European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2006; 10: 163-171

The multi-face expression of familial Mediterranean fever in the child

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Abstract. – Familial Mediterranean fever (FMF) is characterized by recurrent self-limiting flares of fever in the absence of pathogens, autoantibodies or antigen specific T cells and is inherited as an autosomal recessive trait probably deriving from common ancestors of Armenian, Jew, Turk and Arab origin. The underlying pathogenetic mechanisms of FMF have not been fully interpreted, but mutations in the gene MEFV encoding pyrin, a natural repressor of proinflammatory molecules, result in uncontrolled relapsing systemic inflammation, increased leukocyte migration to serosal membranes or joints and inappropriate response to inflammatory stimuli. FMF heterogeneous phenotypic expression could originate both from allelic heterogeneity or from the existence of modulating genes. Proper diagnosis of FMF is needed to begin both specific clinical management and treatment based on continuous prophylactic administration of colchicine, preventing flares or at least the onset of amyloidosis.

Key Words:

Familial Mediterranean fever, Child.

Introduction

The hereditary periodic fevers are a group of genetic disorders, also described as "auto-inflammatory syndromes", in which seemingly unprovoked self-limited febrile attacks and systemic inflammation recur in consequence of a primary dysfunction of the innate immune system without evidence of adaptive immune dysregulation, high-titre autoantibodies or antigen-specific T cells[1]. Innate immune abnormalities include aberrant responses to pathogens, lipopolysaccharides, peptidoglycans and dysregulation of inflammatory cytokines or their receptors. People with hereditary periodic fevers display similar clinical features and widely heterogeneous genotypes, often presenting symptom-free intervals of different duration between febrile attacks. In this group of disorders we can list familial Mediterranean fever (FMF), hyperimmunoglobulinemia D/periodic fever syndrome, tumour necrosis factor receptor-associated periodic syndrome, cryopyrin-associated syndromes, PAPA syndrome (characterized by pyogenic arthritis, pyoderma gangrenosum and cystic acne), chronic recurrent multifocal osteomyelitis, Blau syndrome (also known as early-onset sarcoidosis), Schnitzler syndrome (characterized by periodic fever, urticarial rash, arthropathy with monoclonal IgM-gammopathy) and cyclic neutropenia[2-6].

Familial Mediterranean Fever

FMF was first described in 1908 by Janeway and Mosenthal in a 6-year-old Jewish girl presenting abdominal pain and recurrent fever[7]. In 1945 Siegal, a Jewish allergologist, described as "benign paroxystic peritonitis" his own clinical picture which was similar to features presented by other five Jewish patients: they all had cutaneous signs, recurrent peritonitis and periodic fever attacks[8]. In 1950 two French researchers, Mamou and Cattan, studied the familiar pattern of this disease in Sephardic Jews[9]. In the same period, Reimann et al reported other similar cases in families of Armenian ancestry[10]. Due to all these reports this disease has been described as benign paroxystic polyserositis, Armenian's disease, Siegal-Cattan-Mamou's syndrome and Reimann's periodic disease. In 1958 Heller defined the overall FMF clinical picture and studied its autosomal recessive inheritance with the associated nephropathy deriving from amyloidosis: he also created the name "FMF"[11,12]. This is

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the most common auto-inflammatory disease and the first one with the causing gene identified in 1997[13]. Two independent groups discovered FMF gene, called *MEFV*, on chromosome 16 short arm which encodes a 781 aminoacid-protein implicated in the "down-regulation" of white blood cell activity: the American group named this protein with a molecular weight of 86 kD "pyrin" (the Greek term "πψρετὸσ" means "fever") and the French group named it "marenostrin" ("mare nostrum" is the Latin name for the Mediterranean sea)[14-17]. Most *MEFV* mutations are localized in the exon 10 which encodes for pyrin C-terminal region. This discovery represented the starting point to understand the pathogenesis not only for FMF, but also for other auto-inflammatory diseases and during the last years there have been lots of studies demonstrating the growing scientific interest in the definition of basic inflammation mechanisms.

Epidemiologic Data

It has been estimated that about 170,000 people worldwide are affected with FMF, though a restricted ethnic distribution has been observed in people living around the Mediterranean basin and in the ancient Mesopotamia: Armenians, non-Ashkenazi Jews (above all Sephardic Jews), Turks and Arabs (mostly North-Africans such as Maghrebins)[18,19]. However because of many migrations during the past centuries the gene causing FMF has also been spread in Western Europe and patients have been reported in Brazil, China, Australia, New Zealand and Japan[20,21]. Carrier frequency is very different among the same populations, varying from 1:3 in Armenians to 1:270 in Ashkenazi Jews and fluctuating in a range of 1:5-1:16 in Sephardic Jews who emigrated to the Iberian peninsula (Sephardi means Spain in Hebrew)[22]. Males and females are equally affected, even though there is a slightly higher prevalence in males. A putative selective biological advantage for carriers of mutations in the FMF gene has been suggested, similarly to the advantage of sickle cell trait against malaria. The exceptionally high gene frequencies for FMF could be explained by an increased resistance against specific pathogens or intra-cellular bacteria such as *Mycobacterium tuberculosis* that might result endemic in the same areas where FMF is observed or by a heightened protection against asthma[23]. In Italy FMF is erroneously considered a rare disease ("rare" means that its prevalence is inferior than 1 per 2000 inhabitants): various historical reasons account for the presence of the FMF gene in Italy as Greek colonization of Sicily and Southern Italian regions in the VIII century B.C., the arrival of the first Christians in Rome under the Roman Empire in the I-II century A.D. and the Arab conquest of Sicily in the IX century A.D.[24].

Pathogenesis

The *MEFV* (from *ME*diterranean *Fe**V*er) gene responsible for the disease has been identified on 16p13.3, between the genes linked to polycystic kidney disease and Rubinstein-Taybi syndrome, spans approximately 14 Kb of genomic DNA and comprises 10 exons and 781 codons. Over 60 putative mutations causing FMF have been discovered in less than 10 years. Before *MEFV* discovery it was well-known that FMF crises are characterized by a massive influx of polymorphonuclear leukocytes into the inflamed regions such as serosal membranes and joints. Though we are still far from the complete understanding of pyrin function, a huge number of studies of this intriguing protein is revealing new molecular details about general processes of inflammation and apoptosis. Pyrin action is at the level of cytoskeletal organization, specifically at microtubules and actin filaments of cytoplasm and nucleoplasm[25-28]. The "pyrin domain" of this protein is a member of the death-domain-fold superfamily and is involved in the apoptotic pathway modulation through caspase recruitment and in the production of the potent pyrogenic cytokine interleukin-1[29-39]. *MEFV* mutations might cause longer leucocyte survival producing longer inflammatory responses. Other studies have suggested that when pyrin is mutated a negative-feedback is lacking so that Th-1 polarized inflammation and Th1-dependent proinflammatory cytokine production is enhanced[40,41]. Cytokine transcriptional pathways are misregulated even in attack-free periods supporting the hypothesis that subclinical inflammation between attacks might be present. Triggers stimulating the periodic occurrence of acute FMF attacks are not known, even if different chronic infections such as *Helicobacter pylori* gastritis or small bowel bacterial overgrowth might have a role. Other

current studies suggest that non-*MEFV* genetic systems and environmental modifiers might interplay influencing the pathogenesis of FMF.

Genotypic Studies

The most frequent *MEFV* mutations are contained in the exons 10 and 2 and are heterogeneously distributed on different populations. Five mutations represent more than 70% of the mutated alleles in FMF cases of Mediterranean ancestry: M694V, M694I, M680I, V726A (all in the exon 10) and E148Q (in the exon 2). The most frequently reported mutations are listed in Table I. In these populations the carrier frequencies vary from 1:3 to 1:6, which are the highest ever reported for autosomal recessive disorders. Genotypes including two mutations located within mutational *MEFV* "hot-spots" (codons 680 or 694) in the 10th exon have been associated with the most severe phenotypes. Clinical heterogeneity relies at least partly on genetic heterogeneity. Probably the mutations M694V and V726A appeared about 2500 years ago in the Middle East for the first time: the M694V mutation is the most frequent in various ethnic groups and the V726A is observed mainly among Ashkenazi and Iraqi Jews, Druzes and Armenians. The E148Q is the least penetrant mutation and is recognized to have mild effects on FMF patients, so that it has been questioned whether it represents a polymorphism[43-48]. R202Q is considered a *MEFV* polymorphism present in about 15% of unaffected population[49]. Another important question is the possibility of genotype-phenotype correlations: in some surveys M694V homozygosis, M680I homozygosis and heterozygosis for M608I/M694V genotypes are associated with severe clinic pictures and more frequent incidence of amyloidosis, while V726A is associated with a milder disease and less frequent amyloidosis[50-56]. Understanding the correlation between FMF phenotype and genotype is further obscured by the existence of complex alleles, modifier loci and possible epigenetic factors. Many reports suggest that phenotypic differences might be related to both genetic and environmental influences[57.58]. Some genes have been tested to assess their possible modifying effects on the clinical features of FMF: the alpha/alpha genotype of the serum amyloid-A gene is associated with an increased risk of amyloidosis in FMF patients, especially if homozygous for M694V. The observation of the same mutations and haplotypes in populations that have been isolated for centuries with high rates of consanguinity indicates that most cases of FMF are descended from a very ancient pool of founders[59-61].

Clinical Presentation

FMF is characterized by short recurrent self-resolving attacks of fever, abdominal, thoracic or joint pain and systemic inflammation with inter-critical period of apparent wellness: clinical picture and disease severity may vary among different ethnic groups[62]. Onset symptoms begin in about 50% cases during the first decade and only in 5% after the third decade. In few cases symptoms might appear during the first months of life. Features of a typical attack (see Table II) comprise fever and possibility of serositis or arthritis, lasting from 1 to 3 days, resolving spontaneously. Attacks do not have a regular periodism in consequence of a frequency varying from one a week to one every three-four months or more; in-

Table I. Most frequent mutations observed in patients with familial Mediterranean fever.

Mutations	Associations
M694V	Most frequent among Jews, Turks, Armenians and Syrians
M680I	More common in Armenians and Egyptians
M694I	More common among Arabs
E148Q	Mostly observed in Europeans and Turkish carriers
V726A	Mild phenotype

Table II. Clinical signs of familial Mediterranean fever.

Fever	96%
Peritonitis	91%
Pleurisy	57%
Arthritis or arthralgias	45%
Erysipelas-like erythema at the inferior limbs	13%
Amyloidosis	2-12%
Destructive chronic arthritis	2-5%
Recurrent pericarditis	1-2.5%

tervals between attacks are different both among patients and in the same patient too[63,64]. Fever is present in 96% of inflammatory episodes: body temperature can reach very high values, even over 40°C; it usually appears suddenly and lasts from 12 to 72 hours and is preceded by shivers in about 20-30% patients. Rarely fever is the only FMF manifestation without other signs of localized inflammation. Abdominal pain is present in about 90% patients and is the first manifestation in 50% of them: it is due to peritoneum inflammation with a clinical outline simulating an acute abdominal pathology like appendicitis, cholecystitis, ureteral stones, pelvic inflammatory disease with frequently associated positive Blumberg's sign (sharp rebound tenderness when the examiner presses his hands over McBurney's point), reduced peristalsis, hydroaereal levels on abdominal X-ray film and small amounts of ascites upon ultrasound investigation. Patients might undergo unnecessary surgery in 30-40% cases. Some authors recommend a laparoscopic appendectomy because the exclusion of a true acute appendicitis is not easy at a merely clinical level[65]. Constipation may be present in some patients, but diarrhoea is more common in children. Recurrent peritonitis can cause adherences compromising female fertility[66]. Mono or bilateral pleural effusion can be demonstrated in 50-60% patients and is characterized by quick resolution, whilst recurrent pericarditis can be observed in a small percentage of FMF patients (1-2.5%) during febrile attacks[67,68]. Intense scrotal pain simulating a testicular torsion is frequent in children[69]. The third most frequent FMF clinical manifestation is articular involvement which is described in 45% cases and might present as transient arthralgia, monoarthritis or oligoarthritis: short lasting attacks begin without prodromes, involve large joints in lower limbs (hip, knee, ankle) or upper limbs (wrist) and suddenly disappear in about 24-48 hours with no sequelae. Rarely it is possible to observe prolonged arthritis lasting for more than one week or even destructive chronic arthritides in 2-5% cases[70-72]. A patognomonic skin manifestation for FMF diagnosis is erysipelas-like erythema which can be observed in 13% patients and is often localized over legs or feet. Muscular manifestations can present with febrile severe myalgia having three different patterns: spontaneous, effort-induced and prolonged with an overall duration of some weeks[73]. Other non-specific FMF clinical signs are aseptic meningitis, cryptogenic liver cirrhosis, splenomegaly and oral aphthae. Amyloidosis is the most severe manifestation of FMF resulting from the deposition of amyloid, which is presumed to be a cleavage product of serum amyloid A, an acute-phase reactant produced by the liver. Recent studies have focused on the polymorphism of serum amyloid A as a genetic background for amyloidogenesis[74]. The prevalence of amyloidosis among FMF patients is considered to be independent of the frequency, duration and intensity of FMF flares. Other organs involved by amyloid deposition are gut, spleen, liver, heart and endocrine glands. The pathogenic role of environmental factors in amyloidosis occurrence such as the origin country is suggested by the inferior incidence of amyloidosis in Jews living outside the Mediterranean basin: for instance Armenians living in Armenia have a much higher incidence of amyloidosis than Armenian Americans, even before the introduction of colchicine. In addition amyloidosis appears to be less common among Iraqis, Ashkenazi Jews and Arabs. The association between amyloidosis and the mutation M694V is widely reported, but non-amyloid glomerulopathies such as IgM or IgA nephropathy, focal and diffuse proliferative glomerulonephritis and rapidly progressive glomerulonephritis have also been observed. Moreover some non-granulomatous Th-1 polarized vasculitides have been associated with FMF such as Henoch-Schönlein purpura (in 2.6-5% cases), nodous polyarteritis (0.8-1% cases) and Behçet disease (0.5% cases)[75,76]. Inflammatory bowel disease is 8 to 14 times more frequent in FMF patients and its clinical course appears usually more aggressive[77].

Diagnostic Criteria

Traditionally the diagnosis of FMF has been based on typical clinical manifestations and the physician's experience. Clinical diagnosis is complex if there are only febrile episodes without serositis or if amyloidosis is initially demonstrated without history of fever and serositis. In patients with a typical clinical outline and appropriate ethnic origin FMF diagnosis can be made without genetic confirmation, which can be contributory in cases of atypical presentation, absence of family history or unusual ethnic origin. During the latest years many authors have tried to develop different diagnostic flow-charts,

though the Tel-Hashomer criteria listed in the Table III remain the most widely used in many clinical settings[78]. Genetic testing might reveal no known mutation in 30-40% patients or a single known mutation: in this case if clinical manifestations are convincingly those of FMF the patient is put on an open trial with colchicine. If there is a positive response and symptoms return after colchicine cessation it is assumed that there are mutations in other parts of the *MEFV* gene or in other genes not yet identified.

If 2 major Tel Hashomer criteria or 1 major criterium and 2 minor ones are satisfied the diagnosis of FMF can be confirmed; if only 1 major and 1 minor criteria are satisfied the diagnosis is only probable. There is no specific laboratory examination to support diagnosis of FMF, except for genetic testing. Following *MEFV* cloning the genetic analysis of its mutations has become available providing a new tool for diagnostic confirmation. Genetic diagnosis is positive when two mutations, even if not identical, are present in the two *MEFV* alleles. If only one or no mutation can be found the clinical diagnosis of FMF is still possible due to the occurrence of unknown mutations. Molecular analysis of FMF mutations can confirm diagnosis in about 60% of the referrals with suspected FMF and is mostly contributory among patients with atypical clinical presentation[79]. A second opinion by an expert in FMF might decrease the need for mutation analysis in subjects suspected of having FMF. Metaraminol provocation test (with the intravenous infusion of 10 mg metaraminol in physiologic solution) could trigger typical attacks in a period ranging from 2 to 48 hours since the infusion[80]. Common blood tests in patients who present typical acute attacks show a generalized increase of the inflammatory parameters (erythrosedimentation rate, C-reactive protein, serum amyloid-A, immunoglobulins) with a parallel neutrophil leukocytosis (until 20,000/mm^3). A host of pro-inflammatory cytokines are greatly increased during acute attacks such as interleukin-1, interferon-gamma, interleukin-6 and interleukin-8. In cases of renal amyloidosis urinalysis shows microalbuminuria or proteinuria superior than 1-2 g/l[81].

Table III. Tel Hashomer criteria for the diagnosis of familial Mediterranean fever.

Major criteria
- Recurrent febrile episodes accompanied by serositis
- Amyloidosis of AA-type without a predisposing disease
- Favourable response to continous colchicine treatment

Minor criteria
- Recurrent febrile episodes
- Erysipelas-like erythema
- Familial Mediterranean fever in a first-degree relative

Therapy

FMF therapy is meant to prevent the development of signs and symptoms of acute flares, but also the onset of amyloidosis. No evidence-based guidelines have been published, but since 1972 colchicine is the drug used in the treatment of FMF. The initial dose in children is 0.5-1 mg/day regardless of age and body weight, which can be increased until disease control is achieved. Colchicine displays its effect by fixating the intracellular microtubules, arresting their polymerization in fibrillar structures and finally disrupting mitosis, motility and transport systems within the cells. The discovery that pyrin is largely expressed in neutrophils might imply a direct colchicine action upon this protein with a modulating effect on the production of cytokines and adhesion molecules from the vascular endothelium. Colchicine is uneffective if administered only in the acute attacks, for which intravenous 40 mg methylprednisolone infusion seems to be useful, above all to control inflammatory signs such as pleurisy pain. Continuative colchicine therapy, even if started during childhood, has no effects both on the normal growth and fertility. Complete remission is achieved in 65% patients and partial remission in 30% with 5% patients remaining unresponsive. Protracted arthritis, mostly affecting hip or knees, can be managed with intravenous infliximab or subcutaneous etanercept administration. No alternative to colchicine can be recommended in non-responders, but interferon-alpha or thalidomide might be considered to manage the typical flares, though with discordant efficacy[82]. Treatment of amyloidosis is aimed to reduce the AA fibril precursor protein, to support failing organ function and to maintain blood pressure in a healthy range with constant monitoring of serum amuloid-A concentrations: the most appropriate approach with colchicine, anakinra, tumour necrosis factor-inhibitors, interleukin 6-inhibitors or caspase 1-inhibitors is still debated.

In conclusion, FMF cannot be considered a rare condition only confined to the Eastern Mediterranean countries: this disease is scattered throughout the Western world showing a dynamic face with genetic and environmental aspects cooperating in determining the clinical phenotype. A troubling issue in patients with FMF is related to its misdiagnosis because diagnostic delay leads to therapeutic delay and then to a worse long-term prognosis. Colchicine therapy allows kids with FMF to live a normal life with no restriction or substantial risk of sequelae, whilst the unrecognized disease has a negative influence on kids' and their family's quality of life because of frequent hospitalizations, eventual surgical interventions caused by the wrong interpretation of FMF clinical signs or simply due to recurrence of febrile attacks which reduce school attendance and limit child's social attitudes. Diagnosis of FMF is essentially made on the basis of the typical clinical findings in association with the peculiar ethnicity or family history and response to colchicine. Future investigations are hoped to clarify the exact role of pyrin in the pathogenesis of FMF and other risk factors for the development of amyloidosis. Progress in the knowledge of genetic determinants of FMF could constitute a significant step towards the understanding of the humane genome expression and inflammation mechanisms with possible therapeutic implications. A more diffuse and correct information about FMF (our Center of Periodic Fevers has a specific website devoted to auto-inflammatory diseases: "www.conosciamocimeglio.it/cfp/index3.htm", containing detailed information directed to Italian clinicians, patients and their families) will probably reduce the diagnostic delay in the recognition of the disease and positively affect the quality of life of patients at a lower risk of long-term complications.

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