Familial Mediterranean Fever

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Summary

Familial Mediterranean Fever (FMF) is the oldest and the most frequent of all described hereditary periodic fever syndromes. The populations originating from Mediterranean basin carry the highest risk for FMF however it is being increasingly recognized in many parts of the world. It is an autoinflammatory disease with an autosomal recessive transmission. In the majority of the patients it is related with mutations in the MEFV gene that encodes a protein named pyrin. This protein has been shown to act as a regulator of inflammation mediated by IL-1β, which plays a major role in the pathogenesis of FMF. Approximately one-third of the patients have either a single or no mutation which raise questions about its mode of inheritance. FMF is a clinical diagnosis and characterized by self-limited bouts of fever and serositis. The main long-term complication of the disease is AA amyloidosis. The mainstay of treatment is life-long colchicine given daily to prevent the recurrence of febrile attacks and the development of amyloidosis. Patients with insufficient response to colchicine may be treated with anti IL-1 agents.

Introduction

Familial Mediterranean Fever (FMF) is a fascinating disease, not only because it is the oldest and most frequent of all hereditary periodic fevers, or because it has opened the gate to a new inflammatory pathway, autoinflammation, which has significantly improved and modified our understanding of pathophysiology of disease in general, but because FMF has inspired the students of this disease to question and investigate its relations with history, geography, migration pathways, population studies and maybe even philosophy. However, there have been descriptions of periodic fever since Galen, it was in 1908 that Janeway and Mosenthal had defined an adolescent, with recurrent fever and abdominal pain. In 1945, Siegal had reported several cases, including himself, with recurrent fever. He named this clinical observation as ‘benign paroxysmal peritonitis’ which has been accepted as the first proper description of FMF [1,2]. It has been given several names like periodic serositis, Armenian disease, Siegal, Cattan, Mamou syndrome, Reimann’s disease [3,4]. The name Familial Mediterranean
Fever was proposed in 1955 by Heller and since then accepted worldwide [5]. After the description of the role of MEFV gene however, the nomenclature has become a topic of discussion once again [6].

FMF is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. The high prevalence of the disease among Sephardic Jews, Armenians, Turks and Arabs is well known for decades, however in recent years FMF is being recognized more and more in other populations around the world but in much lower frequencies [7]. If not diagnosed or treated properly patients may develop AA amyloidosis which is the main cause of mortality [8]. One of the milestones in the lifespan of FMF is the year 1972 when two reports related with the efficacy of continuous colchicine administration were published [9,10]. This approach still remains the mainstay of FMF treatment and has significantly improved the prognosis of this once mortal disease. The second milestone is the identification of MEFV (Mediterranean Fever) gene in 1997 [11,12]. This has been followed by the description of pyrin/maranostrin, the protein encoded by MEFV gene. Pyrin has been shown to act as a regulator of inflammation mediated by IL-1β, which plays a major role in the pathogenesis of FMF. With the increasing awareness of FMF and other autoinflammatory diseases in a wider geography, information concerning new disease associations, genotype-phenotype relations, effect of environmental factors, new treatment modalities, and recent advances in the pathogenesis have been accumulated. The purpose of this review is to give an overview and an update on FMF.

Epidemiology

FMF is the most common of all monogenic autoinflammatory diseases. Its prevalence is very high among Sephardic Jews, Armenians, Turks and Arabs [7]. Not many epidemiological data is available for each population, yet there are several studies reported from Turkey. Its prevalence in Israel and Armenia is roughly 1:2-1000 [13,14].

In a field survey in Turkey, the overall prevalence of FMF has been reported as 1:1000 [15]. In early 1990s, when we mapped our patients according to their parental origin, we saw that they originated mainly from mid and east Anatolia, and Black Sea region, but not from Mediterranean part of the country [16,17]. Since these observations 3 field surveys have been performed in 2 cities located in mid Anatolia, (Sivas center, Sivas-Zara and Tokat), which revealed a prevalence of 3:1000, 8:8:1000 and 8:1000 respectively [18-20]. However, another survey from northwest Turkey, close to Balkans, showed a very low prevalence of 6:10.000 [21]. These striking differences show that FMF is not uniformly distributed even within an at-risk geography like Turkey, pointing out the genetic heterogeneity of these populations. A similar observation, the non-uniform distribution of the patients within a given country, comes from Italy. FMF is more prevalent in the south, mainly Sicily, Calabria, Pulia whereas less so in the northern part of the peninsula. This is explained by the historical colonization of the region by Greeks, Jewish diaspora, Christians, Turks and Arabs throughout history since eighth to sixth century B.C. [22].

The carrier frequency among these at-risk populations is also very high for an autosomal recessive inheritance [23], which is 1:3 to 1:10 [7]. A high gene frequency in a given population may be due to founder effect, heterozygote advantage or genetic drift. Recurrent mutations in MEFV suggest a common ancestral origin [24]. Jalkh et al. confirmed the founder effect for the most frequent 5 MEFV mutations by haplotype analysis in 375 FMF patients and controls from Lebanon. The estimated ages of the mutations ranged between 3500 to 18,000 years, E148Q being the oldest [25].

After the description of MEFV gene, FMF is being recognized more in other parts of the world other than Mediterranean basin. However, much rare, significant number of patients is being reported from Iran, England, Greece, Italy, Germany, Spain, US, Brazil, Australia, Japan [7,26-28]. Some of these series include patients from high risk populations who had moved to live in these countries as well as the descendents of the local population.

Genetics

FMF is considered an autosomal recessive disease since its first descriptions, long before MEFV gene was described. Heller et al. had stated that FMF was inherited as a single, recessive autosomal trait, however there was lower than expected proportion of affected offspring [29]. The genetic heterogeneity of FMF has also been mentioned in these early reports [2,8]. They had observed several families with two or more generations affected, like the Armenian family, who had the disease for five successive generations, pointing out possible dominant transmission [30]. H. Armenian had suggested that factors other than a single gene maybe important and the penetrance of the disease may be influenced by extraneous determinants [31]. Identification of MEFV gene in 1997 by two different consortia, has improved our understanding of molecular and genetic basis of FMF [11,12]. MEFV gene is located on the short arm of chromosome 16 (16p 13.3) and composed of 10 exons. It encodes a 781-amino-acid protein which is called pyrin by International FMF consortium or maranostrin by French FMF consortium [12,26]. According to INFEVERS database, an online registry for autoinflammatory diseases (http://fmf.igh.cnrs.fr//infevers) [32], there are over 310 sequence alterations that have been reported by today, however the significance of many of these variants is not clear. Majority of the FMF-associated missense mutations are located in exon 2, 3, 5 and 10. The most frequent ones are M694V, M680I, V726A, M694I in exon 10 and E148Q in exon 2. These account approximately over two thirds of the classical cases from at risk populations. It has been shown by
haplotype analysis that these FMF chromosomes originate from common ancestors who date back to prebiblical era [26]. M694 V is the most prevalent and pathogenic variant of all Mediterranean mutations. Patients who are homozygous for M694 V have an earlier disease onset, are more prone to develop arthritis, amyloidosis and demand higher doses of colchicine to control disease activity. M680I is more common among Turkish and Armenian patients, V726A in Ashkenazi Jews and, M694I in Arabs. On the other hand E148Q is the most common variant in the general population as well as in parts of the world where FMF is rare like in Japan [26,33]. The pathogenic impact of E148Q is not certain. It has been accepted as a benign polymorphism [34], or variant of unknown significance [35], however other studies have reported a milder FMF phenotype in patients who are homozygous for E148Q [36,37]. Gershoni et al. reported that complex alleles were related with severe disease [38]. For clinical interpretation of hereditary recurrent gene variants, a committee has worked to develop guidelines [35]. They classified the gene variants as, a: clearly pathogenic variants (eg. M694 V), b: variants of uncertain significance (eg. E148Q as controversial mutations and eg. L384P as unknown variants), c: variants that are not the genetic cause and therefore not to be reported (eg. R202Q) [35]. The consensus was set to test for 14 variants where 9 were pathogenic, and 5 with unknown significance (table I) [39].

Classically FMF is described as an autosomal recessive disease, where two copies of a disease allele are required to express the phenotype. A study published in 1992, before MEFV gene was mapped, have reported 21 di- and monozygotic twin sets, identified among the 1943 FMF patients. Full concordance was observed in all the 10 monozygotic twin sets, but only in 3 of the 11 dizygotic twins. Authors concluded that these findings support the single gene autosomal recessive model, and provide support for the contention that the lower than expected incidence found in FMF is due to genetically affected but clinically undiagnosed patients [40]. Another twin study compared the intra-pair clinical concordance and concluded that the phenotype of FMF was affected by MEFV mutations, modifier genes and environmental factors in a ratio of 6:1.5:1 [41]. It is well established that even in at-risk populations, approximately one fourth of the patients with clinical FMF carry either one mutation or none. These patients with one detectable mutation generally have a FMF phenotype and respond to colchicine treatment. Thus an extensive search for a second MEFV mutation in heterozygotes with FMF phenotype was performed by Booty et al., yet failed to demonstrate "a second hit". Besides, no common haplotype was identified that cosegregated with a second FMF allele [42]. Lack of significant difference in the clinical expression between FMF patients with one or two mutations has been reported by Marek-Vagel et al. [43]. This was also supported by a group of heterozygous Italian patients who fulfilled the diagnostic criteria for clinical FMF [44]. However another study suggested a "dose effect", where the FMF related symptoms were more frequent among patients with two high penetrance mutations compared to one with low penetrance [45]. On the other hand, majority of the heterozygous individuals are true carriers and therefore symptom-free. Jeru et al. showed that heterozygosity plays a minor role in familial forms of FMF, and not responsible for classical Mendelian forms, however it is a risk factor for the development of the disease. They calculated a RR of 6.3 for Turkish and 8.1 for Sephardic Jew populations compared to non-carriers [46].

The carrier frequency of MEFV mutations is very high among at-risk populations, ranging from 1:3 to 1:10 [26,47,48]. This may imply a selective advantage for heterozygous. Fujikura, by using two population exome studies, performed a genetic epidemiology of FMF mutations [49]. The results showed significant population specificity and much higher carrier frequencies than the clinical incidence rate. The results suggested that a group of MEFV mutations are benign variants and do not have pathogenic significance.

Due to high carrier frequency, it is not rare to observe pseudo-dominant transmission, especially in high risk populations where the rate of consanguinity is also high. There are a number of reports proposing a true autosomal dominant inheritance in FMF, like the single M694del mutation in 3 British patients and a novel MEFV mutation, H478Y, in a Spanish family and T577S mutation detected in a number of families with Dutch, British and Turkish descent [49].

**Table 1**

**Fourteen sequence variants recommended for screening for the genetic diagnosis of FMF [39]**

<table>
<thead>
<tr>
<th>Exons 10</th>
<th>Pathogenic variants</th>
<th>Unknown signification</th>
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<tbody>
<tr>
<td></td>
<td>M694V²</td>
<td>K695R</td>
</tr>
<tr>
<td></td>
<td>V726A¹</td>
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<td></td>
<td>M680I¹</td>
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<td>A7445</td>
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<tr>
<td></td>
<td>1692del</td>
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</tr>
<tr>
<td>Exons 2</td>
<td>E167D</td>
<td>E148Q¹</td>
</tr>
<tr>
<td></td>
<td>T267I</td>
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<tr>
<td>Exons 3</td>
<td></td>
<td>P369S</td>
</tr>
<tr>
<td>Exons 5</td>
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<td>F479L</td>
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<tr>
<td>Exons 9</td>
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<td>I591 T</td>
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</table>

¹The most common gene mutations.
Partial penetrance and variable expression in heterozygous individuals may explain the clinical phenotype and the vertical transmission in some families. Thus FMF may be accepted as a dominant condition with low penetrance, as suggested by Marek-Yagel [43].

The expression of an FMF phenotype in an individual with one MEVF mutation may need the contribution of one or more modifying alleles in other genes and/or environmental factors. SAA (serum amyloid A) gene and MICA (MHCI class I polypeptide-related sequence A) have been reported as modifier genes contributing to the severity of FMF. SAA1α allele is significantly associated with amyloidosis in certain populations [50–52]. One other explanation may be interactions between different periodic fever genes. There are case reports presenting patients who are compound heterozygous for two different monogenic AID genes [53,54].

In at-risk populations, FMF phenotype in MEVF negative families may be related to mutations in other autoimmune disease (AID) genes as shown by Karaca et al. [55]. A homozygous missense MWK mutation and a novel heterozygous TNFRSF1A mutation were detected in two separate Turkish families with FMF phenotype. The interesting observation was that in these cases the clinical presentation was not compatible with the phenotype expected of the mutation identified but rather resembled the most prevalent AID in that population, which was FMF in this occasion. This might be another clue to the impact of environmental factors on the expression of FMF phenotype. Country of residence was the most important risk factor for amyloidosis in patients from 14 countries [56]. The role of MEVF mutations on host-microbiome has been investigated by Khachatryan [57]. Still-unresolved riddle of Armenian patients having more severe disease and increased risk of amyloidosis in Armenia but not in USA is awaiting an explanation [58]. A similar observation shows that Turkish children with FMF who live in Germany have less severe disease compared to the patients living in Turkey [59].

Considering the data at hand, single-gene recessive model is not able to describe the complexity of FMF genetics. Maybe FMF is a multifactorial and polygenic disease and effects of multiple genes and environmental factors are responsible from its phenotypic heterogeneity [49].

As a result, clinical judgment remains the mainstay of diagnosis of FMF. A patient with clinical symptoms compatible with FMF, whatever the MEVF status is, deserves a trial of colchicine treatment.

**Pathogenesis**

FMF is a disease of the innate immune system. MEVF gene encodes pyrin/marenostrin which is expressed predominantly in neutrophils, monocytes, dendritic cells, fibroblasts. There are some controversies regarding the role of pyrin, and its normal function appears to be the regulation of inflammation. Pyrin interacts with ASC, an adaptor protein which is important for the assembly of the inflammasome, a multiprotein complex, for caspase-1 activation. Activation of caspase-1 subsequently leads to processing of pro-IL-1β followed by activation and secretion of IL-1β which plays a major role in the pathogenesis of FMF [60,61]. Pyrin is an intracellular pattern recognition receptor (PRR) but it does not directly recognize molecular patterns like PAMPs/DAMPs, but rather responds to disturbances in cytoplasmic homeostasis caused by the infection. This has been defined as “homeostasis-altering molecular processes (HAMPs)” by Liston et al. [62]. These findings demonstrate how innate immunity copes and detects novel infections.

Recently it has been reported that pyrin may function as an inflammasome sensor against bacterial toxins that modify GTPase RhoA [63]. Inactivation of RhoA leads to pyrin activation, inflammasome assembly and pyroptotic cell death. The binding of mutant pyrin to regulatory proteins (14-3-3, PKN) that normally block pyrin inflammasome by the help of RhoA, is decreased which in turn results in the activation of IL-1β [64]. Initially it was postulated that pyrin mutations are loss-of-function because of its autosomal recessive inheritance [65,66]. However now we know that approximately one third of the patients possess a single mutation and some cases are dominantly inherited [67]. This evidence suggests that FMF cannot be explained solely by recessive loss-of-function mutations. On the contrary, studies performed with knock-in mice show that MEVF mutations are actually gain-of-function with a gene dosage effect. Mutant pyrin forms an ASC-dependent inflammasome which in turn activates caspase-1 and IL-1-mediated inflammation [68].

**Clinical manifestations**

FMF attacks start before the age of 20 in about 90% of the patients [8]. The mean age of onset is between 3–9 years. Early onset is not an exception yet appearance of attacks during the first year of life is not as common as in other AIDs like mevalonate kinase deficiency (MKD) [69]. Although rare, onset after the age of 40 has been mentioned even in the early reports [3,70]. Late onset FMF seems to be more prevalent among males, and associated with mild disease responding to lower dose of colchicine [28,71]. There is a slight male preponderance in several FMF series, male to female ratio being approximately 1.2:1 [17].

**Attacks**

FMF is defined as the most common of all periodic fever syndromes, however the attacks are not periodic, but rather recurrent. The only periodicity observed in about one fourth of female patients is when attacks overlap with menstrual cycle. The frequency of attacks in untreated patients may vary from one attack or more per month to several attacks per year. Severity of the attacks may be different even in the same patient. Some
attacks may be severe enough to require hospital care while some may be mild. Before colchicine era, the number of patients who had undergone surgical interventions was high [23,72]. A classical attack is characterized by fever and serositis, manifesting as abdominal pain and/or chest pain and/or joint pain and swelling. An erythematous rash is also a common feature of the disease. These episodes are generally self-limited and last 1 to 4 days. Patients are symptom-free in between attacks. An individual patient generally has a predominant attack type, like fever and abdominal pain, but may experience other attack types independent from each other. This clinical diversity concerning the frequency, severity and presentation of the attacks is one of the main reasons of diagnostic delay. The clinical picture may get even more complicated with the association of vasculitis, sacroilitis, or neurological manifestation, eg. [73-75]. Some of the patients describe a prodromal phase with some constitutional, emotional symptoms. However not consistent, some triggers of attack have been reported such as cold exposure, emotional stress, long periods of standing or exercise [76,77].

Fever

Fever is the major manifestation of FMF. Attacks without fever are an exception as the only-fever attacks. Generally the temperature rise up to 39–40° C in severe attacks but low-grade fever may be the case in mild episodes. In the majority, fever lasts shorter than the accompanying serositis [72].

Peritonitis

Abdominal attacks are the most common attack type occurring in almost 90% of the patients during their disease course [8,17]. Classically it resembles an acute abdomen associated with rebound tenderness, rigidity and decreased peristalsis. In fact, it is a transient subileus. Air-fluid levels may be detected in x-rays of the abdomen. Generally, they are constipated during a peritonitis attack, followed by a short-lived, postattack diarrhea which may be positive for occult blood [74]. Five percent of the referrals to an emergency unit for abdominal pain were due to FMF [78]. Approximately one-third of the patients undergo surgical interventions like appendectomy or cholecystectomy. Elective appendectomy has been recommended for FMF patients [79]. Peritoneal irritation as a result of surgical or diagnostic procedures as in gynecological work-up for infertility may provoke severe FMF attacks [23]. Recurrent peritonitis may lead to the development of intestinal adhesions that in turn may cause ileus or infertility. This was a late complication and was more common before the colchicine era [80].

Pleuritis

Approximately 30–50% of the patients suffer chest pain because of pleural involvement. Generally, it is unilateral
and interferes with deep breathing. Plain x-rays demonstrate small amounts of transient pleural effusion on the affected site (figure 1a, b). Seldom, large effusions or atelectasis may be seen [72]. The pain may radiate to abdomen, back, or shoulder. Pleuritis may occur simultaneously with peritonitis and rarely with pericarditis [23]. Pleural adhesions secondary to recurrent pleuritis are rare.

**Synovial attacks**
Joint involvement is present in about 50% of the patients and more frequent among children [71,81]. It is associated with recurrent episodes of non-deforming, mono or oligoarticular inflammation of mainly lower extremity joints. This manifestation is more common among North African Jews [8,82]. It is associated with M694V mutation, severe disease and amyloidosis. If it is the presenting attack type, it may cause diagnostic problems. Some are initially diagnosed as JIA (juvenile idiopathic arthritis) or spondyloarthritides. Spectrum of joint involvement in FMF ranges from acute, self-limited synovitis to chronic, deforming arthritis. The most frequent and typical of all is the short-lived monoarthritis of an ankle or a knee. In about half of these attacks an erythematous rash is seen over the involved joint (figure 1c). It may be more prominent over the medial and/or lateral malleol or dorsum of the foot. Therefore, it has been described as "red arthritis". It is a useful tool for differential diagnosis [83]. Large effusions may be detected, especially in the knees. Synovial fluid is sterile, yet is rich from neutrophils with good mucine clot [8]. More than one joint may be involved during an attack, however polyarticular presentation is very rare. Involvement of the upper extremity joints and small joints is also uncommon. The articular attacks generally last less than a week and resolve without a sequel. In a subgroup of patients, it takes couple of weeks to months to resolve. Only in 2-5% of patients with protracted arthritis, irreversible changes may occur, and in some joint replacement may be indicated. Sarcoiditis may be detected. HLA B27 is positive in less than 40% of those who manifest features of spondylarthritis [84-86].

**Erysipelas-like erythema (ELE)**
This is the most typical skin manifestation of FMF. These are tender, red, hot, indurated lesions generally located over the crural areas, ankle joint and dorsum of the foot, sometimes associated with fever. Liver and/or carefully discriminates ELE from red arthritis. Histological examination reveals mild perivascular neutrophilic infiltration without vasculitis [87].

**Myalgia**
FMF patients frequently complain of myalgia. Its impact on the quality of daily life of these patients is more than anticipated. Some are related with exertion, like long periods of standing or walking, and involves primarily the lower limbs. Exertional leg pain is not associated with fever. It is among minor criteria for diagnosis [88]. Acute inflammatory episodes of myalgia and protracted febrile myalgia (PFM) are relatively rare. PFM is related with disabling pain, very high acute phase response, M694V genotype and severe disease course [89]. There is no increase in muscle enzymes and EMG is non-specific. MR images show patchy or diffuse high signal intensity in the involved muscles with myofascial distribution of inflammation (figure 1d, e) [90]. Probably it is another example of serositis rather than true myositis. Colchicine is not sufficient to control PFM, and it is generally treated with high dose of corticosteroids or recently with anti IL-1b agents [91,92].

**Other manifestations**
Compared to other serosal attacks, pericarditis is a rare and a late manifestation of FMF (less than 1%) [93]. Constrictive pericarditis has been reported in few patients [17].
Orchitis is more frequent in pediatric age group. Acute scrotum is diagnosed in about 2-8% of the children [94] and may manifest as the presenting attack in some patients [95]. However the association is not clear, recurrent aseptic menengitis (Mollaret’s menengitis) has been described as a rare manifestation of FMF [96]. These are self-limited attacks of fever, headache, and signs of meningsimus.
Enlargement of spleen and liver may be detected in about one third of the patients with FMF. It may be secondary to AA amyloidosis in some. An association between non-alcoholic liver disease and FMF has been suggested by several centers [97,98]. Non-amyloid kidney disease is a rare yet a well known manifestation of FMF [17].

Amyloidosis is the main complication of FMF related with increased mortality. Following the introduction of prophylactic colchicine treatment, the prevalence of amyloidosis, especially in children has decreased significantly [99,100]. Amyloidosis associated with FMF is amylod A (AA) type. Mainly affects kidneys and gastrointestinal tract. Liver, spleen, heart, thyroid and testis may also be involved. Renal amyloidosis presents with asymptomatic proteinuria and progress to renal insufficiency. It is more prevalent in North African Jews, Turks and Armenians and less in Arabs, Ashkenazi and Iraqi Jews. The main risk factors for amyloidosis are male sex, arthritis, M694V and SAA α/α homozygosity, and a family history of amyloidosis [50]. Especially in the early papers, patients presenting with amyloidosis without a history of FMF attacks have been described as “phenotype II” [8]. Later Melikoglou et al. questioned phenotype II, because it was uncommon among the relatives of patients with FMF amyloidosis [101].

**Diagnosis**
Diagnosis of FMF is based on the recognition of clinical manifestations, assessment of inflammatory indices during and in between attacks, response to colchicine and genetic analysis. In the majority, diagnosis relies essentially on a detailed history taking, including a comprehensive pedigree.
Various diagnostic criteria have been proposed by now (table II). Recently an evidence based provisional classification for FMF together with other AIDs have been also reported [8,33,69,88,102,103].

The change in the magnitude of the acute phase response (APR) between attack and attack-free period has been used as a means of diagnosis. FMF attacks are characterized by increased levels of inflammatory mediators such as ESR, CRP, and SAA [104]. Korkmaz et al. reported high APR in 34% of the attack-free intervals [105]. The presence of APR in between attacks is a sign of ongoing subclinical inflammation and continuing risk of amyloidosis [106].

One of the major criteria for diagnosis of FMF is response to colchicine. This is being used as a diagnostic tool since Tel-Hashomer criteria, yet it has not been fully standardized by now [102,107]. It has been clearly shown that screening the most common mutations instead of sequencing the whole gene appears sufficient to diagnose FMF in the presence of clinical manifestations [42]. A consensus to test 14 MEFV variants was reached in 2012 (table I) [39]. Four most common mutations located in Exon 10 (M694V, M680I, V726A, M694A) and one in Exon 2 (E148Q) account for the vast majority of the disease associated variants in at-risk populations. However, the interpretation of the results of the genetic analysis is not always easy, especially in low-risk ethnicities. Recently evidence-based recommendations for the genetic diagnosis of FMF have been set up by a group of experts (table III) [33].

**Associated diseases**

FMF has been associated with a number of conditions. An increased frequency of MEFV mutations, especially M694V, has been described in many of these diseases, suggesting a modifier gene activity [46]. Among the associated diseases, Henoch-Schönlein’s purpura, and polyarteritis nodosa are the most common (figure 1). However, a decline in the incidence of vasculitis among FMF patients has been reported recently [74,108,109].

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**Table II**

<table>
<thead>
<tr>
<th>Diagnostic criteria sets for FMF [8,33,88,102,103]</th>
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<tbody>
<tr>
<td><strong>Tel Hashomer criteria</strong></td>
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<tr>
<td>Major criteria:</td>
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<tr>
<td>Recurrent episodes of fever accompanied by serositis</td>
</tr>
<tr>
<td>AA type of amyloidosis without predisposing disease</td>
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<td>Response to colchicine</td>
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Minor criteria:
- Recurrent febrile attacks
- Erysipelas-like erythema
- Family history in first-degree relatives

The requirements for diagnosis
≥ two major criteria or one major plus two minor criteria

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1Livneh criteria requirements for diagnosis ≥ 1 major criterion, or ≥ 2 minor criteria. Typical attacks are defined as recurrent (≥ 3 of the same type), febrile (rectal temperature of 38 °C or higher), and short (lasting between 12 hours and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in 1 or 2 features, as follows: 1) the temperature is normal or lower than 38 °C 2) the attacks are longer or shorter than specified (but not shorter than 6 hours or longer than a week); 3) no signs of peritonitis are recorded during the abdominal attacks; 4) the abdominal attacks are localized; 5) the arthritis involves joints other than those specified. Attacks not fulfilling the definition of typical or incomplete attacks are not counted.
With regard to Behçet’s Disease (BD), some suggest an association, especially with vascular BD and FMF, while others deny a true association but propose a coexistence by chance [110,111]. There is an increased prevalence of spondarthritides among patients with FMF, as well as in their first degree relatives [84,112]. A higher frequency of M694V mutation was reported among FMF patients with radiographic sacroiliitis compared to without [113]. Anti-TNF agents are recommended for the treatment of these patients [114].

Co-existence of FMF with JIA has also been observed and related with severe disease [115,116]. In a large Turkish cohort with 2716 FMF patients, 4 cases of systemic lupus erythematosus have been identified [17]. MEFV gene variants were higher among SLE patients with pericardial/pleural effusions [117].

Several reports suggest a possible association between FMF and multiple sclerosis (MS) [118]. Based on a case series from Israel, the frequency of MS in their FMF population was twice higher than the expected rate [119]. Blaschek et al. reported that one third of the 29 childhood MS patients had a heterozygous mutation in the TNFRSF1A and/or MEFV gene [120]. Recently a very strong association has been reported between hidrosadenitis and FMF in a population based study by Hodak et al. [121] and others [122]. In addition an increased frequency of psoriasis in patients with FMF and their relatives has been reported [99].

Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is a newly identified disorder also driven by mutations in pyrin; however, PAAND exhibits a distinct clinical phenotype to FMF [123].

Differential diagnosis list of FMF consists of hereditary recurrent fever syndromes like HIDS/MKD, TRAPS, CAPS and other diseases that simulate symptoms of FMF such as, irritable bowel syndrome, endometriosis, appendicitis, diverticulitis, Crohn’s disease, pancreatitis, palindromic rheumatism, porphyria, crystal arthritis, lymphoma, Still’s disease, PHAPA, infections like malaria, eg. [69,72].

Management

Colchicine

Colchicine is the mainstay of FMF treatment since reported by Ozkan and Goldfinger in 1972 [9,10]. It is generally safe and well-tolerated. It is an alkaloid obtained from the plant colchicum autumnale. However the mechanism of action is not fully understood, primarily colchicine targets microtubules and prevents microtubule elongation by binding to tubulin monomers and inhibits polymer formation [124-126]. It is also known that colchicine is an activator of RhoA and therefore suppresses pyrin inflammasome activation, inhibiting the induction of caspase-1 and IL-1β in FMF patients [63]. Recently Van Gorp et al. reported that microtubule-depolymerizing drugs, like colchicine, selectively inhibited the pyrin inflammasome [127].

Efficacy of prophylactic colchicine treatment has been reproduced in several controlled trials [128,129]. Colchicine controls the recurrence of inflammatory attacks, and also prevents the
development of AA amyloidosis which is the most devastating complication of FMF [130]. The recommended dose of colchicine is less than 0.5 mg/day for children less than 5 years old, 0.5 to 1 mg/day for children 5 to 10 years of age, 1-1.5 mg/day for children older than 10 and for adults. In case the tablets contain 0.6 mg colchicine, dose should be adjusted accordingly. Daily dose can be increased up to 3 mg/day in adults and 2 mg/day in children if there is an increase in attack frequency and/or acute phase response in between attacks [130-132]. Colchicine dose should not be increased to treat an ongoing peritonitis attack because it is effective only if given prophylactically. Besides, its common side effect diarrhea may interfere with the severity of the abdominal attack.

The most common side effects of colchicine are diarrhea, abdominal discomfort and nausea [133]. Intolerant patients are recommended to start with a low dose and increase with small increments, till the effective dose is reached [131]. Lactose intolerance may be an additive factor for the gastrointestinal side effects observed in FMF patients [134].

Colchicine is metabolized partially by the liver and is excreted through the biliary tract and the kidneys [135,136]. A frequent side effect of colchicine is the increase in liver enzyme values which may require dose adjustment if the levels exceed two-fold of the upper limit [131]. Creatinine clearance should be monitored in these cases. GFR levels lower than 25 mL/min is related with risk of colchicine accumulation [136,137]. Another important side effect is myopathy which presents with progressive muscle weakness, generalized myalgia and increase in muscle enzymes. This is rare on regular doses of prophyphatic colchicine, but increase with the simultaneous use of CYP3A4 inhibitors and in patients with impaired renal function. Involvement of peripheral nervous system is usually a sign of colchicine adverse effect which is generally reversible. Creatinine kinase (CK) should be tested together with AST and ALT regularly [131,133,138].

Colchicine, within therapeutic range, seldom causes leukopenia, thrombocytopenia and very rarely aplastic anemia [133,139,140]. Only in very high concentrations, which far exceed suggested treatment doses, colchicine may inhibit mitosis during cell division. Therefore there is no need for male FMF patients to stop colchicine prior to conception, nor female patients to avoid treatment during pregnancy and lactation [141,142].

Co-administration of colchicine with CYP3A4 inhibitors or competitors, including clarithromycin, or with P-gp inhibitors/competitors such as cyclosporine can lead to accumulation of colchicine, resulting in increased risk of toxicity [135,143]. Colchicine is a relatively safe drug within its narrow therapeutic dose range. However, colchicine toxicity is associated with high mortality risk [136,144].

Overall, approximately 60% of the patients respond to daily colchicine treatment, while 20-30% has partial and 5-10% has no response [23]. Compliance to treatment is a major issue in treatment failures. Only 5% of the compliant patients on effective dose of colchicine still have active disease. Single daily dose may increase the compliance [145]. Also compliance improves after the diagnosis of amyloidosis [146].

A group of experts have proposed recurrence of more than 6 typical FMF attacks per year or more than 3 typical FMF attacks within 4-6 months despite maximum tolerated dose of prophyphatic colchicine as the definition of colchicine-resistance. [132]. However in the EULAR recommendations [131] one or more attacks per month has been suggested.

Persistence of increased CRP and SAA levels in attack-free interval is a sign of subclinical inflammation. This is related with insufficient response to colchicine and continuing risk of amyloidosis [105,147]. In addition, colchicine is not effective in controlling some manifestations of FMF such as exertional leg pain, protracted myositis or arthritis, vasculitis or an already established amyloidosis. Therefore, a need for an alternative approach is warranted in a subgroup of patients. Among the several options suggested [114] are interferon alpha [148], azathioprine [149], methotrexate [150], thalidomide [151], anti TNF agents [151], and IL-1β antagonists [152,153]. Anti-TNF inhibitors have been used before the introduction of anti-IL-1 agents in FMF patients with protracted arthritis, spondarthritis, associated vasculitis and amyloidosis [114]. After the pivotal role of IL-1 in FMF pathogenesis has been demonstrated, IL-1 inhibition has become the most promising approach of all alternative treatments. It is important to note that colchicine treatment should continue together with additional therapies.

**Anti IL-1 treatments**

Currently, there are 3 different anti IL-1 agents. The efficacy of these inhibitors has been tested in randomized controlled trials (RCT) [153-155].

**Anakinra**

Anakinra is a recombinant, nonglycosylated homolog of the human IL-1 receptor antagonist (IL-1Ra). It competes both with IL1 α and β. The half-life of anakinra is 4-6 hours, therefore administered daily (100 mg/day) by subcutaneous injections. [156,157]. A RCT, which included 24 colchicine-resistant FMF (crFMF) patients, reported significantly fewer attacks, improvement in health-related quality of life (HRQOL), with a good safety profile on the anakinra arm [154]. Recently published case series also demonstrate significant decrease in attack frequency in over two-thirds of the patients [155,160,161]. Injection site reaction is the most common side effect and the reason for treatment discontinuation. Pneumonia has been reported in 3 patients [152,158,159].
Rilonacept
Rilonacept is a human IL-1β receptor fusion protein which blocks IL-1 signaling pathway. Its half-life is 6.3-8.6 days and therefore injected weekly [156,160]. The first randomized placebo controlled study with an anti IL-1 agent was performed with rilonacept. More than 50% decrease in attack frequency and improvement in HRQoL was reported in 9 of the 12 patients. One patient developed pneumonia on rilonacept. Injection site reactions were the most common side effects [153].

Canakinumab
Canakinumab is a fully human monoclonal anti IL-1β antibody. Canakinumab has the longest half-life of 21-28 days, therefore, it can be administered (150–300 mg) subcutaneously every 4-8 weeks [156,161]. Canakinumab is the first drug approved by FDA for FMF. There are several published case series, two phase 2 [92,162] and one phase 3 clinical trial with canakinumab [155]. In a review of 80 patients, including 32 from one center [156,163], significant decrease was observed in attack frequency while 71% was attack-free. Dramatic response was reported in exertional leg pain [163]. The drug was well tolerated with few adverse effects, including 4 infections. In a recent, multicenter study with 21 patients treated with Canakinumab, complete remission was observed in 65% of the patients [158]. In 63 colchicine-resistant (cr) FMF patients, the effectiveness of canakinumab was tested with a RCT [155]. Primary outcome was described as the resolution of the index flare by day 15 and no new episodes over 16 weeks of treatment. The primary outcome was achieved by 61% of patients in the treatment group compared to 6% in the placebo arm. No opportunistic infections, tuberculosis or death was observed but 3 serious infections were reported in two crFMF patients.

Treatment of FMF related amyloidosis
Regular colchicine intake after the development of amyloidosis is effective if the creatinine level is below 1.5 mg/dL, and colchicine dose is 1.5-2 mg/day [164], but the expected benefit is limited in patients with nephrotic range proteinuria and impaired renal function [130,165,166]. Colchicine is recommended also after renal transplantation [167]. There is no definite treatment of AA amyloidosis. No controlled study on the role of immunosuppressive agents in FMF amyloidosis has been undertaken. Some improvement was reported with azathioprine [149].

The first biologic agents used in FMF amyloidosis were anti-TNF inhibitors [168,169]. A recent study reports some benefit in 37 patients with AA amyloidosis, 9 secondary to FMF, who were treated with anti-TNF agents. There were 4 deaths among 10 patients who developed an infection and 1 case of tuberculosis in a patient with amyloidosis related to BD [170].

There are a number of reports assessing the efficacy of anti IL-1 treatments on FMF amyloidosis, which include patients who are on hemodialysis or transplanted [152,171,172]. This subgroup of patients generally well tolerate anti IL-1 agents, and become eligible for transplantation. Anakinra injections can be given following after each hemodialysis session [173]. Overall there are 3 case reports describing patients with a transplanted kidney on canakinumab together with colchicine [174]. Significant decrease in proteinuria and acute phase reactants were reported in 2 case series with Tocilizumab, a humanized monoclonal IL-6 inhibitor, in patients with FMF amyloidosis [175,176]. A rapid deterioration of renal function was observed in 2 patients when the interval between infusions was increased [176].

Pregnancy and breastfeeding in FMF treatment
Colchicine treatment should be continued throughout pregnancy and lactation without any dose reduction. It is not associated with increased risk of fetal abnormality [142,177,178]. In a recent systematic review and a meta-analysis on colchicine use during pregnancy, the risk of miscarriage was lower but pre-term birth was higher among patients on colchicine. Amnio-synthesis is recommended only in rare selected cases [179].

A multicenter study reported that anakinra and canakinumab treatment were well tolerated in 31 pregnancies, 5 with associated FMF. Unilateral renal agenesis and ectopic neurohypophysis were observed in a single patient with adult onset Stills disease on anakinra [180]. Ozdogan et al. reported 6 pregnant FMF patients given anakinra mainly for severe protracted febrile myalgia. No anakinra-related adverse event was observed either in the mother-to-be or the fetus during pregnancy and delivery [91].

In male FMF patients who have oligo- or azospermia, colchicine can be stopped temporarily and replaced by an anti IL-1 agent [163]. No congenital abnormality or growth retardation was observed in the presence of paternal exposure to anti IL-1 treatments [180]. There is no increase of any side effect in breastfed babies of mothers who receive colchicine [142,181] and/or anti IL-1 inhibitors [142,180,181].

EULAR recommendations for the management of FMF
Recently, an international expert group has proposed a set of recommendations for the management of FMF [131]. It underlines the importance of early diagnosis, colchicine treatment and compliance. Alternative treatments are recommended for compliant patients on a maximum dose of daily colchicine who still have attacks and subclinical inflammation. Last recommendation considers dose reduction in colchicine if there is no attack and no APR for more than 5 years. This should be handled with caution because there is no sufficient data to back this proposal (table IV).

Conclusion
Twenty years after the description of MEFV gene, FMF is still a clinical diagnosis. It is considered an autosomal recessive
disease however about one-fourth of the patients are heterozygous, suggesting a genetic heterogeneity. Besides MEFV variants, environmental factors, and modifier genes also contribute to the expression of FMF phenotype. Exon 10 mutations, especially homozygous M694V is related with severe disease, therefore should receive the maximal tolerable dose of colchicine and should be closely monitored. Other AIDs should be considered in MEFV negative patients with clinical FMF. Colchicine is the drug of choice. In patients with insufficient response or intolerance to colchicine, alternative treatments, especially anti IL-1 agents, may be administered without stopping colchicine prophylaxis. Data on efficacy and safety of IL-1 inhibitors is accumulating.

**Disclosure of interest:** the authors declare that they have no competing interest.

### Table IV

**EULAR recommendations for the management of FMF [131]**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>A</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>01. Ideally, FMF should be diagnosed and initially treated by a physician with experience in FMF</td>
<td>7.6</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>02. The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimising subclinical inflammation in between attacks</td>
<td>9.3</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>03. Treatment with colchicine should start as soon as a clinical diagnosis is made</td>
<td>8.9</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>04. Dosing can be in single or divided doses, depending on tolerance and compliance</td>
<td>9.4</td>
<td>5</td>
<td>D</td>
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<tr>
<td>05. The persistence of attacks or of subclinical inflammation represents an indication to increase the colchicine dose</td>
<td>9.7</td>
<td>3</td>
<td>C</td>
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<tr>
<td>06. Compliant patients not responding to the maximum tolerated dose of colchicine can be considered non-respondent or resistant; alternative biological treatments are indicated in these patients</td>
<td>9.8</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>07. FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required</td>
<td>9.5</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>08. Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily</td>
<td>7.6</td>
<td>5</td>
<td>D</td>
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<tr>
<td>09. Response, toxicity and compliance should be monitored every 6 months</td>
<td>8.6</td>
<td>5</td>
<td>D</td>
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<tr>
<td>10. Liver enzymes should be monitored regularly in patients with FMF treated with colchicine; if liver enzymes are elevated greater than twofold the upper limit of normal, colchicine should be reduced and the cause further investigated</td>
<td>8.4</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>11. In patients with decreased renal function, the risk of toxicity is very high, and therefore signs of colchicine toxicity, as well as CPK, should be carefully monitored and colchicine dose reduced accordingly</td>
<td>9.3</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>12. Colchicine toxicity is a serious complication and should be adequately suspected and prevented</td>
<td>9.4</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>13. When suspecting an attack, always consider other possible causes. During the attacks, continue the usual dose of colchicine and use NSAID</td>
<td>9.5</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>14. Colchicine should not be discontinued during conception, pregnancy or lactation; current evidence does not justify amniocentesis</td>
<td>9.3</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>15. In general, men do not need to stop colchicine prior to conception; in the rare case of azoospermia or oligospermia proven to be related to colchicine, temporary dose reduction or discontinuation may be needed</td>
<td>8.2</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>16. Chronic arthritis in a patient with FMF might need additional medications, such as DMARDs, intra-articular steroid injections or biologics</td>
<td>9.5</td>
<td>2b</td>
<td>C</td>
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<td>17. In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAID and IL-1-blockade might also be a treatment option; NSAIDs are suggested for the treatment of exertional leg pain</td>
<td>9.3</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>18. If a patient is stable with no attacks for more than 5 years and no elevated APR, dose reduction could be considered after expert consultation and with continued monitoring</td>
<td>8.0</td>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>

A: agreement (/>10); APR: acute phase reactants; CPK: creatinine phosphokinase; DMARDs: disease modifying antirheumatic drugs; EULAR: European League Against Rheumatism; FMF: Familial Mediterranean Fever; IL-1: interleukin 1; LoE: level of evidence; NSAID: non steroidal anti inflammatory drugs.
References


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