Familial Mediterranean Fever: an overview
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Familial Mediterranean Fever (MIM # 249100 - FMF) is a monogenic autosomal-recessive disease, which clinically presents with periodic fever and serositis, as well as joint and skin manifestations.

FMF is the prototype of Periodic Fevers of genetic origin, an important chapter of Auto-Inflammatory Disease (AID), a class of immune-mediated diseases, which recognize as basic pathogenesis, alterations of innate immunity. It is possible to refer an updated classification of inflammatory syndromes drive to the site www.printo.it / eurofever / autoinflammatorydisease.asp.

Clinical onset of FMF is, in more than 80% of cases, below 20 years (1). FMF characteristically presents with recurrent attacks of fever, whose occurrence is variable, but whose duration is usually 1-3 days, then self-limiting.

According to data Eurofever, FMF is the most frequent periodic fever with genetic origin in Eurofever countries, second only to another periodic fever of non-genetic origin, the PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis). These data are consistent with those of the Italian Association of Periodic Fevers (AIFP) that, among the AID, FMF is the genetic periodic fever more frequently diagnosed, even in Italy. A significant number of cases is concentrated in Southern Italy (more than half of the Italian cases-unpublished data), probably because of the different colonizations occurred during the centuries: before Greeks, and then Turks and Arabs, as well as the arrival of the first Christians.

The gene responsible for the disease is the MEFV (16p13.3), which encodes the pyrin, a protein expressed in neutrophils, eosinophils, monocytes (2), dendritic cells and fibroblasts (3), implicated in inflammatory mechanisms primarily through the formation of inflammasome. Inflammasome is a multiprotein complex consisting of: pyrin, protein ASC and pro-caspase 1, and is responsible for oligomerization and proteolytic activation of caspases 1, protein which cleaves the pro-IL1β in its active form, IL-1β.

In reality, the physiological role that the pyrin plays in IL-1β pathway, has not yet been defined. Would seem to have a role of constitutive inhibitor of caspase 1, which, in the absence of inhibitors activates IL-1β. The link between pyrin and caspase 1 occurs at the level of C-terminal domain (3).

The 85% of FMF cases is due to 5 specific mutations: M694V, M680I, M694I, M694I and V726A localized on exon 10 and the E148Q mutation localized on exon 2 (4). The last 2 mentioned mutations are considered to be polymorphic variants, capable of giving a clinical phenotype depending on the presence or absence of other allelic mutations (6). In childhood, age of onset of this disease, the diagnosis is not always easy. Difficulty is sometimes to distinguish the onset of a periodic fever of genetic origin from PFAPA or from recurrent respiratory infections, or even the onset of a primary immunodeficiency. From a study of Padeh et al, conducted a pediatric population of 814 Israeli patients with FMF, the symptoms diagnosis comes from clinical criteria (Table 1), adapted to the pediatric population (9) that could provide a useful diagnostic tool, after validation in the Italian pediatric population.

In non responder cases the therapeutic alternative is represented mainly by biologic drugs. Kone-Paut attempted to clarify therapeutic indication for the shift towards anti-IL1 (Anakinra, Canakinumab and Rilonacept), namely: 1) incomplete control of disease activity with colchicine, 2) elevated levels of serum amyloid A (SAA) and / or renal complications despite treatment, 3) adverse reactions to the colchicine and 4) simultaneous presence of FMF and vasculitis (11).

The effectiveness of these drugs on Familial Mediterranean Fever, however, is based on isolated reports demonstrating, in most cases, a benefit in their use, but most studies of large populations are needed to verify their efficacy and safety.
References


www.theChild.it bimestrale di divulgazione scientifica dell'Associazione Pediatrica di Immunologia e Genetica
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