

Familial Mediterranean fever (FMF)

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Abstract

Familial Mediterranean Fever (FMF) manifests as short febrile episodes occurring at variable intervals, with intermittent abdominal, thoracic, joint and/or cutaneous pain, and the possible development of renal amyloidosis. It arises most frequently in subjects originating from the Mediterranean basin. The diagnosis is made by exclusion. The familial notion is being found less-and-less frequently because of its recessive inheritance and the tendency towards smaller families. A highly effective treatment is available: colchicine (1 to 2 mg/day for life). Its mode of action is unknown but this drug is able to inhibit attacks or prolong intervals between them in 90% of the patients. Interferon-alpha has been prescribed for patients with colchicine-resistant disease. Although it is an autosomal recessive hereditary disease, environmental factors are also important in the triggering of attacks: stress, fatigue, infections. The gene responsible is that encoding marenostriin/pyrin, which is expressed in granulocytes, monocytes and eosinophils. Several laboratories in Europe are able to make to genetic diagnosis.

Keywords

febrile episodes, pain, renal amyloidosis, autosomal recessive inheritance, colchicine, *marenostriin/pyrin* gene

Name of the disease and its synonyms

Familial Mediterranean fever (FMF) and periodic disease

necrosis factor), Receptor-associated periodic syndromes) syndrome, Periodic Fever Aphthous stomatitis, Pharyngitis and Adenopathy syndrome ([PFAPA](#)), ...

Names of excluded diseases (non-exhaustive list)

Appendicitis, [Hyper IgD syndrome](#), [Behçet's disease](#), [Porphyria](#), [TRAPS](#) (TNF (tumor

Diagnostic criteria/Definition

The clinical diagnosis was for a long time based on the criteria defined by Heller's group:

- Short febrile episodes occurring at variable intervals
- Intermittent abdominal, thoracic, joint and/or cutaneous pain
- Absence of another disease capable of explaining these symptoms
- Possible development of perireticular renal amyloidosis
- Familial notion
- Predominance in subjects originating around the Mediterranean basin - Sephardic Jews, Armenians, Turks, Maghrebians, ...
- Other criteria have since been proposed, but they are not unanimously recognized because they pertain only to the Israeli.

Comments on the differential diagnosis

FMF is often a diagnosis of exclusion. Most of the patients undergo useless appendectomy. The familial notion is becoming less-and-less common because of the autosomal recessive inheritance and the tendency towards smaller families.

The following diseases can be excluded for diverse reasons:

- recurrent fever with [hyper IgD](#) does not affect the same ethnic groups; it causes diarrhea, headaches, adenopathies and increased IgD levels.
- [Behçet's disease](#) causes more specific clinical criteria - even though they are sometimes absent or poorly defined - that must be sought (aphthae in the digestive or genitourinary tract, vision disorders).
- [TRAPS](#) (TNF (tumor necrosis factor) receptor-associated periodic syndromes) syndrome, responds poorly to colchicine but well to corticosteroids and Etanercept. The cutaneous eruptions are more frequent and migratory. Periorbital edema and cervical stiffness are often noted.

Prevalence

It is extremely high in the most affected ethnic groups (Armenians, Turks, Jews and people from North Africa). The frequency of FMF is 1:200 to 1:1,000. The frequency of heterozygotes can reach 1:3. FMF must not be considered as rare in other mediterranean populations anymore (Italy, Greece, Spain).

Clinical description

Most frequently, the attacks, which last 24-72 hours, associate fever and pain, but sometimes the symptoms are isolated.

Rare atypical forms (orchitis or meningitis) associated or not with classical forms have been described. The symptoms are the consequence of inflammation of the serous membranes (peritoneum, synovium, pleura, ...) and can evolve during the life-long course of the disease.

The manifestations appear in general as of childhood. It is very rare that the onset of FMF occurs after the age of 30 years. Attacks are favored by fatigue and stress. Renal complications with inflammatory AA amyloidosis, are quite frequent and are responsible for the poor prognosis of the disease in the absence of treatment. Form II (very rare) is characterized by the initial appearance of renal insufficiency.

Management

A highly effective treatment is available: colchicine (1-2 mg/day, for life). Its mode of action is unknown but this molecule is able to inhibit attacks or prolong the intervals between them and also to prevent or delay the appearance of renal complications in 2/3 patients. When colchicine appears to be ineffective, patient compliance with the prescribed regimen must be verified and, if necessary, the dose should be adjusted or non-steroidal anti-inflammatory drugs can be added during attacks. Interferon-alpha has been prescribed to patients with colchicine-resistant forms.

Etiology

FMF is an autosomal recessive hereditary disease. The gene (*MEFV*), localized to the short arm of chromosome 16, was identified independently and simultaneously in 1997 by two FMF consortia (one French and one international).

Cases of dominant transmission have been described and could be explained by extensive consanguinity and a high frequency of the gene in the affected populations. Two modifying loci (that influence the expressivity of the disease without causing it) have been identified: MICA (major histocompatibility complex class I chain-related gene A) in the HLA complex and SAA (serum amyloid A). Environmental factors are also important. Some are well known, like stress and fatigue; others have a suspected influence, for example infections, diet, ...). *MEFV* gene codes for a protein, called marenostin (Latin for Mediterranean sea) by the French and pyrin (the Greek word for fever) by Americans, whose role starts to be known. The protein, expressed in granulocytes, monocytes and eosinophils. It contains a pyrin domain (PYD), 4th member of DDF superfamily (Death domain fold) which is involved in the regulation of inflammation and apoptosis *via* to homotypic proteine-proteine interaction. The native Pyrin/Marenostine might be a negative regulator of inflammation that inhibits the regulation way of interleukin 1 and increases apoptosis of inflammatory cells.

Biological diagnostic methods

The non-specific evaluation of inflammation (erythrocyte sedimentation rate (ESR), C-

reactive protein (CRP), ...) was the only biological approach available until now. Thanks to the recent discovery of the gene responsible for FMF (*MEFV*), it is now possible to offer patients a specific diagnosis by searching for mutations (direct diagnosis).

Known mutations

There are five frequent mutations: four regrouped in exon 10 (V726A, M694V, M694I, M680I) and one in exon 2 (E148Q). Nearly 40 mutations have been reported to date. (<http://fmf.igh.cnrs.fr/infevers>)

Indications and methods

The genetic diagnosis relies on the search for mutations in the *MEFV* gene. Only the discovery of a mutation on each chromosome can certify the diagnosis, but a genetic test based only on the search for the most frequent mutations does not allow its exclusion. The diagnosis should always be made in agreement with the biologist.

Genetic counseling

It is useful to know the genetic status of individuals belonging to families at risk. The risk for each child born to a heterozygous couple is 1/4.

Monitoring of renal function is indicated for subjects bearing a mutation in each chromosome. Early diagnosis limits suffering, assures adapted therapy and lowers health expenditures. The French Genetic Society has created a useful checklist to guide genetic counseling of patients with FMF.

Prenatal diagnosis

It is absolutely not indicated.

Unresolved questions and comments

The identification of other rare mutations will increase the sensitivity of the test. The gaps in our knowledge concerning the expressivity of heterozygotes and phenotype-genotype relationships are starting to be filled-in. Patients homozygous for the M694V mutation have a more severe form of the disease. In contrast, other mutations, like E148Q, have poor penetrance or are associated with a milder form of the disease.

Note: The Heller Institute, which is specialized in FMF, is located in Israel.

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