FMF – clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature

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ABSTRACT

The last two years have been marked by many studies trying to better characterise the clinical features of FMF in children and proposal of new treatment for those who are resistant to colchicine. In addition, many studies tried to address the potential effect of genetic modifiers on FMF and the potential effect of MEFV mutations on other inflammatory diseases. The main points arose from these studies include a breakthrough in the therapeutic approach for FMF and the lack of consistency regarding the reciprocal effect of MEFV mutations on other diseases and the effect of genetic modifiers on FMF. The highlights of these studies, their potential clinical implications and the unmet needs, which are still to be addressed, are summarised in this review.

Introduction

Familial Mediterranean fever (FMF) is a hereditary disease characterised by recurrent attacks of fever and serositis (1). Although more than 15 years have passed since the landmark discovery that FMF is caused by MEditeranean FeVer (*MEFV*) mutations, our understanding of this fascinating auto inflammatory disorder continues to evolve as new information accumulates concerning its clinical manifestations and underlying biology. In this article we review developments concerning the pathophysiology and clinical presentation of FMF from the past two years. A systemic Medline search was performed using the term familial Mediterranean fever. Web of science was searched using the term familial Mediterranean fever and *MEVF* in the topic field. An overview of major advances is presented.

Recent insights into the clinical manifestations – in children and adults

FMF initially manifesting in childhood was the subject of studies performed by two groups (2, 3). In an Israeli study, the clinical manifestations in a majority of children with early as compared to late onset disease were found to be comparable. However, diagnosis was delayed significantly in children with early onset disease. The subgroup of patients diagnosed before the age of two years had the highest frequency of attacks, which typically consisted of fever as their sole manifestation, without serositis. Most of these very early onset patients were homozygous for the M694V mutation, and were of North African (Sephardi Jewish) extraction. These findings emphasise the need for vigilance among physicians who provide clinical care for children in FMF endemic areas. Otherwise diagnosis and treatment may be delayed significantly (2). Yalcinkaya *et al*. described FMF manifestations in a cohort of 83 children from Turkey with disease onset before three years of age. This study found that patients with early onset disease tend to have more severe symptoms, require relatively higher doses of colchicine to control attacks, and are often diagnosed after symptoms have been present for a considerable period of time (3). Although one might have expected that a positive family history of FMF would lead to early diagnosis in symptomatic children, these investigators did not find this to be the case. In both these studies a positive family history did not result in a shorter interval between onset of symptoms and initiation of therapy (2, 3).

Children presenting with attacks of fever alone comprised only a small pro-

portion (6%) of the Israeli paediatric cohort of 814 FMF patients (4). Although these children presented with fever alone, typical serositis attacks usually developed over time. It seems that this group of children comprises a snapshot in time of a disease in evolution. FMF attacks can occur following discontinuation or missing colchicine treatment. Nevertheless, such attacks may appear following triggers such as intercurrent infections, physical or emotional stress or menstruation. Yenokyan *et al*. reported an epidemiologic study of triggers in FMF conducted in a cohort of 104 Armenian FMF patients and aimed to quantify the effect of external triggers on FMF attacks (5). The number of stressful events was clearly associated with FMF attacks. The highest risk of stress-associated attacks was on the second day. A negative, statistically significant relation between consumption of high-fat–containing food items and the likelihood of developing FMF attacks was observed. The authors proposed that the possible reason for this finding could be the absence of appetite and low consumption of any food prior to FMF attacks. High levels of perceived stress were also associated with FMF attacks. Unexpectedly, in this study physical exertion and menstrual periods were not associated with FMF attacks.

Recent insights into FMF and pregnancy

The outcome of 480 pregnancies in a cohort of 132 women followed at our center for FMF at Hadassah Hebrew University Medical Center in Israel was evaluated. The outcome of pregnancies in FMF patients treated with colchicine, untreated FMF patients, and healthy controls did not differ with regard to frequency of congenital malformations, or early or late onset abortions. A statistically insignificant trend toward a better outcome was found favouring the colchicine- treated group. Thus it seems that colchicine treatment alone is not an indication for routine amniocentesis (6).In another prospective observational cohort study, the outcome of 238 colchicine exposed fetuses was compared to that of 964 foetuses born to mothers not exposed to teratogens. There were no significant differences in the rate of live births, miscarriages, stillbirths, or ectopic pregnancies between the groups. The rate of preterm delivery was higher and the median birth weight was lower in the colchicine-treated group (7). Taken together, these studies along with previous reports confirm that colchicine does not pose a major teratogenic risk when used in clinically recommended doses.

Ceraquaglia *et al*. retrospectively assessed fertility among 73 women with FMF using a questionnaire (8). The rate of infertility was twice as high as that reported in the general population. However, this finding might be explained by significantly delayed initiation of colchicine treatment in this group of women. In keeping with reports already cited, this study did not find an association between colchicine treatment and congenital malformations. Overall, these studies provide further support for the safe use of colchicine during pregnancy.

Recent insights into the influence of *MEFV* gene mutations on other diseases

The *MEFV* gene, associated with FMF, is localised to chromosome 16 and encodes a 781-amino-acid protein termed pyrin (9). This protein appears to play a pivotal role in the regulation of both inflammation and apoptosis (10, 11). Thus in addition to causing FMF, mutations in *MEFV* might potentially lead to a pro-inflammatory state, resulting in a subclinical inflammation in asymptomatic carriers (12). In addition it is possible that *MEFV* gene mutations might be a modifier gene in other inflammatory or autoimmune diseases. During the past two years a number of studies have evaluated this possibility in different human conditions. The prevalence of *MEFV* mutations in a cohort of 54 patients with ulcerative colitis from Turkey and the impact of these mutations on the clinical phenotype were reported. Mutations were identified in 35% of patients, and were associated with more severe disease phenotype, manifest as the need for higher doses of corticosteroids and the need for colectomy. Interestingly, the most frequently identified mutation was E148Q, which was present in almost 42% of patients who underwent colectomy (13). Since this mutation is known as the least penetrant FMF mutation, even claimed to be a polymorphism (14), the significance of this finding is uncertain. Uslu *et al*. performed a similar study in a small group of 33 children with inflammatory bowel disease (15). A third of this patients carried at least one *MEFV* mutation, and FMF was diagnosed in 7 (21%). *MEFV* mutations were not associated with specific bowel disease manifestations.

Approximately 3% of FMF patients develop vasculitis. By far the most common form is Henoch Schönlein Purpura (HSP). Previous studies have reported that MEFV mutations are more common in Middle Eastern children with HSP than in controls (16). Three recent studies have attempted to further define the relationship between *MEFV* mutations and HSP (17-19). Bayram *et al*. examined the frequency of *MEFV* mutations and the clinical and laboratory findings of 107 children with HSP from Turkey (17). One *MEFV* gene mutation was found in 30% of the cohort, and 14 patients (13.1%) carried 2 mutations, a significantly higher rate than in the healthy control population. *M694V* was the most commonly identified mutation and its presence correlated with certain clinical and laboratory findings in children with HSP. Acute-phase reactants were also higher in the carriers of *MEFV* mutations. Fifteen of these children were subsequently diagnosed with FMF, and colchicine treatment was initiated. Dogan *et al*. reported results of a similar study performed in a different area of Turkey involving 76 children with HSP. Among them, seven children (9%) carried two *MEFV* mutations, but in contrast to the previously mentioned study, the frequency of *MEFV* mutations was not increased, and was not associated with any specific disease manifestation. The authors concluded that *MEFV* gene mutations may not have any effect on the predisposition or clinical manifestations of HSP (18). Finally, in a group of 78 Chinese children with HSP, neither

the *M694V* nor *M680I* mutations were detected. However, *E148Q* mutation was found in 30.5% of patients (versus 13.5% of controls) and was associated with joint involvement, suggesting that this mutation may play a role in the development of HSP (19).

Behçet's disease (BD) is a chronic systemic auto inflammatory disorder prevalent in the Mediterranean countries, whose features include multisystemic vasculitis involving vessels of different size and type. The influence of *MEFV* mutations on susceptibility to this disease and on its clinical manifestations has been the subject of several recent studies (20-23). The rate of *MEFV* mutations in 100 BD patients and 100 healthy controls was examined in a study from Turkey, and found to be comparable in the two groups. *MEFV* mutations were not associated with specific clinical manifestations of disease (20). Similar results were reported in a study of BD patients from Northern Israel (22). In contrast to these results, in a small study involving 53 Azeri Turkish patients with BD from Iran, a higher rate of *M694V* and *M680I* mutations was found in the patients as opposed to the control group, suggesting that *MEFV* mutations might be a susceptibility factor for BD in this population. However, in this study mutations were not associated with specific clinical or laboratory manifestations of BD (21).

Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) syndrome is a non-hereditary periodic fever syndrome of unknown cause. Berkun *et al*. studied the effect of *MEFV* mutations on the clinical and laboratory manifestations and on the disease course in a large cohort of 124 children with PFAPA from Israel. The major finding in this study was that carriage of a *MEFV* mutation may favourably affect the PFAPA phenotype, as carriers had shorter and less regular attacks, a lower rate of aphthae during attacks, and respond to a lower dose of corticosteroids. The mechanism of the "protection" conferred by MEFV mutation in PFAPA has not been elucidated (24).

The presence and clinical relevance of *MEFV* gene mutations in a group of 70 SLE patients from Israel were recently reported. The rate of carriers of mutations was not increased in SLE patients as compared to controls. However patients with mutations had a higher rate of pleuritis and fever, and a lower rate of renal involvement as compared to patients without mutations. This suggests that MEFV mutations might modify the SLE phenotype (25).

A clinical association between Ankylosing Spondylitis (AS) and FMF has been reported previously. Cosan *et al*. examined the possible relation between common *MEFV* mutations and AS in a group of 193 Turkish patients with AS and 103 controls. The rate of mutations was higher in patients as compared to controls. This difference was more prominent for the more penetrant exon 10 mutations, and especially for the most severe *M694V* mutation. Ankylosing spondylitis is strongly associated with HLA-B27 antigen. In this study *MEFV* gene mutations, especially exon 10 mutations, were more frequent in HLAB27-negative patients with AS. *MEFV* mutations were suggested to be a non-HLA genetic susceptibility factor for AS (26). Sixty-two patients with AS, 50 healthy control subjects and 46 patients with rheumatoid arthritis (RA) were assessed for the presence of *MEFV* variants in another study from Turkey. In concordance with previous report, an increased frequency of *MEFV* mutations was found in AS patients compared with healthy and RA controls. This result was mainly due to a higher prevalence of the more severe *M694V* mutation. Neither *M694V* nor any other *MEFV* mutation correlated with measures of disease severity (27).

The rate of *MEFV* mutations was comparable to that of controls in a group of Turkish patients with rheumatoid arthritis (28) and rheumatic heart disease (29). In both studies, the carrier rate was not associated with specific disease manifestations.

In a small group of 53 patients with multiple sclerosis (MS) the rate of *MEFV* mutations was higher in patients then in controls. Moreover, the presence of mutations was associated with more severe disease and relapsing course, suggesting that *MEFV* mutations may predispose to MS (30). Nine patients with both MS and FMF were identified among 12000 FMF patients registered in the Tel Hashomer FMF Center. This corresponds to a calculated MS incidence of 0.075%, which is twice as high as the rate expected in the general population. Consistent with the previously discussed study, homozygosity for the *M694V* mutation was associated with a more severe disease and progressive form of MS (31).

In summary, preliminary data suggest a possible disease modifying effect of *MEFV* mutations on some inflammatory diseases, in particular AS and MS. Nevertheless, small sample size and inconsistent results make interpretation of studies involving other inflammatory diseases very uncertain.

Recent insights into the influence of genetic modifiers on FMF

There is wide clinical variability in FMF that is only partially explained by allelic heterogeneity. Classical FMF may be seen in carriers of only a single *MEFV* mutation, while on the other hand carriers of two mutations may exhibit no overt signs of disease (32). These observations suggested important role for additional disease modifying factors, including possibly modifier genes, on the clinical expression of FMF.

FMF and Crohn's disease (CD) association have been investigated in several studies previously, and *MEFV* mutations were reported to affect the phenotype of CD (33). In a study from Israel, mutations in NOD2/CARD15 gene, a major susceptibility gene for CD, were detected in a comparable rate in a group of children with FMF and their controls (34). However, FMF patients carrying a NOD2/CARD15 mutation had a more severe disease and a higher rate of colchicine resistance as compared to patients without mutations.

The frequency of mutation (R92Q variant) in a gene underlying another auto inflammatory disease, the tumour necrosis factor receptor–associated periodic syndrome (TRAPS), was compared in FMF and control patients in another study from Israel. The R92Q variant was not over-represented in FMF patients as compared to controls. Thus, despite the fact that TRAPS and

FMF share common biochemical pathways, the authors have found no evidence for an interaction between these two genes (35).

Ben-Zvi *et al*. attempted to gain information concerning the relative contribution of environmental and background genetic factors to the FMF phenotype by studying 10 monozygotic and 7 dizygotic twin pairs, each affected by FMF. In 4 pairs (3 of which were monozygotic) there was a full intra-pair concordance for all phenotypic parameters. There was full intra-pair concordance in all twin sets with respect to FMF associated diseases. In addition, all monozygotic twins were fully concordant for erysipelas attacks, exertional leg pain and proteinuria/amyloidosis, while dizygotic twins were not fully concordant for any of the disease manifestations. In general, concordance for all manifestations among the twins was greater than 80%, suggesting that the effect of environmental factors on the FMF phenotype is relatively small (36).

FMF in different countries and populations-genetic studies.

FMF is highly prevalent in countries along the eastern Mediterranean coast, affecting mainly Sephardi Jews, Armenians, Turks and Arabs. Other ethnic groups living in the region such as Druze, Greeks and Italians are also affected relatively frequently. The clinical, genetic and demographiccharacteristics of FMF from non-endemic areas have recently been reported (37-39).

Molecular evaluation of 458 patients referred for clinically suspected FMF from one center in Scandinavia was described. Almost all mutation positive patients were of none Scandinavian descent. None of the three Scandinavian patients in whom mutations were identified had typical FMF manifestations (37).

The recent report of the Chilean experience with periodic fever syndromes shows that FMF is a very rare disease in that country, as only 8 FMF patients were diagnosed in six medical centers during four-year period (38). In a multicenter study from Brazil which included 22 paediatric rheumatology services, only 17 children with FMF were identified (39).

Small group of 38 patients clinically diagnosed with FMF from the Suez Canal region of Egypt were tested for the five most common MEFV gene mutations. No mutations were found in 40% of these patients, and the mutation most commonly detected in this region of the world, M694V, was not found in any patient (40). An even higher rate of mutation negative FMF was reported in a cohort of 120 unrelated Moroccan patients. Among patients in whom *MEFV* mutations were identified, *M694V* and *M694I* where the most common, while *V726A* , the most commonly identified mutation among Arabs from the Middle East region, was not found in this population comprised of individuals of Arab and Berber origin (41).

Ait-Idir D *et al*. examined the spectrum of *MEFV* mutations and mutation carrier frequency in an Algerian population by re-sequencing the promoter region and the entire coding sequence along with all exon-intron boundaries. Similar to other Arabic populations, no *MEFV* mutation was identified in more than half of the FMF patients, even using this comprehensive strategy. M694I was the most commonly identified mutation, while *V726A* was absent in both the patient and control groups. Interestingly, the clinical picture was fairly similar among patients with zero, one or two mutations (42).

Different results were found in a study of 136 FMF patients from Cairo area of Egypt. All patients carried at least one *MEFV* mutation, and more than half carried two or more mutations. *V726A* was the most commonly found mutation. Five founder mutations accounted for the vast majority of cases of FMF, making the analysis of other mutations not cost effective (43).

Using a questionnaire among Armenian schoolchildren from Istanbul Turkey, the prevalence of FMF was found to be 86/10000. Very high carrier rate of *MEFV* mutations was found among the Armenians (36%) compared to that among non-Armenians (44).

It seems that FMF is quite rare in South American countries. Furthermore, the relatively high percentage of FMF patients without mutations reported in some studies raises questions regarding the reliability of the FMF diagnosis.

Recent insights into the treatment of FMF

In this journal, Ozturk and colleagues have recently reviewed the medical literature concerning treatment of FMF with emphasis on newer therapeutic agents and management of patients resistant to or intolerant of colchicine (45). Colchicine has been the drug of choice for treatment of FMF since 1972 (46). Its most commonly observed side effects are gastrointestinal. We recently reported the results of a one year follow up of 153 consecutive pediatric patients with FMF (47). Approximately 15% developed diarrhoea, usually shortly following the initiation of treatment and improving later. Only four children required a dose reduction because of this side effect. Another commonly observed finding was a mild and transitory elevation in hepatic transaminases which occurred in more than 10% of patients usually associated with an inter-current illness. Transaminase levels spontaneously normalised in all but two patients. No other adverse effects were observed. All patients reported a good response to colchicine therapy, with less than two attacks during the year. All patients had normal test of renal function and none had proteinuria. No patient required discontinuation of treatment. We conclude that colchicine is safe for use in FMF, even in infancy.

In another recent study, the impact of disease severity and mutation load on the growth and body mass index (BMI) of children with FMF was evaluated (48). Eighty-six children were included in the study 49 girls and 37 boys. Of these, 77 received colchicine therapy. Compared to the general population target heights of children with FMF were significantly lower. The Z scores of BMI were not different from that of age matched controls. The authors of this study also found a significant difference between Z scores in target heights among children bearing two MEFV mutations compared to those with only one mutant allele, and this difference was independent of FMF severity. In this

study, heights but not BMI was reduced in children with FMF after six years of disease despite colchicine therapy, suggesting that FMF mutations may lead to significant growth impairment. On the other hand Özçakar *et al*. reported a positive effect of colchicine treatment on physical growth in a group of 50 children with FMF who took the medication for more than one year (49).

Terkeltaub *et al*. examined *in vivo* effects of concomitant treatment with colchicine and p450 inhibitors including cyclosporine, ketoconazole, ritonavir, clarithromycin, azithromycin, verapamil and diltiazem on the pharmacokinetics of colchicine. Significant interactions were observed when single doses of colchicine were administered with most of the examined p450 inhibitors, except azithromycin. Recommended dose reductions of 33 to 66% for treatment of acute gout attack and 50 to 75% for prophylaxis where calculated when these agents are used together. Based on these findings the authors recommended a reduction of colchicine dose when used in combination with calcium channel blockers such as verapamil and diltiazem, while the dose of colchicine need not be adjusted when it is used in combination with azithromycin (50).

We performed a study to define the appropriate dose for colchicine in children with FMF by determining the steady-state pharmacokinetics of this medication after multiple oral doses in children as compared to adults with FMF. The data were used to determine optimal starting doses for colchicine in paediatric FMF patients. Similar rates of absorption and exposure across all pediatric and adult age groups were observed, indicating that administration of half the adult daily dose in children ages 2 to 4 years, and two thirds the adult daily dose in ages 6 to 12 years or most appropriate. For children 12 years or above adult doses can be used. In the 4 to 6 year old group the administered dose which was two thirds of the adult dose provided exposures 30% higher than in adults. Therefore we recommend that the starting dose in this age group be reduced to half the adult dose, that is 0.6 mg per day (51).

Ozcakar *et al*. describe long-term treatment of four young FMF patients with amyloidosis using infliximab. Infliximab was effective in controlling gastrointestinal manifestations and protracted arthritis and had a favourable impact on nephrotic syndrome (52).

Ozen *et al*. describe a group of six FMF patients with resistance to colchicine and inadequate response to TNF-antagonists who were successfully treated using a short acting interleukin (IL)-1 receptor antagonist (anakinra) (53). Seven patients from France were treated using anakinra and/or canakinumab, a human monoclonal anti-IL-1β antibody. Six of seven patients had a rapid and salutary response to IL-1 antagonists (54). These preliminary data indicate that IL-1 blockade is a promising approach for treatment of FMF patients who are resistant to or intolerant of colchicine. It seems that colchicine is still an effective and preferred medication for FMF. Nevertheless, in cases of colchicine intolerance or resistance there are a number of promising biological agents which may relieve our FMF patients suffering.

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