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 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.

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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.
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 ‘marinestript/’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](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 some 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 (criteria for the diagnosis of FMF, typical attacks are characterized by Arthritis and Rheumatism criteria [14], the most widely used adult despite the progresses in understanding the genotype-phenotype correlation; 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

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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.

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.

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validation of the Yalcinkaya criteria in a French population of children using an appropriate control group did not show a better contribution to FMF than the Tel Hashomer criteria [17], while a recent evaluation of sensitivity of Yalcinkaya and Tel Hashomer criteria in 110 Turkish children affected found values of 93% and 100% respectively, indicating a also high sensitivity of the new set of criteria in patients with a mutation at a single allele [18]. However, further data regarding vary ethnic groups of children are needed for the definitive validation of these new proposed criteria.

Differential diagnosis is wide, especially in the pediatric population, and includes other autoinflammatory syndromes: hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), TNF receptor-associated periodic syndrome and periodic fever (TRAPS), apthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome, transthyretin-related amyloidosis. Also, an association between FMF and other inflammatory diseases, especially vasculitides such as Henoch–Schönlein purpura, polyarteritis nodosa and Behçet's disease has been described [19,20].

In some patients, a subclinical chronic inflammatory state is responsible of chronic manifestations (i.e. anemia, splenomegaly) and can lead to the development of AA amyloidosis, the most severe complication of FMF [21]. AA amyloidosis is caused by the extra-cellular deposition of amyloid fibrils, which culminates in multi-organ dysfunction, particularly of the kidneys. Renal involvement initially manifests as proteinuria, and gradually progresses into nephrotic syndrome and renal dysfunction. The ethnicity, the carriage of M694V mutation, the serum amyloid-associated (SAA)1 α/α genotype, the male gender, the articular involvement and a family history of FMF increase one's risk of developing amyloidosis [22,23].

Particularly, previous studies reported a rate of FMF-associated amyloidosis of 37% in Sephardic Jews, 27% in non-Ashkenazi Jews, 12% in Turks, 24% in Armenians and in 1–2% of Armenians living in the United States [24].

The comparison of mutations found in patients with FMF-associated amyloidosis with those found in the general population showed that amyloidosis was more frequent in patients with homozygous M694V mutations than in patients with other MEFV gene mutations [25–27]; for this reason M694V mutation is considered an important factor in predicting the development of amyloidosis. However, cases of FMF-associated amyloidosis have been described in patients heterozygous and homozygous for V726A mutation [28,29].

As above mentioned a favorable response to colchicine is one of the Tel Hashomer major criteria that supports the diagnosis of FMF, especially in cases with mild clinical features or incomplete genotype-phenotype correlations.

Colchicine, a tricyclic alkaloid extracted from two plants of the lily family (the genus Colchicum autumnale and the Gloriosa superba), is the oldest drug in the family of antimicrotubule agents, and represents the drug of choice in FMF. Although most anti-inflammatory effects of colchicine are due to the disruption of microtubule function, marked effects are exerted on leukocytes and, as recently demonstrated, on NACHT-LRR-PYD-containing protein 3 (NALP3; cryopirin) activity in macrophages [30,31].

In FMF colchicine modulates the expression of pyrin and interacts in the cytosol. Its most effective results have been obtained in the prophylaxis of FMF, while the administration during the attacks is ineffective [32]; during the attack a non-steroidal anti-inflammatory drug can be administered.

Also, colchicine prevents the occurrence of AA amyloidosis: annual physical examination of patients affected, together with the dosage of SAA is recommended in all FMF patients. Dialysis and organ transplantation might be necessary for those who progress towards renal amyloidosis. Colchicine dosage ranges up to 0.03 mg/kg/body weight/daily, to a maximum of 3 mg/daily, and must be taken regularly on a life-long basis.

Actually, patients intolerant to colchicine have no alternative as efficient, although interleukin-1 (IL-1) receptor antagonist (Anakinra), anti-IL-1 monoclonal antibody (Canakinumab), interferon-alpha and selective serotonin reuptake inhibitors (SSRIs) have shown encouraging results in some patients. Colchicine can enhance B12 malabsorption and in rare cases can cause alopeacia and bone marrow suppression. Macrolides, diltiazem, grapefruit and cyclosporine should not be taken with colchicine as fatal toxicity can occur [33].

2. The FMF phenotypes

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 amyloidosis 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 [34].

2.1. Phenotype 1

2.1.1. Typical clinical manifestations

Generally, a typical attack lasts between 12 and 72 hours, and raises a peak within 12 hours of onset. The interval between attacks is variable from few weeks to months or years; the higher frequency of attacks is observed in M694V, M680I and M694I homozygous patients.

The attack may be triggered by common factors such as cold exposure, emotional or physical stress, infections or menstruation [35]. 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 molecules. During menstruation the protective effect of oestrogens disappears, leading to the acute attack. The prodromic syndrome occurs 12–24 hours before FMF attacks: the preliminary symptoms include discomfort, abnormal taste sensation, dizziness, increased appetite, irritability [36,37].

Recurrent fever, which may be the only detectable manifestation of FMF in childhood, is characterized by temperature from 38 to 40 °C. Fever can partially respond to antipyretics or steroids administration, while antibiotics do not have any effect. In course of fever, laboratory exams can typically show a neutrophils leukocytosis, together with the increase of inflammation indexes, such as erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), SAA and fibrinogen, which disappear in intercurrent well-being periods, except in patients with persistent subclinical inflammation.

Abdominal pain is experienced by about 90% of affected individuals and usually involves the entire abdomen. Physical examination reveals board-like rigidity of the abdominal muscles, rebound tenderness, abdominal distension, and loss of peristaltic sounds. As the radiographic evidence of multiple small air-fluid levels in the small bowel may occur, the diagnosis of ‘acute abdomen’ usually results in exploratory laparotomy. Otherwise, the signs and symptoms resolve without sequelae over 24–48 hours. Some individuals have constipation lasting all the attack length, while diarrhea is more frequent in children [38]. In a small percentage of patients the attacks are characterized by afebrile recurrent abdominal pain.

Articular involvement is present in approximately 75% of cases, frequently as monoarthritis localized in the large joints of the leg (hip, knee, ankle); shoulder, temporomandibular or sternoclavicular joint may also be affected. In case of synovial effusion, the synovial fluid analysis shows a sterile synovitis with high white blood cells count. Acute arthritic attacks tend to subside within the same time frame as described for abdominal attacks; local redness, swelling and tenderness resolved in 48–72 hours without sequelae [39]. In a small percentage of patients (~5%) protracted arthropathia has been reported, resulting in a joint damage and permanent deformity; arthritis of upper extremity
joints and seronegative spondiloarthropathies have also been reported [40,41].

Recurrent monoarthritis can be the first and unique manifestation of FMF and requires a scrupulous differential diagnosis with similar entities (palindromic/reactive arthritis, inflammatory bowel disease, Reiter’s syndrome, chronic juvenile arthritis, Behçet disease, gout) [42].

Chest attacks are due to the inflammation of the pleura or pericardium and occur in 30%–40% of patients affected; they are characterized by a sudden onset, a unilateral localization and a spontaneous resolution within in 48–72 hours, with a course similar to the abdominal and joint attacks. Chest radiograph may reveal an obliteration of the costophrenic angle by a small pleural effusion.

As concerns the pediatric population, medical literature is poor of reports referring to FMF in patients younger than 2 years of age, because symptoms are often noted only when children become more verbal. This causes low awareness of the possibility of FMF in this age group and a delay in diagnosis [43].

2.1.2. Other clinical manifestations

Other clinical manifestations of FMF include protracted febrile myalgia, which generally responds to steroid therapy, and also erysipelatoid-like erythema, aseptic meningitis (also known as Mollaret syndrome) and vasculitides, entities that are generally present in ≤ 5% of patients.

2.2. Phenotype 2

On the basis of several case reports and of two large Turkish series, phenotype II has been defined as the occurrence of proteinuria or renal failure as expression of AA amyloidosis before the clinical onset of FMF or as an isolated finding in a member of an FMF family [44–47]. The reported incidence ranges from 7% to 25% of FMF patients affected, according to large studies conducted in the 1990s [48,49]. However, the actual incidence and prevalence of this clinical variant have not yet been accurately assessed.

Usually, the phenotype II is detected in patients receiving a diagnosis of renal AA amyloidosis who have relatives with clinically apparent FMF [50]. In these individuals, the typical attacks may become apparent some years after the detection of renal amyloidosis; alternatively, patients could fail to develop any symptoms of FMF through the entire life, suggesting persistently high levels of SAA protein even in the absence of typical attacks, which are generally associated to pulsatile increase of SAA. The MEFV analysis is mandatory in those cases.

Also, once the prevalence of phenotype II has been clearly assessed by means of large population studies, a cost-effectiveness analysis could be useful to verify if the routine search of MEFV mutations in all first-degree relatives of FMF patients have a contributory role, in order to reduce the clinical complications of the disease and the costs of treatments due to the absence of medical supervision and colchicine prophylaxis.

2.3. Phenotype 3: the ‘silent’ carriage

Phenotype III is defined as the presence of two MEFV mutations (homozygote or compound heterozygote state) without clinical manifestations of FMF nor of reactive amyloidosis. The frequency of subjects with phenotype III was estimated 1:300 in Ashkenazi Jews and 1:25 in Iraqi Jews, exceeding the previous reported rate of overt FMF in these ethnic groups by 40–240 fold, and suggesting that among these ethnic groups most subjects with FMF were unaffected [51]. However, even in absence of signs or symptoms, the ‘silent’ carriage of two mutations could predispose to developing renal AA amyloidosis, finally configuring the phenotype II.

To assess the rate of population at risk for evolution to phenotype II, recently Camus and colleagues [34] sought to determine the prevalence of phenotype III in seven large families with only one subject affected with FMF.

The frequency of phenotype III resulted 10% in these families, significantly higher than that expected in general population (1%); considering the risk of the ‘silent carriers’ individuals to develop a reactive amyloidosis, the authors suggest that screening for mutations should be actively undertaken in families with members affected with FMF. Also, they proposed to follow individuals with phenotype III in dedicated clinics for the development of FMF symptoms, asymptomatic proteinuria and/or elevation of inflammatory markers, in order to promptly initiate colchicine therapy and to accurately determine the rate of transformation to phenotype II.

2.4. The ‘FMF-like’ disease: a new phenotype?

Interestingly, 5.7% of siblings evaluated by Camus and colleagues [34] were heterozygous mutation carriers and were found to suffer from a mild or incomplete form of FMF, named ‘FMF-like’ disease and characterized by episodic arthritis without fever, afebrile abdominal attacks, or febrile abdominal attacks in childhood which spontaneously remitted in adult age.

As the disease is traditionally considered an autosomal recessive condition, in the past years several investigators assumed that the heterozygous mutation carriers clinically symptomatic for FMF could harbor less common MEFV mutations on the second MEFV allele; surprisingly, all studies aimed to detect such mutations in the coding region, the exon and intron boundaries, or in the promoter region of the gene, failed to identify additional mutations, even when complete sequencing of the gene was performed [52–54].

The percentage of patients with a single gene mutation varies between 16.5% and 33.8% [55,56]. The reason why some of these patients remain asymptomatic for the entire life, while others display only subclinical inflammation (i.e. elevated CRP or SAA levels) and some others manifest clinical disease is still unknown; some authors proposed the existence of a clinical phenotype even in patients heterozygous for FMF, in which maybe other modifiers genes and environmental factors play a role in the determining the variable penetrance and expressivity of the disease. Partial penetrance could also explain vertical transmission and ‘FMF-like’ forms in some family members [52].

Otherwise, the study of MEFV genotype can also orientate the clinician to other non-specific periodical clinical conditions, with inflammatory or autoinflammatory findings, which could be associated to a single MEFV mutation, such as incomplete form of Behçet disease [57,58], spondiloarthopathies [59,60], severe form of rheumatoid arthritis associated to periodic fever [61], cryopyrin associated periodic syndrome (CAPS) and TRAPS.

2.5. The phenotypic variability: role of genetic and environmental factors

Environmental and genetic factors, including MEFV mutations and background modifiers genes, contribute to affect the FMF phenotype.

In the past years, many population-studies have been conducted to investigate the genotypes-phenotypes correlations, particularly the role of genetic factors on the phenotype and on the development of amyloidosis.

Several studies suggested that patients with some of the MEFV mutations, mainly the M694V mutation had more severe symptoms and findings and/or a higher risk for the development of amyloidosis [12,62–64].

However, different mutations are not always correlated with phenotypic variations: great diversity of clinical characteristics has been observed among patients carrying the same mutations, even in the members of the same family [65].

Also, the role of E148Q sequence variation remains controversial: initially it was described as a disease-causing mutation with low penetrance and mild symptoms. Other studies, due to a similar frequency
of E148Q among FMF patients and healthy controls, suggested to consider it a benign polymorphism [66,67], although there are evidences that when E148Q appears on the same allele with the V726A mutation and constitutes the E148Q–V726A complex allele, patients who are homozygous or compound heterozygotes for the complex allele had more severe disease compared to patients homozygous for V726A [13,68].

Thus, the influence of other modifiers gene activity in addition to MEFV mutations, has been investigated and included the role of SAA1, SAA2 [23,69,70], Toll-like receptor 2 (TLR2) [71] and major histocompatibility complex class I chain-related gene A [72], which were shown to correlate with a higher risk for the development of amyloidosis and higher frequency of attacks.

As regards the environmental influence, the first evidence for the effect of environmental factors on FMF phenotypes was described in the 1970s in the Armenian FMF patients living in the United States, who developed amyloidosis less frequently than patients living in Armenia [73]. Several years later, Touitou and colleagues [74] confirmed that the country of residence contributes to affect the severity of the disease more significantly than MEFV genotype. Similarly, Ozcan and colleagues [75] observed a more severe disease in Turkish children with FMF living in Turkey, compared to those living in Germany; as a possible explanation of these observations, it has been hypothesized the exposition to different strains of exogenous microbial triggers.

Also, the clinical observation of a major self resistance to microbial infections as well as a minor necessity to recur to antibiotic therapy during the childhood in the pediatric FMF population in comparison with general pediatric population made some clinicians to speculate as FMF could be interpreted as an ancient mechanism of protection, similarly to sickle cell anemia for the Plasmodium falciparum infection (Kastner DL, personal communication). Furthermore, several studies have shown that FMF may have a protective effect against development of asthma, atopic sensitization, and allergic rhinitis (7% in individuals with FMF compared with 20% in the general population) [76].

Other well-known environmental factors shown to modulate FMF phenotype are psychosocial factors such as emotional stress, cold exposure, menstrual periods and pregnancy [77,78].

Recently, to quantify the relative contribution of environmental and genetic factors to the FMF phenotype, Ben-Zvi and colleagues [79] compared the intra-pair clinical concordance of 10 mono and 7 dizygotic twins affected by FMF. The part played by environmental factors was compared the intra-pair clinical concordance of 10 mono and 7 dizygotic twins; the results showed that MEFV gene, genetic factors to the FMF phenotype, Ben-Zvi and colleagues [79] commented that the country of residence contributes to the severity of the disease more significantly than MEFV genotype. Similarly, Ozcan and colleagues [75] observed a more severe disease in Turkish children with FMF living in Turkey, compared to those living in Germany; as a possible explanation of these observations, it has been hypothesized the exposition to different strains of exogenous microbial triggers.

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Recently, to quantify the relative contribution of environmental and genetic factors to the FMF phenotype, Ben-Zvi and colleagues [79] compared the intra-pair clinical concordance of 10 mono and 7 dizygotic twins affected by FMF. The part played by environmental factors was determined by the phenotypic discordance of the monozygous twins, and the modifiers genes effect was determined by deducing the environmental effect, computed for monozygotic twins, from the phenotypic discordance of the dizygous twins; the results showed that MEFV gene, modifiers genes and environmental factors influence the FMF phenotype in an estimated ratio of about 6:1.5:1 respectively.

3. Our experience

Since 1990s the Periodic Fevers Research Centre of Catholic University of Sacred Heart of Rome had dedicated its attention to the diagnosis and treatment of patients with periodic autoinflammatory syndromes, accruing a patients experience of more than 1100 individuals and providing us an extensive clinical familiarity with these conditions.

Since 1998 to 2011, among all patients evaluated in our Centre for fever of unknown origin (FUO), 311 (163 M: 148 F) received certain diagnosis of FMF, configuring actually the largest case-series of FMF patients in Italy (data last updated: June 2011).

Clinical diagnosis is established by Tel Hashomer criteria; genetic testing by complete MEFV sequencing is performed routinely in all patients. In our case-series it was positive in 69% of patients.

Most patients come from the South (52.7%) and the Centre (23.5%) of Italy, probably because of the geographical position of Italy and the migratory changes of its population during the last 20 centuries; 13.5% of patients come from near countries such as Malta, Syria, Tunisia (Fig. 1).

The age of onset is below 20 years in 70% of patients, although only 21.4% of patients received the diagnosis within the 20 years of age. 56.5% of patients received the diagnosis between 21 and 50 years.

The diagnostic delay, commonly observed before the diagnosis, could be justified by the fact that FMF has been considered a very rare disease in Italy for long time [3]; furthermore, as previously underlined, diagnosis remains clinical, thus requires an awareness of FMF prevalence in the population as well as referee Centres dedicated to the diagnosis, treatment, and follow-up of these patients. In Italy the diagnostic delay, which was estimated to be 18 years in 2002, actually decreased to 13 years.

Because of diagnostic delay many patients underwent unnecessary surgery, without resolution of symptoms; appendectomy was the most frequent surgical intervention and was performed in 20% of patients.

In our case-series the most typical attack presents fever (93.23%) and abdominal pain (80.7%), followed by fever and articular pain (66.88%) or thoracic pain (40.19%). Only 18 patients (6.25%) have abdominal and thoracic pain, or abdominal and articular pain, or abdominal, thoracic and articular pain without fever. 48 patients have a compromised renal function and the damage goes from microalbuminuria to renal failure; 3 patients developed amyloidosis. Among minor manifestations we observed acute orchitis in 3.5% of cases. 72.1% of patients have 1 ≥ 2 attacks/month.

FMF attacks may be triggered by common factors such as cold exposure, emotional or physical stress, infections, vaccinations or menstruation [35]. More than 15% of female patients experience perimenstrual attacks; an increase of colchicine dosage five days before menstruation has been found useful to control the symptoms.

In 2009 we observed that genotype-phenotype correlations in Italian patients were also similar to those reported in literature: prevalent mutations in severe phenotypes were M694V (38.7%), M680I (14.2%) and M694I (6%) in homo- or heterozygosis, although in 20% of the cases no mutations have been detectable. In mild phenotypes the most frequent mutation was E148Q, but in 22% of patients no mutations have been found and in 35% of cases M694V, M680I, M694I have been detected.

The response to colchicine in terms of persistence/disappearance of frequency, length and intensity of attacks resulted as ‘good’ response in 68.0%; partial response in 27.5% while the non-responders rate was less than 5%. The collected data suggested that the characteristics of the Italian series are: less severe disease, low prevalence of amyloidosis, higher incidence of late onset, higher incidence of responders to colchicine [37]. Furthermore, given the wide clinical variability of the disease, clinical observation of cases not completely explainable with the current definitions of the FMF phenotypes are always more frequent.

Recently, we observed the case of a 14-year-old boy, son of a M694V homozygous male patient with FMF clinical onset at the age of 20 years, who presented to our attention with a history of arthritis occurred till the age of 6 years old, never associated with fever. An initial diagnosis of juvenile recurrent idiopathic arthritis was made, for which he did not receive any treatment.

At presentation he had been asymptomatic for arthritis since 8 years (from the age of 6 to 14), but laboratory exams revealed proteinuria on two occasions, never detected before (0.5 and 1 g of protein per 24 hours, respectively); the administration of colchicine at the dosage of 1 mg/day led to disappearance of proteinuria.

The analysis of MEFV revealed M694V single allele mutation. We could speculate that this patient experienced in the course of his life three FMF phenotypes: (1) the ‘FMF-like disease’ till the age of 6, when he presented episodes of arthritis without fever and/or any other manifestation of FMF; (2) partial phenotype III (because of carrying a single allele MEFV mutation), from 6 to 14 years of age, when he remained asymptomatic; (3) phenotype II at the age of 14, when ‘silent’ proteinuria appeared.

Similar cases reported in literature suggested that FMF could be considered a clinical condition, not yet completely defined; the insight into
complex clinical and genetic cases will add further details for the comprehension of the mechanisms of this disease.

4. Conclusions

As diagnosis of FMF is clinical, an accurate clinical history, together with the monitoring of disease activity through the parameters of inflammation (CRP, SAA, ESR, fibrinogen, white blood cell count), is pivotal for the clinician to determine a correct diagnosis in suspected cases of FMF.

The awareness of FMF prevalence in the population as well as the presence of referee Centers with expert-field clinicians, have a major role to achieve an early diagnosis and thus, to shorten the diagnostic delay in some Western European countries.

Early diagnosis contributes to avoid further unnecessary investigations and therefore, to decrease the costs of management of any FMF phenotype carriers. The subsequent cost recovery could be useful to strengthen genetic counselling and routine screening programs for members of affected families.

Take-home messages

- FMF is an autosomal recessive disease caused by MEFV gene mutations on chromosome 16
- The identification of MEFV mutations contribute to the different FMF phenotype diagnosis.
- MEFV mutation may aggravate the autoimmune disease course and influence the therapy.
- There are variable penetrance and expression of FMF, also in heterozygous subjects.

Conflict of interest statement

The authors deny any financial and personal relationships with other people or organizations that could inappropriately influence the content of this article.

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Fig. 1. Italian geographical distribution of familial Mediterranean Fever (FMF) patients. Most patients come from the South of Italy, probably because of migratory changes during the last 20 centuries [3]; 13.5% of patients come from other Mediterranean countries. Case-series of Periodic Fever Research Centre, Catholic University of Sacred Heart, Rome, Italy (data last updated: June 2011). P.t. patients.
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