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Review

Familial Mediterranean fever: New phenotypes

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ABSTRACT

Familial Mediterranean fever (FMF) is an inherited autosomal recessive disorder, ethnically restricted and commonly found among individuals of Mediterranean descent, caused by MEditerranean FeVer gene (MEFV) mutations on chromosome 16. It is the most frequent periodic febrile syndrome among the autoinflammatory syndromes. Clinically, FMF can be distinguished into three phenotypes: type 1, which is commonly associated with recurrent short episodes of inflammation and serositis, including fever, peritonitis, synovitis, pleuritis, but also pericarditis, orchitis or meningitis episodes; type 2, characterized by the evidence of reactive amyloid-associated (AA) amyloidosis, the most severe complication of FMF, as the first clinical manifestation of the disease in an otherwise asymptomatic individual; type 3, referred to the 'silent' homozygous or compound heterozygote state, in which two MEFV mutations are detected without signs or symptoms of FMF nor of AA amyloidosis. In the recent years it has been observed that also heterozygous mutation carriers can suffer from a mild or incomplete form of FMF, named 'FMF-like' disease. The influence of other modifiers genes and/or environmental factors can contribute to the variable penetrance and to the phenotypic variability of FMF. The insight into complex clinical and genetic cases will provide adjunctive details for the comprehension of the mechanisms of this kaleidoscopic disease.

Contents

1. Familial Mediterranean fever (FMF): definition and diagnostic criteria

Familial Mediterranean fever (FMF, OMIM ID: 249100) is an autosomal recessive disease characterized by recurring self-limited short episodes of fever and serositis resulting in pain in the abdomen, chest, joints and muscles; it is the most common of the periodic hereditary fevers.

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FMF mainly affects Middle Eastern populations and other ethnic groups living around the Mediterranean basin, such as Jews, Armenians, Turks, Arabs, with high prevalence (1/200–1/1000); also, it is not considered rare in Italy, Spain and Greece [1–3].

In 1997 the MEditerranean FeVer gene (MEFV) was identified on chromosome 16p13.3 using the 'positional cloning' approach by a French and an International consortium, in parallel and independently [4,5]. Its product, named 'marenostrin'/'pyrin', a protein consisting of 781 amino acids, was found to play a pivotal role in the regulation of inflammation [6,7].

MEFV gene is composed of 10 exons and most patients have mutations in exon 10, the longest exon in this gene.

Through the network 'Infevers' (http://fmf.igh.cnrs.fr/ISSAID/infevers) a website dedicated to mutations responsible for hereditary autoinflammatory diseases, it is possible to check the number of variants of MEFV identified. To date, 218 MEFV mutations have been detected as responsible for the phenotypic variance seen in the disease [8].

M694V, V726A, M680I, M694I (conservative mutations clustered in exon 10) and E148Q (clustered in exon 2) are considered as common mutations related to FMF, and they are detected with a frequency that changes according to ethnicity. M694V is more commonly seen among Sephardic Jews, Turks, and Armenians; E148Q among European and Turks patients; M694I is more frequent among Arabs; M680I is detected particularly among Armenians [9–12].

Generally, M694V homozygosis is associated with a severe form of the disease, while mutations E148Q and V726A have been correlated with reduced penetrance and milder form of the disease. However, it has been observed that also homozygotes for the complex V726A–E148Q allele are as severely affected as M694V homozygotes, bearing evidence to the wide allelic variability in the disease expression [13].

Genetic testing only has a 70–80% positive predictive value and despite the progresses in understanding the genotype-phenotype correlations, the diagnosis of FMF remains clinical. According to the 1997 Arthritis and Rheumatism criteria [14], the most widely used adult criteria for the diagnosis of FMF, typical attacks are characterized by the following features: (1) pain, (2) recurrence of the attacks (≥3 of the same type), (3) short duration (12 to 72 hours), and (4) presence of fever in most attacks (rectal temperature ≥38 °C), associated with signs of serositis involvement such as generalized peritonitis, unilateral pleuritis or pericarditis, orchitis, monoarthritis (involving hip, knee, ankle), or erysipelas-like eruption in the calf and/or symmetric myalgia.

The minor criteria included 'incomplete attacks', defined as painful and recurrent attacks that differed from typical attacks because of (1) the normal or lower value of the rectal temperature (<38 °C); (2) the different duration (<6 hours or >72 hours); (3) the absence of signs of serositis despite the presence of the pain; (4) the limitation of the abdominal pain to only some quadrants; (5) the arthritic involvement in other joints than those specified. Also, minor criteria are the presence of exertional leg pain and a favorable response to colchicine.

Finally, the supportive criteria included (1) a family history of FMF, (2) an appropriate ethnic origin, (3) the age <20 years at disease onset, (4–7) the attacks of pain requiring bed rest, with a spontaneous remission and a symptoms-free interval, and with laboratory signs of transient inflammatory response, (8) the detection of episodic proteinuria/hematuria, (9) the anamnestic data of unproductive laparotomy or removal of white appendix, (10) the consanguinity of parents.

The presence of 2 major criteria, or 1 major plus 2 minor criteria, or 1 minor plus ≥5 supportive criteria, or 1 minor plus ≥4 of the first 5 supportive criteria, are needed to be present for diagnosis (Table 1).

The Arthritis and Rheumatism 1997 criteria have been revisited on the basis of clinical experience of Tel Hashomer National Centre for FMF in Israel. Major criteria were considered (1) the presence of recurrent febrile episodes with serositis, (2) the diagnosis of reactive amyloid-associated (AA) amyloidosis without apparent predisposing disease and (3) the favorable response to colchicine, while (1) the presence of recurrent episodes of fever without serositis, (2) erysipelas-like erythema and (3) the diagnosis of FMF in a first-degree relative were considered as minor criteria.

Table 1
Arthritis and Rheumatism criteria for diagnosis of familial Mediterranean fever (FMF) [14]. Incomplete attacks differ from typical attacks because of (1) the normal or lower value of the rectal temperature (<38 °C); (2) the different duration (<6 hours or >72 hours); (3) the absence of signs of serositis despite the presence of the pain; (4) the limitation of the abdominal pain to only some quadrants; (5) the arthritic involvement in other joints than those specified. The presence of 2 major criteria, or 1 major plus 2 minor criteria, or 1 minor plus ≥5 supportive criteria, or 1 minor plus ≥4 of the first 5 supportive criteria, are needed to be present for diagnosis.

Arthritis and Rheumatism criteria set for the diagnosis of familial Mediterranean fever (FMF)	
Major criteria	Minor criteria
Typical attacks	'incomplete' attacks of the:
Peritonitis (generalized)	–abdomen
Pleuritis (unilateral) or pericarditis	–chest
Monoarthritis (hip, knee, ankle)	–joint
Fever alone	exertional leg pain
	favorable response to colchicine
Supportive criteria	
Family history of FMF	age <20 years at disease onset
Appropriate ethnic origin	transient inflammatory response
Features of attacks:	episodic proteinuria/hematuria
- severe, requiring bed rest	Unproductive laparotomy/removal of white
- spontaneous remission	appendix
- symptom-free interval	Consanguinity of parents

According to the so-called Tel Hashomer criteria a definitive diagnosis of FMF requires the presence of 2 major criteria or 1 major and 2 minor criteria; conversely, the diagnosis is 'probable' if only 1 major and 1 minor criteria are present.

Significantly, the response to colchicine, considered as minor criterion in the first elaboration of FMF criteria in 1997, became major criterion in the Tel Hashomer revisited criteria (Table 2).

As recently observed by Yalçincaya and colleagues [16], major criteria of Tel Hashomer have some limitations in children, who often are unable to express the severity and the location of the pain. Also, the high rate of consanguinity in some countries and the fact that children are often diagnosed before appendectomy [15] decrease the power of some supportive 1997 Arthritis and Rheumatism criteria. On the basis of these observations, the sensitivity and specificity of Tel Hashomer criteria were validated in 170 FMF children with mutations at both alleles, and the results were compared with sensitivity and specificity of a proposed new set of 5 criteria for the FMF diagnosis in childhood, including fever (axillary temperature ≥38 °C), abdominal pain, chest pain, arthritis (for all the conditions the number of the attacks has to be ≥3, with a 6–72 hours of duration), and family history of FMF. The presence of 2 of these 5 criteria resulted to have a higher specificity compared to that of Tel Hashomer criteria (93.6% versus 54.6%, respectively) [16]. The

Table 2
Tel Hashomer criteria for diagnosis of familial Mediterranean fever (FMF). A 'definitive' diagnosis of FMF requires the presence of 2 major criteria or 1 major and 2 minor criteria; the diagnosis is considered as 'probable' if only 1 major and 1 minor criteria are present. Relevantly, the favorable response to colchicine, first considered as minor criterion, becomes major criterion for the diagnosis.

Tel Hashomer revisited criteria set for the diagnosis of familial Mediterranean fever (FMF)	
Major criteria	Minor criteria
Recurrent febrile episodes *with* serositis	Recurrent febrile episodes *without* signs of serositis
AA Amyloidosis detection	Erysipelas-like erythema
Favorable response to colchicine	FMF in a first-degree relative