

Clinical features of familial mediterranean fever: an italian overview

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Abstract. – Familial Mediterranean Fever (FMF) is the most frequent periodic febrile syndrome among the autoinflammatory syndromes (AS), nowadays considered as innate immunity disorders, characterized by absence of autoantibodies and autoreactive T lymphocytes.

FMF is a hereditary autosomal recessive disorder, characterized by recurrent, self-limiting episodes of short duration (mean 24e72 h) of fever and serositis. In FMF, periodic attacks show inter- and intra-individual variability in terms of frequency and severity. Usually, they are triggered by apparently innocuous stimuli and may be preceded by a prodromal period. The Mediterranean FeVer gene (MEFV) responsible gene maps on chromosome 16 (16p13) encoding the *Pyrrine/Marenostrin* protein. The precise pathologic mechanism is still to be definitively elucidated; however a new macromolecular complex, called inflammasome, seems to play a major role in the control of inflammation and it might be involved in the pathogenesis of FMF.

The most severe long-term complication is type AA amyloidosis, causing chronic renal failure. Two types of risk factors, genetic and non-genetic, have been identified for this complication.

Currently, the only effective treatment of FMF is the colchicine. New drugs in a few colchicine resistant patients are under evaluation

Key Words:

Familial Mediterranean Fever, Autoinflammatory disease, Inflammasome, Trigger factors, Colchicine.

Introduction

Familial Mediterranean fever (FMF, OMIM *249100) is an autosomal recessive disorder characterised by short, recurrent, apparently un-

provoked attacks and with spontaneously resolved attacks of fever and serositis, or erysipelas-like skin lesions¹.

FMF is the most frequent *Periodic Febrile Syndrome* among *Autoinflammatory Syndromes*¹. It has been calculated by M. Pras that it affects more than a 100 thousand people in the world. Although it is prevalent among Turks, Armenians, Arabs and Jews, cases of FMF have been reported in other countries, including Italy².

Familial Mediterranean Fever was first described in 1945 but the responsible gene (MEFV) was discovered in 1997 by two different study groups (French and American)^{3,4}. The MEFV gene is located on chromosome 16p13.3 and encodes a 781-aminoacid protein (pyrin/marenostrin), involved in the regulation of inflammation and apoptosis⁵.

Pyrin is expressed in the myeloid cell lineage and participates in *inflammasome* formation, a macromolecular complex, which has been defined the linebacker of innate immunity. Its dysfunction determines autoinflammatory syndromes⁶. *Pyrin* consists of four domains; the most important are the N-terminal *pyrin domain* and the C-terminal *B20.3 domain*. The first one is intimately connected to protein-protein homotypic interactions, inflammation, apoptosis and immunity against tumors. The second one participates in processes of innate immunity and is codified by sequences in exon 10, whose mutations as M694V, M694I M680I, are associated with severe phenotype.

FMF attacks may be triggered by common factors such as cold exposure, emotional or physical stress, infections or menstruation⁷. More than 15% of female patients experience perimenstrual attacks. It is proposed that oestrogens normally inhibit IL-6 production and mimic colchicine's effect on tubuli and adhesion mole-

cules. During menstruation the protective effect of oestrogens disappears, leading to the acute attack.

The prodromic syndrome occurs 12-24 hours before FMF attacks⁸; the preliminary symptoms include discomfort, abnormal taste sensation, dizziness, increased appetite, irritability and so on.

Laboratory tests during attacks show leukocytosis (predominantly neutrophils), increase of inflammation parameters (ESR, CRP, SAA...), microalbuminuria, which normalize in asymptomatic periods, except for patients with persistent subclinic inflammation.

Diagnosis is based on Tel-Hashomer clinical criteria (more recently on Montpellier criteria). Genetic analysis can confirm diagnosis but it's not indispensable.

Colchicine is still the only suitable drug to prevent the attacks and the development of amyloidosis, at a daily dose of 1-2 mg¹⁰. Alternative experimental treatments – including prazosin, TNF-antagonists (etanercept, thalidomide, infliximab), methotrexate, IL1 receptor blockers (as Anakinra), Selective Serotonin Reuptake Inhibitors (SSRI) – have been proposed in non-responder cases, but further studies are necessary¹⁰.

In the current study we analyzed clinical data of 229 patients (114 males; 115 females), aged from 2 to 93, affected by FMF, attending the adult section of a Periodic Fevers Research Centre in the last 10 years. Clinical diagnosis was established by Tel-Hashomer criteria; genetic testing by complete MEFV sequencing in all patients was performed and is positive in 68.7% of patients. All patients can contact us by mail or telephone and understand better the disease through a website. A database file of genetic and clinical recordings of patients is available in *Excel*, *Word* and *papery* format. Most patients come from the South (53.27%) and the Centre of Italy (25.32%); probably because of the geographical position of Italy and the migratory changes of its population during last 20 centuries. Some patients come from near countries (Malta, Syria, Tunisia). The age of onset is under 30 in 82.5% of the patients. The frequency of the attacks goes from less than 1 attack/month (22.3%) to more than 2 attack/month (27.1%). According to Pras severity score a mild disease was documented in 38.9%, a moderate disease in 36.2% and a severe one in 24.9% of patients. The most typical attack presents fever (94.3%) and abdominal pain (83.0%) followed by fever and articular pain (64.2%) and by thoracic pain (37.5%). Only 14

patients have abdominal and thoracic pain or abdominal and articular pain or abdominal, thoracic and articular pain without fever. Thoracic, pleural, pericardial or pleuro-pericardial pain affects 114 patients. 147 patients had joints involvement: arthritis in 50, arthralgias in 70; 27 complained of myalgias. Abdominal pain affects 190 patients with nausea (33.6%), vomiting (33.6%) and in few cases diarrhoea or constipation. 23 patients have a renal function compromised and the damage goes from microalbuminuria to renal failure; 3 patients developed amyloidosis. FMF attacks may be triggered by common factors such as cold exposure, emotional or physical stress, infections or menstruation⁷. More than 15% of female patients experience perimenstrual attacks. 183 patients received colchicine treatment (68.0% good effectiveness; 27.5% mild effectiveness; 4.5% no response). Among *minor* manifestations we observed *splenomegaly* (13.5%) and *acute orchitis* (1.35%).

The genetic test is positive in 68.7% of patients (one mutation in 22.6%, two mutations in 32.21%), according to literature. M694V is the most frequent mutation (22.0%), followed by E148Q (13.2%), M680I (13.2%), M694I (6.1%), V726A (7.9%). Rare mutations are observed in less than 20% of cases. Genotype-phenotype correlations are similar to those of literature (16): prevalent mutations in severe phenotypes are M694V (38.7%), M680I (14.2%) and M694I (6%) in homo- or heterozygosis are in, although in 20% of the cases there are no mutations. In mild phenotypes the most frequent mutation is E148Q, but in 22% of patients no mutations have been found and in 35% M694V, M680I, M694I have been detected. The presence of protective genomic factors cannot be excluded.

Because of diagnostic delay (14.8 years in these series), many patients underwent unnecessary surgery, without resolution of symptoms (appendectomy was the most frequent and was performed in 1/5 pt).

About 80% of patients regularly takes colchicine (up to 0.03 mg/kg/die). About 22% don't take it: 8% has never started treatment, 14% has stopped it for gastrointestinal effects, hepatotoxicity, inefficacy or personal decision. We estimated the response to colchicine in terms of persistence/disappearance of frequency, length and intensity of bouts (good response in 68.0%; partial response in 27.5%). The non-responder rate is less than 5% (4.5%). Therapeutic options include the addition of a non-steroidal anti-in-

flammatory drug during attacks, or an increase of colchicine five days before menstruation. We are testing the etanercept efficacy in non responder patients and preliminary results seem to be promising.

The collected data suggest that the characteristics of this Italian series are: a less severe disease, low prevalence of amyloidosis, higher incidence of late onset, high rate of colchicine responders. Moreover the foundation of a centre devoted to periodic autoinflammatory diseases allows frequent consultations and monitoring of the patients. Moreover investigations about new genes, early diagnosis, reduction of cost of diagnosis and disease complications, colchicine analogues are currently ongoing.

All patients can contact us by mail or telephone and understand better the disease through the website of Catholic University (www.rm.unicatt.it).

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