

# Familial Mediterranean fever: current perspectives

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**Abstract:** Familial Mediterranean fever (FMF) is the most frequent monogenic autoinflammatory disease, and it is characterized by recurrent attacks of fever and polyserositis. The disease is associated with mutations in the *MEFV* gene encoding pyrin, which causes exaggerated inflammatory response through uncontrolled production of interleukin 1. The major long-term complication of FMF is amyloidosis. Colchicine remains the principle therapy, and the aim of treatment is to prevent acute attacks and the consequences of chronic inflammation. With the evolution in the concepts about the etiopathogenesis and genetics of the disease, we have understood that FMF is more complicated than an ordinary autosomal recessive monogenic disorder. Recently, recommendation sets have been generated for interpretation of genetic testing and genetic diagnosis of FMF. Here, we have reviewed the current perspectives in FMF in light of recent recommendations.

**Keywords:** familial Mediterranean fever, recommendation, child

## Introduction

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease (AID) mainly affecting the populations of eastern Mediterranean descent.<sup>1,2</sup> It is characterized by recurrent, self-limited flares of fever associated with polyserositis.<sup>3</sup> The gene mutated in patients with FMF is the *MEFV* gene, which encodes pyrin, which forms an element of the NLRP3 inflammasome complex.<sup>2</sup> Mutations in the *MEFV* gene are associated with increased interleukin-1 $\beta$  (IL-1 $\beta$ ), which causes excess inflammation.<sup>4</sup> The majority of FMF patients demonstrate a Mendelian autosomal recessive pattern of inheritance.<sup>5-7</sup> However, since the *MEFV* gene was found to underlie FMF in 1997,<sup>5,6</sup> the concepts about the etiopathogenesis and genetics of the disease have evolved. Progress in molecular biology suggested that this AID was more complicated than we had anticipated.

Colchicine still constitutes the mainstay of FMF treatment,<sup>8</sup> and the aim of the treatment should be preventing acute attacks and amyloidosis, decreasing the chronic inflammation, and providing an acceptable quality of life. Recent insights into the pathogenesis of FMF have made anti-IL 1 treatments important in colchicine-resistant or -intolerant patients. The most severe complication of FMF is secondary amyloidosis,<sup>9</sup> however, it is less common in the colchicine and anti-IL 1 era.

In 2012, Shinar et al<sup>10</sup> proposed recommendations for interpretation of genetic testing in AIDs. Most recently, the SHARE (a pediatric initiative to develop better care and management for rheumatology patients; Single Hub and Access point for pediatric

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Rheumatology in Europe) initiative has developed evidence-based recommendations for genetic diagnosis of FMF.<sup>11</sup>

In this paper, we have reviewed the current perspectives in FMF in the light of recent recommendations.

## Etiopathogenesis

The *MEFV* gene encodes the protein pyrin, which is a part of the inflammasome complex, NLRP3, an intracellular organelle required for the production of IL-1 $\beta$ .<sup>12</sup> Thus, FMF may be classified as an inflammasomeopathy.<sup>2</sup> Pyrin has been suggested to interact with the inflammasome adaptor protein ASC, and this results in increased caspase-1 activation and IL-1 $\beta$  processing.<sup>13</sup>

In 2007, Yu et al<sup>14</sup> have shown that activated pyrin interacts with ASC and PSTPIP1 to form a trimolecular complex that directly activates caspase-1 and then leads to the secretion of active IL-1 $\beta$ . Booty et al<sup>15</sup> demonstrated a significant increase in pyrin expression in FMF patients in comparison with healthy controls. Supporting the hypothesis of a gain-of-function model, an elegant study by Chae et al<sup>16</sup> revealed that FMF-associated B30.2 mutations knock-in mice, but not pyrin deficient ones, showed severe spontaneous inflammatory phenotype.

On the other hand, Papin et al<sup>17</sup> showed that pyrin knock-down resulted in increased caspase-1 activation and IL-1 $\beta$  secretion. In another study by Hesker et al,<sup>18</sup> enhanced IL-1 $\beta$  release by macrophages was demonstrated in response to a spectrum of inflammatory stimuli in a mouse line lacking the *MEFV* gene. The findings of these two studies suggest a loss-of-function model.

However, it is still controversial whether *MEFV* mutations cause loss of function or gain of function.

A recent study by Xu et al<sup>19</sup> has elegantly shown that pyrin is a specific immune sensor for bacterial modifications of Rho GTPases, and responds to *Clostridium difficile*, which is a frequent cause of nosocomial diarrhea. Pyrin does not directly recognize the microbial products but detects pathogen virulence activity. This recent finding has shed some light on FMF pathogenesis.

## Diagnosis

Since FMF usually requires lifelong treatment, it is crucial to establish a timely, correct diagnosis. The diagnosis of FMF relies mainly on clinical findings, and molecular analysis of the *MEFV* gene provides genetic confirmation.<sup>20</sup>

There are different sets of classification and diagnostic criteria for FMF. The first set of criteria was created for adults by the experts in Tel Hashomer Hospital (Table 1).<sup>21</sup>

Livneh et al<sup>22</sup> validated the new criteria in 1997, excluding some manifestations of the Tel Hashomer criteria such as amyloidosis (Table 1). However, there were certain differences between adult and pediatric FMF cases (such as shorter attacks in children, lack of unilateral characteristic of chest pain in some pediatric cases, more febrile attacks or even fever-only attacks in some children, and inability of some pediatric patients to express the severity and exact location of the pain), and some of the Tel Hashomer criteria were of less relevance to pediatric FMF patients. Thus, in 2009, our group attempted to define criteria for children as well (Table 1).<sup>23</sup> Among Turkish children, the criteria (two out of five criteria for diagnosis) reached a sensitivity and specificity of 88.8% and 92.2%, respectively.<sup>23</sup> In French children, the presence of three instead of two criteria yielded a better specificity of 95%.<sup>24</sup> Validation of these criteria in a larger and genetically more heterogeneous group is crucial.

It is important to keep in mind that FMF diagnosis is a clinical one, and if the phenotype is consistent with FMF, the physician should not exclude the diagnosis when there is no genetic confirmation.

## Genetics

### Variants to be checked in the *MEFV* gene

When the genetic association of FMF with the *MEFV* gene was first described in 1997,<sup>5,6</sup> only a few mutations had been reported. Since the number of variants recognized associated with FMF has increased, concerns emerged about the adequacy of checking for four to six mutations only. Booty et al<sup>15</sup> sequenced the *MEFV* gene in heterozygote FMF patients and demonstrated that additional sequencing of the whole gene did not yield a second mutation in any of the screened patients. Currently, all reported *MEFV* variants and the associated phenotypes are recorded in the INFEVERS database (<http://fmf.igh.cnrs.fr/ISSAID/infevers/>), and there are approximately 300 known sequence variants of *MEFV*.<sup>11</sup> The most common disease-associated pathogenic variants are M694V, V726A, M680I, and M694I, whereas E148Q is the most frequent variant among carriers.<sup>25,26</sup> An agreed set of best practice guidelines was proposed for genetic diagnostic testing of hereditary recurrent fevers including FMF in 2012.<sup>10</sup> The consensus was to test for a total of 14 variants (the first nine are defined as clearly pathogenic, while the remaining five variants have unknown significance): M694V, M694I, M680I, V726A, R761H, A744S, E167D, T267I, I692del, K695R, E148Q, P369S, F479L, and I591T. We now suggest testing for these variants only.

**Table 1** The clinical criteria sets for FMF diagnosis**Tel Hashomer criteria (long version)<sup>22</sup>****Major criteria**

Typical attacks ( $\geq 3$  of the same type, rectal temperature  $\geq 38^\circ\text{C}$ , attacks lasting 12 hours to 3 days)

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

**Minor criteria**

- Incomplete attacks (typical attacks including one of the following sites: abdomen, chest, or joint with one or two of the following exceptions: 1) Temperature  $< 38^\circ\text{C}$ ; 2) attacks lasting 6–12 hours or 3–7 days; 3) no signs of peritonitis during abdominal attacks; 4) localized abdominal pain; 5) arthritis in joints other than hip, knee, or ankle
- Exertional leg pain
- Favorable response to colchicine

**Supportive criteria**

- Family history of FMF

- Appropriate ethnic origin

- Age  $< 20$  years at disease onset

The first four criteria below are related to the features of attacks

- Severe, requiring bed rest
- Spontaneous remission
- Symptom-free interval
- Transient inflammatory response with one or more abnormal test result(s) for white blood cell count, erythrocyte sedimentation rate, serum amyloid A, and/or fibrinogen
- Episodic proteinuria/hematuria
- Unproductive laparotomy or removal of “white” appendix
- Consanguinity of parents

Diagnosis:  $\geq 1$  major or  $\geq 2$  minor criteria or 1 minor  $+ \geq 5$  supportive criteria or 1 minor  $+ \geq 4$  of the first 5 supportive criteria

**Tel Hashomer criteria (short version)<sup>22</sup>****Major criteria**

- Recurrent febrile episodes accompanied by peritonitis, synovitis, or pleuritis
- Favorable response to continuous colchicine treatment
- AA-type amyloidosis without predisposing disease

**Minor criteria**

- Recurrent febrile episodes
- Erysipelas-like erythema
- FMF in a 1st degree relative

Diagnosis: 2 major or 1 major  $+ 2$  minor criteria

**Livneh criteria (simplified)<sup>22</sup>****Major criteria**

- Typical attacks recurrent (three of the same type), febrile (rectal temperature  $\geq 38^\circ\text{C}$ ), and short duration (12 hours to 3 days):
  - Generalized peritonitis
  - Unilateral chest pain (pleuritis or pericarditis)
  - Hip, knee, or ankle monoarthritis
  - Fever alone
- Incomplete abdominal attacks

**Minor criteria**

- 1–2 incomplete attacks involving  $\geq 1$  of the following:
  - Chest
  - Joint
- Exertional leg pain
- Favorable response to colchicine

(Continued)

**Table 1** (Continued)

Diagnosis: 1 major or 2 minor criteria

**Turkish FMF pediatric criteria<sup>23</sup>**

- Fever (axillary,  $> 38^\circ\text{C}$ ,  $\geq 3$  attacks of 6–72-hour duration)
- Abdominal pain ( $\geq 3$  attacks of 6–72-hour duration)
- Chest pain ( $\geq 3$  attacks of 6–72-hour duration)
- Arthritis (oligoarthritis,  $\geq 3$  attacks of 6–72-hour duration)
- Family history of FMF

Diagnosis: 2 out of 5 criteria

**Notes:** Adapted from: Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.* 1997;40:1879–1885.<sup>22</sup> Copyright © 1997 American College of Rheumatology Yalcinkaya F, Ozen S, Ozcakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology (Oxford).* 2009;48:395–398.<sup>23</sup>

**Abbreviation:** FMF, familial Mediterranean fever.

## Heterozygotes

FMF is an autosomal recessive disease. Thus, one would expect a heterozygote individual to be a carrier and lack the FMF phenotype. However, as FMF patients were genotyped, it has become evident that the mutation in the second allele could not be demonstrated in about one-quarter of patients with clinically confirmed FMF.<sup>10</sup> As we previously mentioned, resequencing of the entire *MEFV* genomic region did not provide additional benefit.<sup>15</sup>

In 2009, Marek-Yagel et al<sup>27</sup> studied the clinical and genetic characteristics of heterozygous FMF patients and performed haplotype studies. They concluded that although the heterozygotes tend to have a relatively mild disease, the disease could not be distinguished from that of homozygous patients and that FMF could be viewed as a dominant condition with low penetrance in some cases.<sup>27</sup>

In addition, convincing data indicate that heterozygous individuals have an increased propensity to display signs of inflammation. In the eastern Mediterranean population, the carrier rate is higher among the patients with rheumatic diseases than in the general population.<sup>28,29</sup> Kalyoncu et al<sup>30</sup> revealed that rheumatoid arthritis, acute rheumatic fever, arthralgia, and febrile episodes of  $\geq 4$  times/year were significantly more common in asymptomatic heterozygous parents of children with FMF than healthy controls. Along the same lines, Lachmann et al<sup>31</sup> showed greater basal and peak acute-phase reactant concentrations in *MEFV* heterozygotes in comparison with wild-type controls which suggest a proinflammatory phenotype in carriers.

One explanation for heterozygote individuals displaying FMF phenotype may be the effect of other modifier genes associated with inflammation.<sup>15</sup> One example is the serum amyloid A (*SAA*) gene, encoding an acute-phase protein, SAA, which activates NLRP3 inflammasome causing increased secretion of active IL-1 $\beta$ .<sup>32</sup>

Name:		Age:			Month:			Year:					
Symptoms associated with autoinflammatory syndrome today													
Day	Fever ≥38°C (100.4°F)	Overall symptoms	Abdominal pain	Nausea/ vomiting	Diarrhea	Head aches	Chest pain	Painful nodes	Arthralgia or myalgia	Swelling of the joints	Eye manifestations	Skin rash	Pain relief drug taken
Score	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	
1													
2													
3													
...													
31													

**Figure 1** AID activity index diary.

**Notes:** Each line refers to a day in a month. Reproduced from Píram M, Kone-Paut I, Lachmann HJ, et al. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. *Ann Rheum Dis.* 2014;73:2168–2173.<sup>62</sup>

**Abbreviation:** AID, autoinflammatory disease.

We also know that epigenetics and environment may affect the disease phenotype, and this will now be discussed later in the paper.

### Genotype–phenotype correlation

Since the first description of the *MEFV* mutations, most experts agree that M694V was related with a severe disease phenotype.<sup>5,6,33</sup> Ozturk et al<sup>34</sup> demonstrated that both patients homozygous and compound heterozygous for M694V were at increased risk for severe disease in comparison with patients with one mutant allele and patients not displaying M694V. Giaglis et al<sup>35</sup> and Mattit et al<sup>36</sup> confirmed these findings in two separate studies. Giaglis et al<sup>35</sup> also showed that a more severe phenotype was evident in patients homozygous for M694V as well as mutations at position 680–694 on exon 10. In evidence-based recommendations, the experts concluded that FMF patients homozygous or compound heterozygous for M694V or with mutations at position 680–694 on exon 10 must be considered at risk of having a more severe and early-onset disease.<sup>11</sup> In addition, the individuals homozygous for M694V without disease manifestations should be evaluated and followed closely in order to decide about therapy.<sup>11</sup>

Besides issues about mutations at position 680–694 on exon 10, in a recent study, Federici et al<sup>37</sup> demonstrated that the frequency of FMF-like symptoms increased from patients carrying a single low penetrance mutation toward patients with two high penetrance mutations, suggesting a “dose effect” associated with the mutations.

The pathogenic role of E148Q on exon 2 (one of the most common alterations in the *MEFV* gene) still remains

controversial.<sup>11</sup> It might be a polymorphism since it is present in >1% of the healthy population. It has been reported to be present as high as 21% of healthy in some eastern Asian populations.<sup>38</sup> A consensus conference led by Shinar et al<sup>10</sup> has defined E148Q as a variant of unknown significance. According to the recent recommendations by SHARE, as the only *MEFV* variant, E148Q does not support the diagnosis of FMF.<sup>11</sup> However, there are rare reports of patients with homozygous E148Q variation having FMF phenotype.<sup>26</sup> Furthermore, patients carrying E148Q with a clearly pathogenic mutation on the other allele often display disease phenotype.<sup>2</sup>

The recent evidence-based recommendations for genetic diagnosis of FMF are as follows:<sup>11</sup>

- FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing.
- Consider patients homozygous for M694V at risk of developing, with very high probability, a severe phenotype.
- FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680–694 on exon 10, must be considered at risk of having a more severe disease.
- The E148Q variant is common, of unknown pathogenic significance, and, as the only *MEFV* variant, does not support the diagnosis of FMF.
- Patients homozygous for M694V mutation are at risk of early-onset disease.
- Individuals homozygous for M694V who are not reporting symptoms should be evaluated and followed closely to consider therapy.

- For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for AA amyloidosis (such as the country, family history, and persistently elevated inflammatory markers, particularly serum amyloid A protein), close follow-up should be started and treatment considered.
- Consultation with an AID specialist may be helpful to aid in the indication and interpretation of the genetic testing and diagnosis.

## Epigenetics and environment

FMF patients with similar genotype may express different disease phenotypes. This difference may be due to other modifier genes, epigenetics, or the effect of the environment. The first clue suggesting the effect of environment on FMF was the observation of lack of secondary amyloidosis among Armenian FMF patients in the USA.<sup>39</sup> We also know that the eastern Mediterranean patients had a less severe disease if they migrated to Europe.<sup>9</sup> Touitou et al<sup>40</sup> demonstrated that country of recruitment, rather than *MEFV* genotype, is the likely key risk factor for development of amyloidosis. We had previously shown that Turkish children with FMF living in Germany expressed a less severe disease phenotype in comparison with the ones living in Turkey.<sup>41</sup> These findings emphasize the effect of environment on FMF disease severity.

The epigenetic mechanisms such as histone modification, methylation, and microRNAs may play role in the pathogenesis of FMF. Kirecetepe et al<sup>42</sup> demonstrated a slightly higher methylation level of exon 2 of *MEFV* in FMF patients when compared to healthy controls.

MicroRNAs (miRNAs) are small, noncoding RNAs that regulate gene expression at a posttranscriptional level by degrading mRNA molecules or blocking their translation.<sup>43</sup> Their circulating levels have already been described in inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, and tumor necrosis factor (TNF) receptor-associated periodic syndrome.<sup>44–47</sup> Circulating miRNAs in FMF have not been investigated, but this might have a role in the disease pathogenesis of FMF as well.

Microorganisms may affect FMF since pyrin is a component of NLRP3, which is a pathogen recognition receptor.<sup>9</sup> Pyrin has also been shown to detect virulent pathogenic activity.<sup>19</sup> The cross-talk between the innate immune system and commensal gut bacteria (microbiota) may affect (or may be affected by) the inflammatory status of the patient, as well. In a study by Khachatryan et al,<sup>48</sup> they showed that the composition and divergence of microbiota were different during attack and attack-free periods as well as between FMF patients and healthy controls.

Further studies on the effect of epigenetics, microbiota, and environment on FMF may enable us to answer more unsolved questions about the pathogenesis.

## Treatment

Colchicine is still the main form of treatment for patients with FMF. Since 1972, colchicine has been used for treatment in FMF patients.<sup>8</sup> It decreases attack frequency and increases the quality of life.<sup>49</sup> Furthermore, Livneh et al<sup>50</sup> have shown that colchicine can effectively prevent the complication of secondary amyloidosis in FMF patients.

In pediatric FMF patients, colchicine was shown to be a well-tolerated drug, even when given in infancy.<sup>51</sup> The commonest side effects of colchicine are gastrointestinal, with vomiting, diarrhea, and transient elevation of transaminases. These mild side effects can occur in 5%–10% of patients even at recommended doses. It has a narrow therapeutic index; colchicine doses of 0.5–0.8 mg/kg are highly toxic, and doses of more than 0.8 mg/kg are typically lethal. In fact, the US Food and Drug Administration withdrew approval for intravenous colchicine to reduce the risk of irreversible bolus overdose.<sup>52,53</sup>

Colchicine is undoubtedly the main treatment for FMF, but approximately one-third of the patients treated with colchicine have a partial remission, and approximately 5% are nonresponders; another 2%–5% do not tolerate the drug mainly due to gastrointestinal symptoms.<sup>54</sup> Lidar et al<sup>55</sup> have suggested that colchicine efficacy differs between patient groups depending on the *MEFV* genotype. M694V homozygotes showed a more severe disease and were treated with higher doses of colchicine compared to patients with the V726A genotype.

In recent years, biologic agents have been used in treatment of FMF patients unresponsive to colchicine therapy.<sup>56</sup> Pyrin, the mutated protein in FMF, plays an important role in the regulation of interleukin-1 (IL-1) activation; anti-IL-1 treatment has proven beneficial in suppressing inflammation in colchicine-resistant FMF patients. Anakinra, a recombinant, human IL-1 receptor antagonist that competitively inhibits binding of IL-1 $\alpha$  and IL-1 $\beta$  to the IL-1 receptor; canakinumab, a human IgG1 monoclonal antibody directed against IL-1 $\beta$ ; and rilonacept a fully human dimeric fusion protein that binds the extracellular domains of IL-1 $\alpha$  and IL-1 $\beta$  were used in FMF patients.<sup>57</sup> There are small series or trials about anti-IL-1 treatment in colchicine-resistant FMF patients.<sup>56,58</sup> The only randomized controlled study was with rilonacept, in 14 colchicine-resistant FMF patients.<sup>59</sup> Recently, a 6-month Phase II, open-label, single-arm pilot study showed the efficacy of canakinumab in pediatric

patients with colchicine-resistant FMF.<sup>60</sup> The major limitation of this study was the small sample size. A larger controlled study is needed to explain the benefit, optimal dose, and side effect of canakinumab better in FMF patients.

Recently, French and Israeli experts have suggested evidence-based recommendations for the management of FMF.<sup>49</sup> The treatment recommendations are about colchicine dosage, maximum dosage of colchicine in children and adults, definition of colchicine resistance, and treatment alternatives in colchicine-resistant patients. Colchicine dose should be increased if patients have more than one FMF attack every 3 months and/or persistent elevation of inflammatory markers during the attack-free period. If a patient suffers from more than six typical FMF attacks per year, the patient should be accepted to be resistant to colchicine. The experts have suggested alternative treatment, such as IL-1 inhibitors, if there are persistent attacks despite the maximum doses of colchicine (2 mg in children; 3 mg in adults).<sup>49</sup>

TNF blockade with etanercept, infliximab, or adalimumab has been studied especially in FMF patients. Anti-TNF treatment can have beneficial effects for controlling FMF attacks in FMF patients with chronic arthritis and/or sacroiliitis.<sup>61</sup>

## Monitoring disease activity and response to treatment

The AutoInflammatory Disease Activity Index (AIDAI) is used to assess disease activity in FMF and the other common monogenic AIDs. AIDAI is a patient-based symptom diary that consists of 13 items as follows: fever, overall symptoms, abdominal pain, nausea/vomiting, diarrhea, headaches, chest pain, painful nodes, arthralgia or myalgia, swelling of the joints, eye manifestations, skin rash, and pain relief. It is scored daily as yes (1 point) or no (0 point) by patients or parents. All items but pain relief are used in the calculation of the activity score (Figure 1). Validation of AIDAI revealed a cutoff score of  $\geq 9$ , discriminating active from inactive patients with a sensitivity of 89% and specificity of 92%.<sup>9,62</sup>

Turkish physicians have suggested the FMF50 score to assess the response to treatment, given the patient is compliant and is receiving the maximum tolerated dose of the drug. The items of this score are: percentage change in the frequency and duration of attacks with the treatment, patients'/parents' and physicians' global assessment of disease severity (10 cm visual analog scale), percentage change in arthritis attacks with the treatment, percentage change in C-reactive protein (CRP), erythrocyte sedimentation rate, or serum amyloid A level with the treatment. At least 50% improvement in five of six criteria, without worsening in any one, was

defined as response to treatment with very high sensitivity and specificity.<sup>63</sup> However, this score needs further validation before use in clinical trials.

## Prognosis

The prognosis of a compliant FMF patient is now excellent thanks to the advances in management of FMF and the use of biologics, especially anti-IL-1 drugs. Secondary amyloidosis was the most serious complication. However, because of the advances in the management of AIDs, this complication is now very rare. Many studies have focused on the role of factors affecting the development of amyloidosis in patients with FMF, such as male sex, M694V homozygosity, and SAA1.1 $\alpha/\alpha$  genotype.<sup>64-66</sup> Colchicine treatment prevents the development of amyloidosis. However, some patients are refractory to colchicine treatment. Biologic treatments, including anti-TNF agents and IL-1 and IL-6 antagonists, have been suggested to be effective in the treatment of amyloidosis.<sup>67,68</sup>

There are limited data on long-term comorbidities and mortality among patients with FMF. Twig et al<sup>69</sup> studied long-term comorbidities and mortality among patients with FMF and found that FMF causes increased risk of mortality associated with amyloidosis, but does not have an increased incidence of cancer.

Rheumatic diseases may be risk factors for atherosclerosis. Studies have shown that inflammatory processes had played a significant role in atherosclerosis and have demonstrated an important association between high CRP levels and risk of atherosclerosis.<sup>70</sup> Several studies have shown that FMF might be a risk factor for early atherosclerosis because of its inflammatory nature.<sup>71-73</sup> However, a recent study from Israel showed that there were lower rates of metabolic syndrome compared to normal subjects, unlike other inflammatory diseases.<sup>74</sup>

Thus, FMF is a disease in which we can promise our compliant patients a normal life expectancy and remission with medication with a good quality of life.

## Disclosure

The authors report no conflicts of interest in this work.

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