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Review Article

Familial Mediterranean Fever: Assessing the Overall Clinical Impact and Formulating Treatment Plans

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Abstract. Recurrent self-limited attacks of fever and short-lived inflammation in the serosal membranes, joints, and skin are the leading features of familial Mediterranean fever (FMF), the most common autoinflammatory disorder in the world, transmitted as autosomal recessive trait caused by *MEFV* gene mutations. Their consequence is an abnormal function of pyrin, a natural repressor of inflammation, apoptosis, and release of cytokines. FMF-related mutant pyrins are hypophosphorylated following RhoA GTPases' impaired activity and show a propensity to relapsing uncontrolled systemic inflammation with inappropriate response to inflammatory stimuli and leukocyte spread to serosal membranes, joints or skin. Typical FMF phenotype 1 consists of brief episodes of inflammation and serositis, synovitis, and/or erysipelas-like eruption, whereas phenotype 2 is defined by reactive amyloid-associated (AA) amyloidosis, which is the most ominous complication of FMF, in otherwise asymptomatic individuals.
Furthermore, FMF phenotype 3 is referred to the presence of two *MEFV* mutations with neither clinical signs of FMF nor AA amyloidosis. The influence of epigenetic and/or environmental factors can contribute to the variable penetrance and phenotypic heterogeneity of FMF. Colchicine, a tricyclic alkaloid with anti-microtubule and anti-inflammatory properties, is the bedrock of FMF management: daily administration of colchicine prevents the recurrence of FMF attacks and the development of secondary AA amyloidosis. Many recent studies have also shown that anti-interleukin-1 treatment is the best therapeutic option for FMF patients nonresponsive or intolerant to colchicine. This review aims to catch readers' attention to the clinical diversity of phenotypes, differential diagnosis, and management of patients with FMF.

Keywords: Familial Mediterranean fever, Autoinflammation, Periodic fever, Colchicine, Interleukin-1, Innovative biotechnologies, Anakinra, Canakinumab, Personalized medicine.

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Introduction. Primary dysfunction of the innate immune system is the architrave of autoinflammatory disorders, in which there is no evidence of adaptive immunity involvement, neither high-titer autoantibodies nor antigen-specific T cells, and no infectious triggers.[1] People with hereditary autoinflammatory disorders display periodically-recurring clinical features consisting of fever and inflammation with symptom-free intervals of different duration between febrile attacks.[2] In this group of

diseases, familial Mediterranean fever (FMF) occupies a primary seat, as it is the most common autoinflammatory disorder worldwide,[3] although it has been historically associated with people living around the Mediterranean basin as Turks, Arabs, Sephardic Jews, and Armenians.[4]

The Ancient Heredity of Familial Mediterranean Fever. In 1945 the allergologist Sheppard Siegal described as "benign paroxysmal peritonitis" his own disease, which was similar to the characteristics presented by other five Jewish patients: they all had cutaneous signs, recurrent peritonitis, and periodic fever attacks.[5] In 1954 Hobart Reimann was the first clinician who talked about "FMF," defining its "periodic" outstanding features, noting that the adjectives *cyclic*, *rhythmic*, *episodic*, *relapsing*, *recurrent*, *paroxysmal* and *intermittent* had been used interchangeably to highlight the disease.[6] In 1955 professor Harry Heller and his colleagues described the overall FMF clinical picture in detail, studied its inheritance, and found FMF-associated nephropathy deriving from amyloidosis as an ominous long-term complication of FMF.[7] FMF was the first autoinflammatory disorder for which the causing gene was identified in 1997 by two independent groups, American and French.[8-10] The gene was called *MEFV* (from *Me*diterranean *F*e*V*er) and is located on the short arm of chromosome 16 (p13.3) between the genes linked to polycystic kidney disease and Rubinstein-Taybi syndrome, spanning approximately 14 Kb of genomic DNA and comprising 10 exons: it encodes a 781 amino acid-protein with a molecular weight of 86 kD which was called "pyrin" (meaning "fever" in Greek) by the American group and "marenostrin" (using the ancient Latin name "mare nostrum" for the Mediterranean sea) by the French one.[11] This discovery represented the starting point to understand the pathogenesis not only for FMF but also for other autoinflammatory disorders. During the last years, there have been lots of studies demonstrating a growing interest of the scientific community in the search for autoinflammatory mechanisms in many other inflammatory conditions.[12,13]

The Size of a Borderless Disease. Although genetic research into FMF began around 1997, we still lack a complete picture of its genetic variation, carrier frequency, and penetrance.[14] Ethnic distribution of peculiar *MEFV* variants was initially considered a feature of FMF, and the disease was mostly recognized in people living around the Mediterranean basin and deriving from the ancient Mesopotamia or Phoenician lands: Armenians, non-Ashkenazi Jews (above all *Sephardic* Jews, who emigrated to the Iberian peninsula, in fact, *Sephardi* means "Spain" in Hebrew), Turks, Arabs (mostly North-Africans such as Maghrebins) and Druze population (an ethnoreligious Arabic-speaking group originating in Western Asia). The clinical diagnosis of FMF among these populations is enhanced by the widely-recognized higher prevalence of the disease. In addition, it is unclear whether all *MEFV* variants are true disease-causing mutations, as only five founder mutations (V726A, M694V, M694I, M680I, and E148Q) have been related to 74% of typical FMF cases in Armenians, Arabs, Jews and Turks.[15] However, because of so many migrations during the past centuries, the gene causing FMF has also been spread to Western Europe as well as to the Americas, China, Japan, Australia and New Zealand.[16] The higher frequencies of *MEFV* variants in some populations could be explained by an increased resistance against specific pathogens, such as *Yersinia pestis* or intracellular bacteria such as *Mycobacterium tuberculosis*, or by raised protection from asthma.[17] In Italy, FMF is erroneously considered a rare disease ("rare" means that its prevalence is less than 1 per 2000 inhabitants): various historical reasons account for the presence of the FMF gene in Italy, as Greek colonization of Sicily and Southern Italian regions in the VIII century B.C., the arrival of the first Christians in Rome under the Roman Empire in the I-II century A.D., and the Arab conquest of Sicily in the IX century A.D.[18,19] The observation of the same mutations and haplotypes in populations that have been isolated for centuries with high rates of consanguinity indicates that most cases of FMF are descended from a very ancient pool of founders.

Pyrin, an Intracellular Sentinel against Infections. Before *MEFV* discovery, it was commonly known that FMF attacks were characterized by a massive sterile flux of polymorphonuclear leukocytes into some body regions, which were serosal membranes, joints, and skin.[20,21] A huge number of studies dedicated to pyrin is revealing new molecular details about the general processes of cellular defense against infections, inflammation and apoptosis. Indeed, pyrin is largely expressed in the white blood cells and has a pivotal role in the activation of inflammasome and processing of the potent pyrogenic cytokine interleukin (IL)-1ß: in fact, it is involved in the activation of caspase-1 and release of active IL-1, as a structural part of the inflammasome complex.[22] In particular, the "pyrin domain" of this protein is a member of the death-domain-fold superfamily and is involved in the apoptotic pathway modulation through caspase recruitment and production of IL-1.[23] IL-1 transcriptional pathways are also misregulated in FMF attack-free periods, supporting the presence of subclinical inflammation between attacks, though different studies have not confirmed this hypothesis.[24,25] Pyrin activity is at the level of cytoskeletal assembly, and specific microtubule

assembly inhibitors prevent pyrin-mediated caspase-1 activation and secretion of IL-1 in peripheral blood mononuclear cells of FMF patients.[26] Recent experimental studies have suggested that pyrin function is mediated by RhoA (Ras homolog gene family-member A) GTPases, enzymes targeted to the plasma membrane by the addition of a geranylgeranyl lipid tail: more specifically, FMF mutations in the pyrin B30.2 domain decrease the threshold of activation of the pyrin inflammasome, generally activated by various RhoA-inhibiting toxins produced by both Gram-negative and Gram-positive bacteria. In a normal condition, the phosphorylated pyrin binds to regulatory proteins that block the pyrin inflammasome, but inhibition of RhoA effector kinases decreases the phosphorylation of pyrin, which in turn activates pyrin inflammasome.[27] Triggers stimulating at a cellular level the periodic occurrence of acute clinical attacks of FMF are not known, even if different chronic infections such as *Helicobacter pylori* infection or small bowel bacterial overgrowth might tune patients' inflammatory responses.[28,29] Other current studies suggest that non-*MEFV* genetic systems, epigenetic, and environmental modifiers might interplay with pyrin, influencing the clinical expression of FMF. Colchicine, a major neutral alkaloid from *Colchicum* species, suppresses pyrin inflammasome activity through direct activation of RhoA, disabling host cell cytoskeletal organization and causing an anti-chemotactic effect on the polymorphonuclear cells.[30]

A Host of Genotype Studies. FMF is inherited in a recessive manner, although recent studies have suggested that some heterozygotes manifest a spectrum of findings from classic FMF to mild FMF.[31] The most frequent *MEFV* mutations are contained in the exons 10 and 2 and are heterogeneously distributed in different populations.[32] Four mutations represent more than 70% of the mutated alleles in FMF cases of Mediterranean ancestry: M694V, M694I, M680I and V726A, all in the exon 10. Genotypes including two mutations located within mutational *MEFV* "hot-spots" (codons 680 or 694) in the exon 10 have been associated with the most severe phenotypes of FMF.[33] An unsolved issue is the possibility of genotype-phenotype correlations: for instance, M694V homozygosis, M680I homozygosis and heterozygosis for M608I/M694V genotypes are usually associated with severe clinical pictures and more frequent incidence of amyloidosis, while V726A is associated with milder disease and less frequent amyloidosis.[34] Understanding the correlation between FMF phenotype and genotype is further obscured by the existence of complex alleles, modifier loci, and potential epigenetic factors. In the United States FMF is frequently encountered in Ashkenazi Jews and immigrants from the Middle East and Armenia. In Germany, most FMF patients are of Turkish origin. In France, there is a relatively large FMF population that originated from North Africa. Among Armenians, the carrier rate for FMF is approximately 1:7 with a disease rate of roughly 1:500.[35] The E148Q is the least penetrant mutation of FMF, frequently found in the less severe pictures so that it has been considered a polymorphism, not a true disease-causing mutation.[36] The R202Q mutation is also considered a genetic polymorphism, present in about 15% of unaffected populations.[37] Some genes have been tested to assess their possible modifying effect on the clinical features of FMF: for instance, the alpha/alpha genotype of the serum amyloid-A gene (*SAA1*) is associated with increased risk of amyloidosis in FMF patients, especially if homozygous for the M694V mutation.[38] Moreover, Berkun et al. showed that FMF patients carrying mutations in the *NOD2/CARD15* gene, which is involved in Blau syndrome, an autoinflammatory disorder starting in the first years of life with noncaseating epithelioid granulomas affecting joints, skin and eye, variably associated with heterogeneous systemic features,[39] are prone to a more severe FMF course and higher development of colchicine resistance.[40]

A Kaleidoscopic Disease with Protean Faces. FMF is characterized by short-lived and self-resolving attacks of fever, abdominal, thoracic or joint pain and systemic inflammation which recur over time combined with intercritical periods of apparent wellness:[41] both clinical features and disease severity may vary among different ethnic groups.[42] General triggers of FMF attacks may be emotional stress, strenuous physical activity, menses, nutritional changes, use of contraceptives, hypovitaminosis D, etc. Bouts of fever with painful symptoms related to the abdomen, chest or one or multiple joints, singularly or in various combinations, are the most frequently declared symptoms by people living throughout many areas of the Mediterranean basin. Fever is present in 96% of inflammatory episodes: body temperature can peak over 40°C; it usually appears suddenly and lasts from 6 to 72 hours, preceded by chills in about ¼ of cases. Two phenotypically independent pictures of FMF can be recognized: [a] acute short-lasting painful febrile attacks of peritonitis, pleuritis, or arthritis (phenotype 1), and [b] nephropathic amyloidosis (phenotype 2), which can lead to terminal renal failure even at a young age, and no other clinical symptom. There is a third picture (phenotype 3) characterized by two *MEFV* mutations with neither clinical signs of FMF nor of amyloid-associated (AA) amyloidosis.[43] Attacks do not have a regular periodism: their frequency varies from once per week to once per decade. Over the course of this lifelong illness, an affected individual will probably have several forms of febrile and painful

episodes, but the recurrence of one type over many years is most frequent.[44] Onset is usually during the first decade in about 50% of cases, and symptoms might also start in the first months of life. As clinical manifestations of FMF appear quite early; they might be confused with a variety of diseases occurring in the pediatric age: for instance, recurrent febrile tonsillitis may be a symptom of FMF attacks, especially in early childhood,[45] entering in a challenging differential diagnosis with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, a typical recurrent disorder occurring in children less than 5 years, but also reported in adults.[46-49]

Abdominal pain, due to peritoneum inflammation resembling acute abdominal disease like appendicitis, cholecystitis, ureteral stones or pelvic inflammatory disease, is present in about 90% of patients and is frequently associated with small amounts of ascites upon ultrasound investigation. Peritoneum inflammation may also occur in the form of massive ascites with myofibroblast proliferation in the mesenteric region as an initial presentation of FMF.[50] Sometimes (in 30-40% of cases) patients might undergo unnecessary surgery.[51] Unilateral or bilateral pleural effusion can be demonstrated in 50-60% of patients and is characterized by quick resolution, while recurrent pericarditis can be observed in a small percentage of FMF patients (1-2.5%) during febrile attacks.[52,53] Intense scrotal pain simulating a testicular torsion is frequent in children with FMF, but it usually requires a conservative management.[54] Joint involvement is reported in 45% of cases and might present as transient arthralgia or oligoarthritis: short-lasting attacks begin without prodromes, involve large joints and suddenly disappear after 24-48 hours with no sequelae. Rarely arthritis may last for more than one week or even develop destructive features.[55] Some patients have painful, swollen and self-limited erythematous skin lesions on the legs: these lesions resemble a skin infection called erysipelas and are quite specific for FMF.[56] Another symptom associated with FMF is muscle pain, which might be severe and paralyzing: this muscular involvement is not prevented by colchicine and does not respond to nonsteroidal anti-inflammatory drugs, but only to corticosteroids. Muscular manifestations can present with severe febrile myalgia having three different patterns: spontaneous, effort-induced (i.e., exertional leg pain) and prolonged with an overall duration of 6 weeks.[57,58]

In recent times the clinical spectrum of FMF has expanded and many non-canonical manifestations have been reported.[59] For instance, neurologic signs other than constitutional headache have been described in some FMF patients, such as recurrent aseptic meningitis, demyelinating disorders, recurrent peripheral facial palsy and even stroke.[60]

Amyloidosis is the most dreadful complication of late-diagnosed, untreated or neglected FMF, which results from the deposition in different organs of a fatty-like substance, which is a cleavage product of serum amyloid-A, an acute-phase reactant produced by the liver. Main organs involved by amyloid deposition are kidney, gut, spleen, liver, heart and endocrine glands. Renal amyloidosis culminating in renal failure, which occurs in as many as 60% of untreated patients with FMF, is the major cause of death in FMF. Recent studies have focused on the polymorphism of the *SAA1* gene as a genetic contributor to the development of amyloidogenesis, but found no influence by the major histocompatibility complex.[61] The pathogenic role of environmental factors in FMF-related amyloidosis such as the country of origin is suggested by the lower incidence of amyloidosis in Jews living outside the Mediterranean basin: for instance, Armenians living in Armenia have a much higher incidence of amyloidosis than Armenian Americans, even before the introduction of colchicine. In addition, amyloidosis appears to be less common among Iraqis, Ashkenazi Jews and Arabs.[62] The association between amyloidosis and the mutation M694V is widely reported,[63] but non-amyloid glomerulopathies such as IgM or IgA nephropathy, focal and diffuse proliferative glomerulonephritis, and rapidly progressive glomerulonephritis have also been observed. Also, some non-granulomatous vasculitides, such as Henoch-Schönlein purpura (in 2.6-5% of cases), polyarteritis nodosa (0.8-1%) and Behçet's disease (0.5%) have been associated with FMF.[64-66] Over the years, an increased rate of *MEFV* carriers has also been found in complex multifactorial diseases such as ankylosing spondylitis and multiple sclerosis, implicating this gene and its pathways in the development of such disorders.[67] A few patients with FMF might also have attacks characterized by macrophage activation syndrome, in which well-differentiated mononuclear cells exhibiting hemophagocytic activity have swarmed different organs and systems, giving rise to a dramatic clinical picture consisting of persistent fever, multi-organ damage, cytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia with high mortality rates.[68,69] Lastly, a retrospective study related to over 8.000 Jewish patients with FMF registered at the Tel Hashomer Hospital (with a mean age of 43.74 ± 14.7 years) revealed that there is a significantly lower incidence of cancer in FMF patients than in the general population of Israel, and which might be attributed to a direct physiologic effect of FMF or the antimitotic effects of colchicine administered on the long run.[70] **Table 1** shows the main clinical features reported by 373 patients managed in the Periodic Fevers Research Center of our University.

Table 1. List of the main clinical features of familial Mediterranean fever in the cohort of patients managed in our Centre.

Clinical manifestations	**N. of patients** (373)	%
Fever	290	**93,25**
Abdominal pain	251	**80.70**
Articular pain	208	**66.88**
Thoracic pain	125	**40,19**
Muscular symptoms	113	**36.33**
Skin lesions	97	**31.18**
Oral aphthosis	89	**28,61**
Kidney involvement	48	**15.43**
Recurrent orchitis	11	**3.53**

Searching for Universal Diagnostic Criteria of Familial Mediterranean Fever. Traditionally, diagnosis of FMF has been based on the typical clinical manifestations and physician's insight, though a purely clinical diagnosis is complicated if there are febrile episodes without serositis or if amyloidosis is initially demonstrated without a clear history of fever and serositis. There is no specific test for FMF diagnosis, and some diagnostic criteria have been suggested, all based on clinical data and supported by the patient's ethnic origin or family history. During past years many authors have tried to develop different diagnostic flow-charts and several sets of criteria have been proposed since 1967, when Sohar et al. deduced that periodically-recurrent fevers and self-limited painful manifestations in various sites (abdomen, chest, joints, or skin), not explained by any other causative factor, were a mandatory FMF feature. They also recognized the importance of AA amyloidosis and the patient's origin from the areas around the Mediterranean sea. The Tel Hashomer Hospital criteria by Sohar's group (listed in **Table 2**) were promulgated starting from clinical observations in adult Israeli population, and are the most widely used for diagnosis of FMF in most clinical settings. If 2 major Tel Hashomer criteria or 1 major criterion and 2 minor ones are satisfied the diagnosis of FMF can be confirmed.[71]

In 1997 new criteria were validated by Livneh et al. to corroborate the clinical elements included in the Tel Hashomer criteria, but excluding other manifestations, like amyloidosis not explained by any other causative factor, less common at the onset of FMF. Two versions of these criteria, one more conservative and extensive than the other, were created, both with a sensitivity and specificity above 95%: the presence of at least 1 of 4 major criteria related to "typical" disease attacks or 2 of 5 minor criteria or 1 minor criterion plus 5 of 10 supportive criteria should suggest the diagnosis of FMF (see **Table 3**).[72]

Table 2. Classification Criteria for the Clinical Diagnosis of Familial Mediterranean Fever (FMF) according to the Tel Hashomer criteria. Diagnosis is made when 2 major criteria or 1 major and 2 minor criteria are satisfied, while diagnosis is probable if 1 major and 1 minor criterion are present.

Tel Hashomer criteria
Major criteria
Recurrent febrile episodes accompanied by peritonitis, synovitis, pleurisy
AA amyloidosis without a predisposing disease
Favorable response to continuous colchicine administration
Minor criteria
Recurrent febrile episodes
Erysipelas-like erythema
FMF diagnosed in a first-degree relative

Table 3. Classification Criteria for the Clinical Diagnosis of Familial Mediterranean Fever (FMF) according to Livneh et al. Diagnosis of FMF requires ≥ 1 major criteria, or ≥ 2 minor criteria, or 1 minor criterion plus ≥5 *supportive criteria* (family history of FMF, appropriate ethnic origin, age less than 20 years at disease onset, severity of attacks requiring bed rest, spontaneous remission of symptoms, presence of symptom-free intervals, transient elevation of inflammatory markers, episodic proteinuria or hematuria, nonproductive laparotomy with removal of a "white" appendix, consanguinity of parents) or 1 minor criterion plus ≥ 4 of the "first" five *supportive criteria*. "**Incomplete**" attacks are defined as painful and recurrent flares that differ from **typical** attacks in 1 or 2 features, as follows: 1) normal temperature or lower than 38°C; 2) attacks longer than 1 week or shorter than 6 hours; 3) no signs of peritonitis recorded during acute abdominal complaint.

Livneh's criteria
Major criteria
Typical attack of generalized peritonitis
Typical attack of unilateral pleuritis/pericarditis
Typical attack of monoarthritis
Presence of fever alone (rectal temperature of 38°C or higher)
Minor criteria
Incomplete attack involving abdomen
Incomplete attack involving chest
Incomplete attack involving one large joint
Exertional leg pain
Favorable response to colchicine

Diagnosis of FMF in children has been established using the same clinical criteria created for adults. However, a frequent delay in the appearance of a complete clinical picture in very young children, the presence of atypical signs, and absence of a suggestive family history may cause additional difficulty. Moreover, the evidence that some criteria were of poor relevance for children with FMF and differences of some clinical manifestations in younger children (who might have shorter attacks, infrequent chest pain, or even fever alone) prompted a Turkish group of clinicians in 2009 to formulate new FMF criteria for the pediatric population (the so-called Turkish FMF Pediatric criteria), listed in the **Table 4**.[73] The pediatric cohorts where these criteria were evaluated included only cases genetically ascertained to have two *MEFV* mutations, regardless of their phenotypes.

Table 4. Classification Criteria for the Clinical Diagnosis of Familial Mediterranean Fever (FMF) according to Yalçinkaya and Ozen (Turkish FMF Pediatric Criteria). Diagnosis of FMF requires the presence of 2 out of 5 criteria (in Turkish children).

Turkish FMF Pediatric Criteria
Fever (axillary temperature >38°C, 6-72 hours of duration, ≥3 attacks)
Abdominal pain (6-72 hours of duration, ≥3 attacks)
Chest pain (6-72 hours of duration, ≥3 attacks)
Oligoarthritis (6-72 hours of duration, ≥3 attacks)
Family history of FMF

These Turkish criteria for the diagnosis of FMF yielded a better sensitivity in an international cohort of children from either European or Eastern Mediterranean regions, though their specificity was lower than in previous criteria.[74] Anyway, all used diagnostic criteria should need further improvements, such as validation on broader cohorts of probands, and the inclusion of genetic data. Federici et al. developed new classification criteria for the diagnosis of different autoinflammatory disorders through the identification of 'positive' and 'negative' criteria correlated with each disease, suggesting that the presence of aphthous stomatitis, urticaria-like rashes, cervical lymph node enlargement and febrile episodes lasting more than 6 days should exclude the diagnosis of FMF.[75]

There is no specific laboratory examination to support the diagnosis of FMF, except for *MEFV* analysis. During typical acute attacks, blood tests show a generalized increase of the inflammatory parameters (erythrosedimentation rate, C-reactive protein, serum amyloid-A, immunoglobulins) with a parallel neutrophil leukocytosis (until and over 20.000/mm^3).[76]

The role of genetics in supporting the diagnosis of FMF is essential, but the genetic analysis should never substitute both clinical process and clinician's judgment. Following *MEFV* cloning, the genetic test for FMF has become available in many countries, providing a new exciting tool for diagnostic confirmation. Genetic diagnosis is definite when two mutations, also nonidentical, are present in the two *MEFV* alleles; if only one or no pathogenic mutation is found the clinical diagnosis of FMF is still possible due to the potential occurrence of occult mutations. Of course, for patients with typical clinical pictures and appropriate ethnic origin, FMF diagnosis can be made without a genetic confirmation, which is vice versa contributory for cases with atypical presentation, the absence of family history, or unusual ethnic origin. In particular, genetic testing might reveal no known mutation in 30-40% of patients: in this case if clinical manifestations are convincingly those of FMF the patient is put on an open trial with colchicine for 3-6 months. If there is a positive response and symptoms reappear after stopping colchicine, it is assumed that the patient has FMF.[77]

Furthermore, diagnosis of FMF in very young heterozygous children should be made with caution, as FMF heterozygous children can present with an FMF-like disease in early childhood, which does not differ from that seen in patients carrying two mutated alleles, although it may disappear with age. Therefore, a careful follow-up of heterozygous children is of paramount importance before establishing a definite diagnosis.[78] For individuals with two FMF-related mutations who do not report symptoms, if there are risk factors for amyloidosis (such as the country, family history, and persistently elevated inflammatory markers, particularly serum amyloid-A), a close follow-up should be started and at least colchicine prophylaxis considered.

Ancient and Modern Treatments. Since 1972 colchicine is the anchor drug used in patients with FMF. Lifelong prophylaxis with colchicine is safe and effective in preventing attacks of FMF and also the well-known complication of amyloidosis:[79] a therapeutic trial with colchicine for at least three-six months is useful to ascertain whether there is a decrease in the severity or in the frequency of FMF flares in every patient suspected to have FMF.[80] Continuative colchicine prophylaxis, even if started during childhood, has no effects on the normal final expected growth of children. By contrast, colchicine is not effective if administered during acute flares of FMF. The minimal daily dose in adults is 1 mg/day, but in children there is no definitely suggested dose, and management should be driven by the occurrence of clinical symptoms and inflammation on laboratory tests. Other factors, such as the genotype or body surface area may help to manage colchicine dose in a more individualized fashion.[81] The initial dose in children is usually 0.5-1 mg/day regardless of age and body weight, with little increases until disease control is achieved. The rate of adverse events for colchicine, mainly gastrointestinal effects, is low. Neutropenia, hair loss and allergies are infrequent side effects. A colchicine-related myopathy combined with the mild-to-severe elevation of creatine kinase may appear two weeks to several months after initiation of treatment. Moreover, since in vitro high doses of colchicine stop mitosis and colchicine displays its effect by fixating the intracellular microtubules, arresting their polymerization and finally disrupting mitosis and motility systems within the cells, in theory, this drug could interfere with patients' fertility, though many studies have proved no clearly adverse effects on gametogenesis.[82] However, if untreated, FMF itself can lead to amyloid deposits in the testis and ovary, resulting in infertility: therefore, patients with FMF may safely continue to use colchicine throughout the reproductive phase of their life.[83]

Complete remission of FMF under colchicine is achieved in 65% of patients and partial remission in 30%, while around 5% of patients remain nonresponsive.[84] True resistance to colchicine is a rare event, mostly observed in patients displaying peculiar *MEFV* genotypes and occurring despite the regular use of colchicine at the maximal doses. Low adherence to colchicine administration may be a key component of resistance and should be assessed.[85] Since long-term colchicine prophylaxis may be complicated by gastrointestinal side effects, by our experience, we usually recommend lactose-free diet and treatment of intestinal bacterial overgrowth to improve colchicine tolerance.[86] There are also FMF patients with low disease activity who might become utterly free of attacks for a long time and even stop colchicine prophylaxis: long-term remission of FMF, characterized by a time interval of at least 3 years without FMF clinical manifestations and off-colchicine, after a period of FMF activity, is rather infrequent. The prevalence of disease remission in the FMF population is estimated at 3.3%, based on a study by Ben-Zvi et al. from the largest center for diagnosis and treatment of FMF in Israel.[87] These patients seem to have distinct clinical, demographic and molecular characteristics, allocating them to the mildest end of the disease severity spectrum of FMF. This phenotype is comparable to that of patients with late-onset FMF.[88]

FMF protracted arthritis, mostly affecting hip or knees, has shown results following treatment with tumor necrosis factor inhibitors.[89] Characterization and early identification of FMF patients with uncontrolled inflammatory activity have become more important after the availability of new treatment options for the prevention of disease-associated complications and permanent damages of FMF. After the demonstration of inflammasome dysregulation as the dominating pathogenetic mechanism in different autoinflammatory disorders including FMF, IL-1β has been shown as the most intriguing target to attack.[90,91] An increasing experience of IL-1 blockade has been matured over recent times and, after showing its dramatic efficacy in cryopyrin-associated periodic syndrome, a rare and totally IL-1-mediated hereditary autoinflammatory disorder,[92] several case reports and case series dedicated to FMF have documented both efficacy and safety of anti-IL-1 agents, such as anakinra, canakinumab and rilonacept in patients inadequately responding to colchicine.[93-96] All IL-1 inhibitors are effective for controlling attacks and inflammatory activity in patients with refractory FMF and even in those complicated with AA amyloidosis, reducing or stabilizing the amount of proteinuria and preserving renal function in short-term follow-up studies. Structured scores rating FMF activity or severity by the use of attack parameters (site, duration and frequency) have been used to classify and settle disease diversity, while response to treatment has been evaluated by patients'/parents'/physicians' global assessment of disease severity, laboratory parameters performed every 6 months, and different scores related to symptoms and organ damages.[97-102]

How to Put Patients in Differential Diagnosis. Diagnosis of FMF is mainly a clinical process based on the fever recurrence combined with different symptoms: the final phenotype is not determined by the *MEFV* genotype alone, but a combination with other modifier genes and environmental factors. In addition, many diseases share recurrent fever as a common presenting feature. The problem remains relevant at whatever age, but mostly in children who frequently may show recurrent infections requiring assessment and even hospitalization.[103] A frequent and misdiagnosed cause of recurrent fevers in the pediatric age is PFAPA syndrome, but a detailed history-taking combined with a mindful collection of physical findings during flares is crucial to identify FMF. It is important to be aware that colchicine prophylaxis has been adopted by different research groups on PFAPA patients, although complete responses have not been observed.[104] The discrimination between PFAPA syndrome during childhood, early onset-Behçet's disease, and FMF may be challenging: in particular, Behçet's disease involves primarily the oral and genital mucosa, but also skin and eyes.[105] An Israelian large-scale population-based study has shown that FMF is more frequently diagnosed in female patients with Behçet's disease of Arab descent.[106] Quite similar to FMF is mevalonate kinase deficiency/hyperimmunoglobulin D syndrome, though the median age at the onset of this disease is 0.5 years, and these children have concurrent clinical symptoms involving the gastrointestinal, mucocutaneous and musculoskeletal system lasting more than three days:[107] increased urinary levels of mevalonate during febrile flares can consent to identify patients with mevalonate kinase deficiency.[108] Another autoinflammatory disorder to differentiate is tumor necrosis factor receptor-associated periodic syndrome: its presenting features include a high-grade fever of much longer duration (in comparison with FMF), abdominal pain, arthralgia, myalgia caused by monocytic fasciitis, conjunctivitis and periorbital edema, though the genetic diagnosis remains discriminating.[109] The quite characteristic recurrence of abdominal pain in FMF patients should also require to consider alternative diagnosis, such as inflammatory bowel disease, biliary and renal lithiasis, cholecystitis, pancreatitis, hemolytic syndromes, Behçet's disease and acute hepatic porphyrias, which are rare inborn errors of heme biosynthesis characterized by acute neurovisceral attacks heralded by severe abdominal pain. Porphyria is commonly diagnosed during acute attacks by the

demonstration of a striking urinary elevation of the neurotoxic porphyrin precursors aminolevulinic acid and porphobilinogen, that correlate with severity of abdominal symptoms.[110]

General Conclusions. In our modern era, FMF cannot be considered a rare condition confined to the Eastern Mediterranean countries as in the more recent past: indeed, this disease is scattered throughout the world showing a dynamic face with genetic and environmental aspects which are diversely tangled to determine its clinical phenotype.[111] Colchicine prophylaxis allows all age-patients with FMF to live a normal life with no restriction or substantial risk of sequelae. However, the undiagnosed disease has a negative influence on patients' and their families' quality of life because of frequent hospitalizations, potential surgical interventions caused by a wrong interpretation of FMF clinical signs or simply due to the recurrence of febrile attacks, which reduce school or work attendance and limit any social attitudes for patients.[112] Diagnosis of FMF is mainly made on the basis of the typical clinical findings in association with the peculiar ethnicity, family history, and response to colchicine.[113,114] Despite the great steps in our understanding of FMF, we still have a number of hanging questions: for instance, what is the exact role of additional genes in the definition of the final FMF phenotype, what is the pathophysiology of the disease in patients with only one *MEFV* mutation or in those without any *MEFV* mutation, which are further unexplored inflammatory pathways which might be involved in the disease expression or progression to amyloidosis, and so on. The progress in the knowledge of genetic determinants of FMF could constitute a significant step towards the understanding of the human genome power and general mechanisms of inflammation with future relevant therapeutic implications. Wider awareness of FMF will probably reduce the diagnostic delay in recognition of the disease and positively affect the quality of life of patients who will have a lower risk of long-term morbidity and complications.

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