children and may be misdiagnosed as an infectious erysipelas or cellulitis [11,12]. Children with myalgia and erysipelas-like skin lesions during attacks are at increased risk for subclinical inflammation during attack-free intervals, as evidenced by elevation of acute phase reactants [13]. Recovery is spontaneous and does not require antibiotics. (See 'Laboratory findings' below and "Cellulitis and skin abscess: Epidemiology, microbiology, clinical manifestations, and diagnosis".)

Other manifestations — Other rare manifestations of FMF include the following:

- **Exertional myalgia** – Exercise-induced myalgia is a typical manifestation of FMF. It usually affects the lower limbs (thighs and calves) in children and adolescents with the disease. It does not have an episodic characteristic and is not controlled by treatment with colchicine. It resolves with rest or treatment with nonsteroidal antiinflammatory drugs (NSAIDs). (See "Management of familial Mediterranean fever", section on 'Exertional myalgia'.)

- **Acute pericarditis** – Symptomatic acute pericarditis occurs in less than one percent of patients with FMF [14]. In one study, the frequency of pericarditis was found to be 11-fold higher than in the general population [15]. However, even in FMF, acute pericarditis is still a rare event. Clinical features of pericarditis include chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rub, and widespread ST segment elevation on electrocardiogram [15]. The length of such an attack is similar to or slightly longer (four to five days) than that of a typical FMF attack. Usually, recurrent attacks of FMF pericarditis do not lead to constrictive pericarditis. (See "Acute pericarditis: Clinical presentation and diagnosis".)

- **Acute scrotum** – In children with FMF, acute scrotum is characterized by mostly unilateral painful and swollen scrotum. Operative findings show normal testes and epididymis and a thick and hyperemic tunica vaginalis, which is an extension of the peritoneum. Acute scrotum should be differentiated from testicular torsion and does not require surgical intervention. Acute scrotal swelling and tenderness due to orchitis is a rare manifestation of FMF [16,17]. (See "Acute scrotal pain in adults".)

- **Protracted febrile myalgia** – Patients with FMF can present with protracted bouts of febrile myalgia that can last up to eight weeks. Febrile myalgias usually involve the lower extremities but, in some cases, may be more diffuse [18]. Patients with febrile myalgia have an increased erythrocyte sedimentation rate but a normal serum creatine kinase level and a normal electromyogram (EMG). Protracted febrile myalgia is associated with severe course of FMF and homozygosity for M694V mutation. Although the etiology is not clear, febrile myalgia is considered to be a vasculitic manifestation of FMF. However, in none of muscle biopsies taken from these patients could frank vasculitis be shown [19]. (See "Management of familial Mediterranean fever", section on 'Management of specific features'.)

- **Headache and aseptic meningitis** – Headache may accompany acute FMF attacks and are usually mild. A more severe type of headache in the form of recurrent aseptic

meningitis has also been reported, but it is still unclear whether this clinical feature is part of FMF [20]. (See "Aseptic meningitis in adults".)

- **Rash and oral ulcers** – Skin rash and oral ulcers have been reported in European and Japanese patients [5,21]. These are not typical features of FMF and may present in patients with other autoinflammatory diseases, such as tumor necrosis factor (TNF) receptor-1 associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), and mevalonate kinase deficiency (MKD), who were wrongly diagnosed with FMF. Very rarely, skin rash may be seen in cases of atypical FMF [6]. (See "The autoinflammatory diseases: An overview".)

- **Associated diseases** – Systemic nongranulomatous vasculitides such as immunoglobulin A vasculitis (IgAV; Henoch-Schönlein purpura [HSP]) and classical polyarteritis nodosa have a higher incidence among FMF patients [22]. The possibility that these diseases are actually rare manifestations of FMF has also been suggested [23]. In most of these cases, the patients carry at least a single M694V mutation in the *MEFV* gene. While some studies suggest that Behçet syndrome, ankylosing spondylitis, and inflammatory bowel diseases are more prevalent in FMF patients, this association remains controversial [24,25]. (See "IgA vasculitis (Henoch-Schönlein purpura): Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of polyarteritis nodosa in adults" and "Clinical manifestations and diagnosis of Behçet syndrome".)

LABORATORY FINDINGS

Acute attacks of familial Mediterranean fever (FMF) are accompanied by elevation of serum markers of systemic inflammation. Common laboratory findings include leukocytosis with a predominance of neutrophils as well as elevated acute phase reactants such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA) protein, and fibrinogen. The presence of otherwise unexplained proteinuria in between attacks may suggest renal amyloidosis. However, FMF patients with proteinuria who are treated with colchicine should be evaluated for causes other than amyloidosis. (See "Renal amyloidosis".)

LONG-TERM COMPLICATIONS

Secondary (AA) amyloidosis — Progressive secondary (AA) amyloidosis is a major cause of mortality in patients with familial Mediterranean fever (FMF) [26]. Rarely, patients can present with renal amyloidosis as the first and only manifestation of FMF [27]. Patients with renal

amyloidosis can present with asymptomatic proteinuria or clinically apparent nephrotic syndrome and gradually develop progressive nephropathy with end-stage kidney disease. End-stage kidney disease develops 2 to 13 years after the onset of proteinuria [1]. Amyloid deposition can also occur in the spleen, liver, and gastrointestinal tract and subsequently in the heart, thyroid, and testes. Patients with gastrointestinal tract amyloidosis usually present with diarrhea and malabsorption. The clinical manifestations of amyloidosis are discussed in detail, separately. (See "Overview of amyloidosis" and "Renal amyloidosis" and "Gastrointestinal amyloidosis: Clinical manifestations, diagnosis, and management".)

In some patients, there is poor correlation between the severity or frequency of attacks of FMF and the extent of amyloidosis. It is unclear whether the deposition of amyloid is due solely to the byproducts of recurrent systemic inflammation or whether there is a contribution from the underlying genetic defect. In the pre-colchicine period, in FMF patients aged 40 years and above, the incidence of amyloidosis has been reported in 60 to 75 percent of the patients [28]. The incidence of amyloidosis has markedly decreased with the regular use of colchicine. Nevertheless, amyloidosis complications are still a problem, especially in communities where the disease is common and access to colchicine is limited [29]. In two large population-based studies conducted in Turkey, the frequencies of amyloidosis were reported as 12.9 [30] and 8.6 percent [31]. Additional significant risk factors for developing amyloidosis in FMF patients include: male sex, a positive family history of AA amyloidosis, and the country of origin (with higher risk for patients from the eastern Mediterranean and Armenia) [32]. The term "country of origin" may include carriage of common genetic factors, general quality of health services, and access to medical treatment (colchicine, anti-interleukin [IL] 1 agents, etc).

Analysis of the phenotypic expressions of the two most frequent mutations of the *MEFV* gene, V726A and M694V, suggested that amyloidosis and severe arthritis are much more frequently observed with the latter defect [33,34]. Other modifier proteins have also been implicated. Patients without amyloidosis are more likely to have beta and gamma alleles of type 1 serum amyloid A (*SAA1*) gene, suggesting that these alleles may be protective [34]. Carrying the alpha allele is associated with a three- to fourfold higher risk for developing amyloidosis. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis" and "Pathogenesis of AA amyloidosis" and "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis", section on 'Other genetic factors'.)

Small bowel obstruction — Recurrent attacks of peritonitis may lead to adhesions and small bowel obstruction [35]. Treatment with colchicine, which controls the FMF attacks, is also effective in preventing the development of peritoneal adhesions [36]. (See "Etiologies, clinical

manifestations, and diagnosis of mechanical small bowel obstruction in adults" and "Management of small bowel obstruction in adults".)

Infertility — In the pre-colchicine era, pelvic adhesions and fallopian tube obstruction led to mechanical infertility in female patients. In men, fertility may be decreased due to azoospermia from testicular amyloidosis or impairment in sperm penetration. (See "Causes of male infertility" and "Female infertility: Causes", section on 'Fallopian tube abnormalities/pelvic adhesions'.)

DIAGNOSIS

When to consider the diagnosis — The diagnosis of familial Mediterranean fever (FMF) should be suspected in individuals with recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis, recurrent erysipelas-like erythema, repeated laparotomies for an acute abdomen with no identifiable underlying pathology, a first-degree relative with FMF, and/or membership in an at-risk ethnic group. FMF has been described primarily in non-Ashkenazi Jews, Armenians, Turks, Arabs, Greeks, and Italians. However, the disease is not restricted to these groups. In the United States, for example, FMF is frequently encountered in Ashkenazi Jews. In Japan, there are more than 500 FMF patients of original ethnicity. Because cases of FMF have been diagnosed in a wide variety of other populations, ancestry should not be used to rule out the diagnosis if other clinical characteristics are present [6]. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis", section on 'Epidemiology' and 'Our diagnostic approach' below.)

Our diagnostic approach — The diagnosis of FMF is made on the basis of clinical symptoms and supported by ethnic origin and family history. Genetic testing for FMF serves to support the diagnosis in patients who meet clinical criteria for FMF, to counsel at-risk relatives, and to guide the therapeutic approach [37]. In individuals who meet clinical criteria for FMF but in whom genetic testing is not diagnostic (only one or no pathogenic *MEFV* mutation), the diagnosis of FMF is supported by a six-month trial of colchicine therapy that results in a relief of attacks and recurrence after cessation of treatment [38]. However, a **definitive diagnosis** of FMF can be made only on a genetic basis. This is based on the observation that additional autoinflammatory diseases (eg, tumor necrosis factor [TNF] receptor-1 associated periodic syndrome [TRAPS] and mevalonate kinase deficiency [MKD, hyperimmunoglobulin D syndrome]) may present clinically identical to FMF [39]. (See "Management of familial Mediterranean fever", section on 'Initial management' and "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis", section on 'MEFV gene mutations'.)

We diagnose FMF in patients with **typical attacks** and the following combination of criteria (table 1):

- ≥1 major criteria
- ≥2 minor criteria
- 1 minor plus 5 supportive criteria
- 1 minor criterion plus ≥4 of the first 5 supportive criteria

Typical attacks are defined by the presence of all of the following features: pain due to serositis, recurrence of attacks (≥3 of the same type), presence of fever (rectal temperature of 38°C or higher), and short duration (lasting between 12 hours to 3 days). Attacks of fever alone are considered typical if they appear to be recurrent and of short duration and have no other detectable cause [40].

Major criteria — Major criteria for the clinical diagnosis of FMF consist of a typical attack involving one or more of the following:

- Peritonitis (generalized)
- Pleuritis (unilateral) or pericarditis
- Monoarthritis (hip, knee, ankle)
- Fever alone

Minor criteria — Minor criteria for the clinical diagnosis of FMF consist of an incomplete attack involving one or more of the following:

- Abdomen
- Chest
- Monoarthritis
- Exertional leg pain
- Favorable response to colchicine

Supportive criteria — Supportive criteria for FMF include the following:

- Family history of FMF
- Appropriate ethnic origin
- Age <20 years at disease onset
- Severe attack requiring bed rest
- Spontaneous remission of attack

- Symptom-free interval between attacks
- Attacks associated with transient inflammatory response with one or more abnormal laboratory results for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
- Episodic proteinuria/hematuria
- Negative laparotomy or removal of normal appendix
- Consanguinity of parents

This approach is consistent with criteria developed at the Tel Hashomer Medical Center in Israel (table 1) [40]. These remain the most widely used and well-accepted criteria, although several other diagnostic criteria have also been proposed [41-43]. The sensitivity and specificity for the diagnosis of FMF varies based on the number of criteria that are met (algorithm 1) [40-43]. Notably, however, these criteria do not include the results of genetic analyses that are an essential tool for the definitive diagnosis of FMF.

Subsequently, newer **classification criteria** for FMF have been proposed [44]. These criteria require the presence of confirmatory *MEFV* genotype and at least one of the following four clinical features: duration of episodes one to three days, arthritis, chest pain, or abdominal pain. Alternatively, in cases with no confirmatory *MEFV* genotype, the patient should have at least two of the above features. Confirmatory genotype means carriage of pathogenic or likely pathogenic mutations as homozygotes or compound heterozygotes. Non-confirmatory genotype means carrying a single mutation (heterozygotes). The scoring of the pathogenicity of the genetic variants has been published recently [45]. For example, exon 10 mutations in the *MEFV* gene (eg, M694V, M680I) are considered pathogenic or likely pathogenic variants, whereas exon 1 or 2 mutations (eg, R42W, E167D) are considered benign or likely benign variants. These classification criteria are recommended for inclusion of patients in translational and clinical studies and should not be used as diagnostic criteria. However, they can be supportive for diagnosis of FMF by excluding other hereditary fever syndromes.

Most individuals carrying a single pathogenic mutation (heterozygotes) remain asymptomatic for life. As a matter of fact, only approximately 2 percent of them will present with full blown FMF disease. In many cases, these patients display the disease only in their second or third decade of life. Few of them may become "attack-free" after several years of an active disease. In addition, there are rare individuals carrying two pathogenic mutations who remain asymptomatic, but we are unable to predict whether they will develop the disease later in life.

Genetic testing — Genetic testing is used to support the diagnosis of FMF and to exclude other autoinflammatory diseases that may clinically mimic FMF. FMF is usually inherited as an autosomal recessive trait. The detection of two pathogenic mutations in the *MEFV* gene in an individual confirms the diagnosis. However, in Middle Eastern communities, approximately 33 percent of patients who meet clinical criteria for FMF have only one identifiable mutation [38,46]. Furthermore, 10 to 20 percent of patients who meet clinical diagnostic criteria do not carry any known mutation for FMF [47,48]. In these cases, the diagnosis of FMF is probable rather than definitive. (See "Familial Mediterranean fever: Epidemiology, genetics, and pathogenesis", section on 'MEFV gene mutations'.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies with the patient's predominant clinical features.

- **Periodic fever syndromes** – Familial Mediterranean fever (FMF) must be distinguished from other hereditary periodic fever syndromes since they all share the common finding of periodic or episodic fevers. However, each of the periodic fever syndromes is also accompanied by a constellation of clinical features that differ from those of FMF. The other periodic fever syndromes include periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA); tumor necrosis factor (TNF) receptor-1 associated periodic syndrome (TRAPS); hyperimmunoglobulin D syndrome (HIDS or mevalonate kinase deficiency [MKD]); and cryopyrin-associated periodic syndromes (CAPS). PFAPA, as the name suggests, differs from FMF in that patients present with aphthous ulcerations, pharyngitis, and lymphadenopathy. In addition, the attacks are periodic and appear every three or four weeks and last three to seven days. The febrile attacks in patients with TRAPS are typically accompanied by conjunctivitis and periorbital edema in addition to focal migratory myalgias and rash. The attacks of TRAPS usually last from 7 to 21 days. Patients with MKD generally have pharyngitis, painful cervical lymphadenopathy, abdominal pain, and vomiting or diarrhea in the setting of elevated levels of immunoglobulin (Ig) D. Moreover, the attack duration in MKD is usually between three to seven days. CAPS represent a family of syndromes in which urticarial rashes and sometimes neurologic involvement accompany episodic fevers. The attack duration in CAPS is usually shorter, lasting one to two days. (See "The autoinflammatory diseases: An overview" and "Cryopyrin-associated periodic syndromes and related disorders".)

- **Systemic juvenile idiopathic arthritis/adult-onset Still's disease** – Another diagnostic consideration is the febrile-onset arthritis in childhood known as systemic juvenile idiopathic arthritis and in adults as adult-onset Still's disease. Patients with these

conditions present with features including high-spiking fevers, rash, serositis, and lymphadenopathy. Arthritis is often evident at onset but may sometimes present weeks or months later. Unlike FMF, patients with these conditions usually have a specific daily fever pattern that does not resolve after several days. (See "Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of adult-onset Still's disease".)

- **Systemic vasculitis involving the abdomen** – A variety of vasculitides can present with severe abdominal pain, including polyarteritis nodosa, immunoglobulin A vasculitis (IgAV; Henoch-Schönlein purpura [HSP]), and Behçet syndrome. However, these vasculitides can be distinguished from FMF by the presence of multiorgan system involvement with findings such as cutaneous small vessel vasculitis and glomerulonephritis. Moreover, the flares of these diseases do not last one to three days and resolve spontaneously. (See "Clinical manifestations and diagnosis of polyarteritis nodosa in adults" and "IgA vasculitis (Henoch-Schönlein purpura): Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of Behçet syndrome".)

- **Systemic rheumatic diseases** – Fever, serositis, and arthritis can be the predominant manifestations of other systemic rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Unlike FMF, patients with SLE have antinuclear antibodies (ANA) along with possible hypocomplementemia, glomerulonephritis, and cytopenias. RA can generally be distinguished from FMF by the pattern of a symmetric polyarthritis of the small joints of the hands and feet, and sometimes by the presence of a positive rheumatoid factor and/or anticyclic citrullinated peptide antibody. Palindromic rheumatism may cause a diagnostic dilemma in endemic countries for FMF since both clinical conditions have recurrent attacks of arthritis and fever. The presence of extraarticular features of FMF and genetic testing may help in making the exact diagnosis. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults" and "Diagnosis and differential diagnosis of rheumatoid arthritis".)

- **Infection** – A number of infections can mimic FMF but can be usually distinguished from FMF with blood cultures and/or serologic assays. Organisms that can cause subacute or chronic infections are the ones most likely to imitate FMF. Relapsing fever, caused by spirochetes of the *Borrelia* genus, is an arthropod-borne infection that causes recurrent episodes of fever (see "Clinical features, diagnosis, and management of relapsing fever"). Human parvovirus B19 can also cause flu-like symptoms and arthralgias or arthritis (see "Clinical manifestations and diagnosis of parvovirus B19 infection"). A variety of other

infectious sources that can lead to a persistent or recurrent fever are discussed elsewhere. (See "Etiologies of fever of unknown origin in adults".)

- **Malignancy** – Recurrent fever can also be the predominant manifestation of malignancies such as lymphoma, leukemia, or myelodysplastic syndromes. However, monoclonal expansion of B and T cells (as assessed by immunophenotyping), monocytosis, or macrocytosis can distinguish these malignancies from FMF. Patients with lymphoma also typically have additional findings such as splenomegaly, lymphadenopathy, or increased lactate dehydrogenase levels. (See "Approach to the adult with fever of unknown origin" and "Fever of unknown origin in children: Evaluation".)

- **Other causes of abdominal pain** – Other causes of acute abdominal pain can mimic the abdominal pain associated with FMF, such as appendicitis, cholecystitis, pancreatitis, and small bowel obstruction. Genetic disorders that are associated with recurrent bouts of abdominal pain include acute intermittent porphyria, hereditary angioedema, and genetically conferred hypertriglyceridemia. Unlike FMF, these conditions do not usually present with episodic fevers and arthritis. The approach to the patient with abdominal pain is discussed in detail, separately. (See "Evaluation of the adult with abdominal pain" and "Causes of acute abdominal pain in children and adolescents" and "Emergency evaluation of the child with acute abdominal pain" and "Chronic abdominal pain in children and adolescents: Approach to the evaluation".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Familial Mediterranean fever".)

SUMMARY AND RECOMMENDATIONS

- **Definition** – Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever and serosal inflammation. (See 'Introduction' above.)

- **Clinical manifestations** – Recurrent attacks are characterized by abrupt onset of fever and severe pain due to serositis at one or more sites. Serositis may result in abdominal, chest, or joint pain due to peritonitis, pleuritis, or synovitis, respectively. Episodes last for one to three days and then resolve spontaneously. In between attacks, patients are

asymptomatic. Most patients with FMF experience their first attack in early childhood. The initial attack occurs before the ages of 10 and 20 years in 65 and 90 percent of cases, respectively. Other manifestations include an erysipelas-like erythema, which mimics cellulitis in the ankle or dorsum of the foot (unilaterally), and exertional myalgia. Rare manifestations include acute pericarditis, acute scrotum, and protracted febrile myalgia. (See 'Clinical manifestations' above.)

- **Laboratory abnormalities** – Acute attacks of FMF are accompanied by elevation in many of the serum markers of systemic inflammation. Common laboratory findings include leukocytosis with a predominance of neutrophils, as well as elevated acute phase reactants such as the erythrocyte sedimentation rate, C-reactive protein, serum amyloid A protein, and fibrinogen. In FMF patients not treated with colchicine, the presence of proteinuria is suggestive of renal amyloidosis. However, in those treated with colchicine, a thorough investigation is warranted in order to evaluate for causes other than amyloidosis. (See 'Laboratory findings' above.)

- **Long-term complications** – Complications of FMF include secondary (AA) amyloidosis, small bowel obstruction, and infertility. The most frequent site of amyloid deposition is the kidney, although amyloid deposition can also occur in the spleen, liver, and gastrointestinal tract and subsequently in the heart, thyroid, and testes. Rarely, renal amyloidosis can be the first and only manifestation of FMF. Patients with renal amyloidosis can present with asymptomatic proteinuria or clinically apparent nephrotic syndrome and gradually develop progressive nephropathy with end-stage kidney disease. (See 'Long-term complications' above.)

- **Diagnosis** – The diagnosis of FMF should be suspected in individuals with recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis, recurrent erysipelas-like erythema, repeated laparotomies for an acute abdomen with no identifiable underlying pathology, a first-degree relative with FMF, and/or membership in an at-risk ethnic group. The diagnosis of FMF is made based on clinical symptoms and supported by ethnic origin and family history (table 1). Genetic testing is used to further confirm the diagnosis of FMF and to exclude other autoinflammatory syndromes mimicking FMF. In individuals who meet clinical criteria for FMF but in whom genetic testing is not diagnostic (only one or no pathogenic *MEFV* mutation), the diagnosis of FMF is supported by a six-month trial of colchicine therapy, which results in a relief of attacks and recurrence after cessation of treatment. (See 'Diagnosis' above.)

- **Differential diagnosis** – The differential diagnosis of FMF varies with the patient's predominant clinical features and includes other periodic fever syndromes, systemic

juvenile idiopathic arthritis, adult-onset Still's disease, systemic vasculitides involving the abdomen (eg, polyarteritis nodosa, immunoglobulin A vasculitis, Behçet syndrome), systemic lupus erythematosus, rheumatoid arthritis, a variety of infections, and malignancy. (See 'Differential diagnosis' above.)

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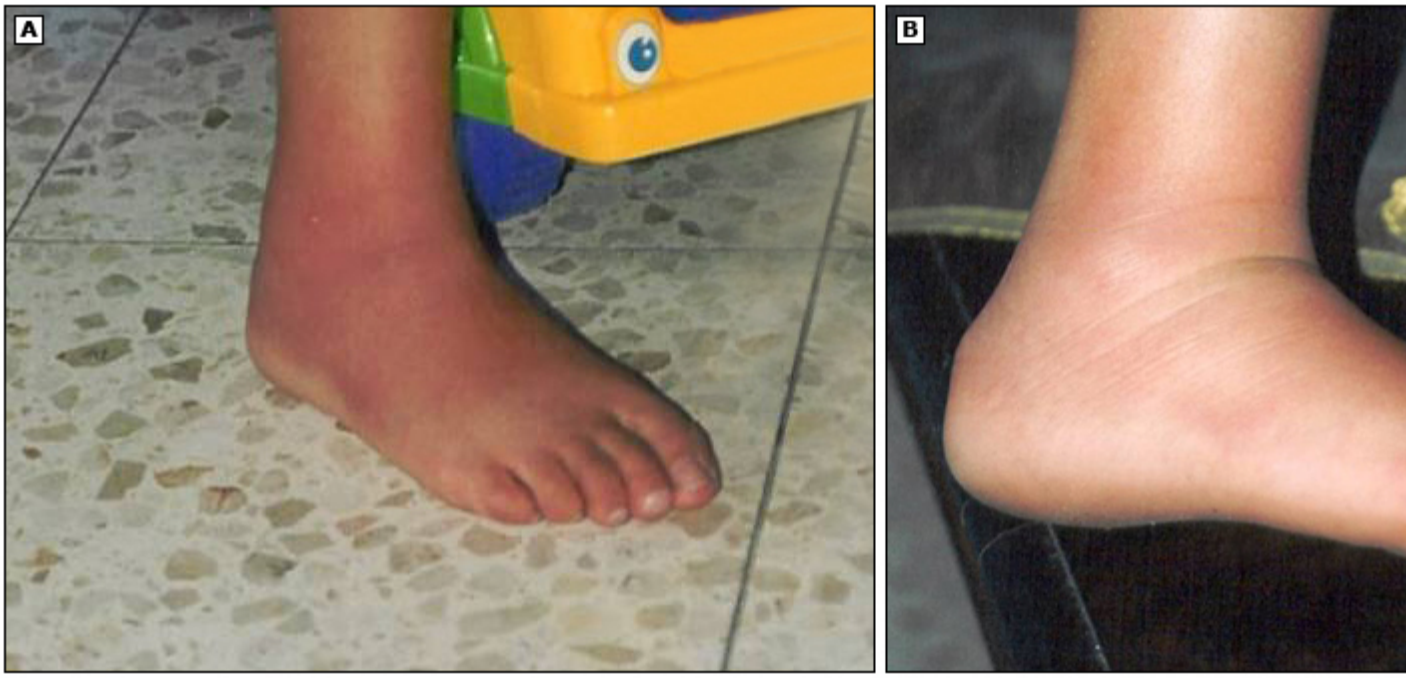
Topic 2635 Version 32.0

GRAPHICS

Erysipelas-like skin lesion



Erysipelas-like erythema (A) and, following three days, a full spontaneous recovery (B).

Courtesy of Eldad Ben-Chetrit, MD.

Graphic 111977 Version 1.0

Detailed criteria for the diagnosis of familial Mediterranean fever

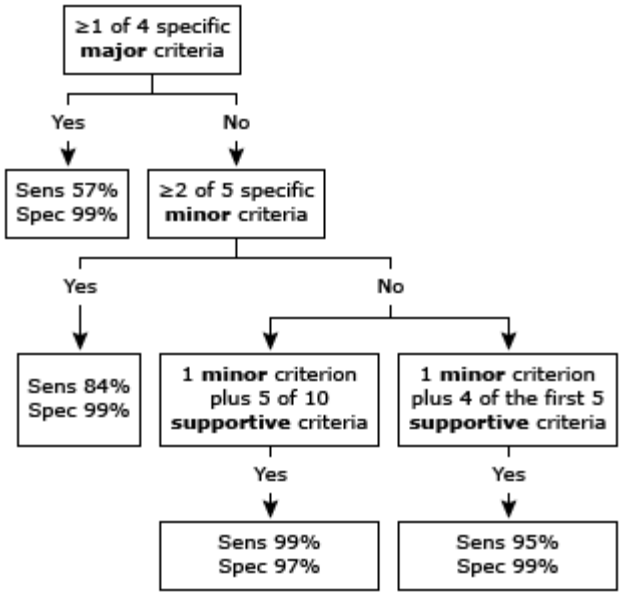
Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritis (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
Minor criteria
1-3. **Incomplete** attacks involving one or more of the following sites:
1. Abdomen
2. Chest
3. Joint
4. Exertional leg pain
5. Favorable response to colchicine
Supportive criteria
1. Family history of FMF
2. Appropriate ethnic origin
3. Age <20 years at disease onset
4-7. Features of attacks:
4. Severe, requiring bed rest
5. Spontaneous remission
6. Symptom-free interval
7. Transient inflammatory response, with one or more abnormal test result(s) for the white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibronogen
8. Episodic proteinuria/hematuria
9. Negative laparotomy or removal of normal appendix
10. Consanguinity of parents

FMF: familial Mediterranean fever.

Adapted from: Livneh A, Langevitz P, Zemer D, et al. Arthritis Rheum 1997; 40:1879.

Graphic 67666 Version 7.0

Classification tree using the detailed criteria for the diagnosis of familial Mediterranean fever



FMF: familial Mediterranean fever; sens: sensitivity; spec: specificity.

Adapted from: Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40:1879.

Graphic 77816 Version 5.0

Contributor Disclosures

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Conflict of interest policy

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