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Familial Mediterranean fever-associated diseases in children

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Summary

Background: MEditerranean FeVer (MEFV) gene encodes for the pyrin protein and a mutated pyrin is associated with a prolonged or augmented inflammation. Hence, various diseases were reported to be associated with familial Mediterranean fever (FMF) or carriers of *MEFV* mutations. However, systematic evaluation of all associated diseases in children with FMF has not been done previously.
Aim: The aim of this study was to investigate the frequency and type of FMF-associated diseases in children.
Design and Methods: Files of FMF patients who had been seen in two reference hospitals in Ankara, in the last two years, were retrospectively evaluated. Patients with FMF and concomitant diseases were included to the study.
Results: Among 600 FMF patients, 77 were found to have a concomitant disease (12.8%). Thirty patients (5%) had vasculitis; 21 (3.5%) had juvenile idiopathic artritis (JIA); 7 (1.16%) had inflammatory bowel disease (IBD) and 19 had other diseases including 5 patients with isolated sacroiliitis. Overall, 13 (2.17%) patients had sacroiliitis in our cohort. The most frequent mutation was M694V/M694V (44%) and 81% of the patients had at least one M694V mutation. Majority of the patients (74%) developed associated diseases while they were not receiving colchicine therapy.
Conclusions: Certain inflammatory diseases including vasculitis, chronic arthritis and IBD were more frequently detected in patients with FMF during childhood. M694V mutation is a susceptibility factor for associated diseases. In countries where FMF is prevalent, clinicians dealing with FMF and other inflammatory diseases should be aware of these associations.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent irregular self-limited attacks of fever and polyserositis accompanied with increased acute phase reactants (AFRs).[1] In 1997, two independent groups defined the MEditerranean FeVer (*MEFV*) gene responsible for the disease and it was a major milestone in better understanding and treating this auto-inflammatory disease.[2,3] *MEFV* gene encodes for the pyrin protein which belongs to a class of proteins involved in the regulation of apoptosis and inflammation. A mutated pyrin is associated with loss of the delicate control of the inflammatory pathways, probably via apoptosis pathway which results in a prolonged or augmented inflammation that predispose these patients and carriers of the *MEFV* mutation to have a pro-inflammatory state.[1] Chronic subclinical inflammation, manifested by elevated AFRs during clinical quiescence,

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may be found in 30–63% of the cases and this would be especially marked in untreated patients.[1,4,5] Furthermore, this inflammatory syndrome is also a facilitating factor in the manifestation of associated inflammatory diseases like vasculitis. Hence, various diseases were reported to be associated with FMF or carriers of *MEFV* mutations in the literature.[6] However, systematic evaluation of all associated diseases in children with FMF has not been done previously. Accordingly, the aim of this study was to investigate the frequency and type of FMF-associated diseases in pediatric patients.

Materials and methods

Files of FMF patients, who had been followed in two reference hospitals within the last two years, were retrospectively evaluated. Patients with FMF and concomitant diseases were included in the study. The diagnosis of FMF was based on the presence of clinical criteria or atypical clinical findings with two mutations.[7,8] The diagnoses of FMF associated diseases were made according to the internationally recognized criteria[9–13] and inflammatory bowel disease (IBD) was diagnosed according to clinical and laboratory features.[14] For genetic analysis, at least six predominant mutations (p.M694V, p.M680I, p.M694I, p.V726A, p.K695R, p.E148Q) in the *MEFV* gene were studied. Exon 10 of the *MEFV* gene was screened using direct sequencing of the PCR amplified fragments. The p.E148Q mutation was analyzed with a previously reported PCR restriction fragment length polymorphism protocol.[15,16] The study was approved by the Ethics Committee of Ankara University.

Results

Among 600 FMF patients, 77 (45 F, 32 M; mean age 15.02 ± 5.21 years) were found to have a concomitant disease (12.8%). Demographic and clinical features of the subjects are seen in Table 1. Mutation analysis was performed in 73 of the 77 patients. Thirty-four (46.6%) patients had homozygous, 20 (27.4%) had compound heterozygous and 15 (20.5%) had heterozygous mutations. Four patients (5.5%) had none of the screened mutations. The most frequent mutations were M694V/M694V (n = 32), M694V/- (n = 11), M694V/M680I (n = 11) and M694V/V726A (n = 5). Overall, 59 of the 73 patients (80.8%) had at least one M694V mutation. FMF diagnosis was done prior to the concomitant disease in 20 (26%); concurrently in 26 (33.8%) and afterwards in 31 (40.2%) patients. Classical FMF attacks were present in 68 patients (88%); the remaining 9 patients had atypical symptoms but had 2 mutations.

Thirty patients (5%) had vasculitis; 21 (3.5%) had juvenile idiopathic artritis (JIA); 7 (1.16%) had IBD and 19 had other diseases including 5 patients with isolated sacroiliitis (Table 2). Among vasculitis patients, 19 had Henoch-Schönlein Purpura (HSP), 9 had polyarteritis nodosa (PAN) and 2 had unclassified vasculitis. Two vasculitis patients had also sacroiliitis (1 HSP, 1 PAN), one HSP patient had acute lymphoblastic leukemia and one PAN patient had amyloidosis. Among 21 JIA patients; 8 had oligoarticular, 4 had polyarticular rheumatoid factor (−) JIA, 7 had enthesitis-related arthritis (ERA) and 2 had psoriatic arthritis (PsA). Sacroiliitis was present in four ERA patients (3 had HLA B27 positivity) and one PsA patient. Uveitis was detected in four JIA patients (two had ERA, two had oligoarticular JIA). Among patients with IBD; five had Crohn disease (CD), two had ulcerative colitis (UC). One of the CD patients had amyloidosis and one UC patient had sacroiliitis. Five patients had isolated sacroiliitis and all of them had at least one M694V mutation. All patients with acute rheumatic fever (ARF) had carditis.

Table 1. Demographic and clinical features of the study population

	n = 77 (%) Mean ± SD
Sex	
Male	32 (41.6)
Female	45 (58.4)
Consangiunity	16 (20.8)
Family history of FMF	43 (55.8)
Age at FMF onset (months)	55.11 ± 47.08
Age at associated disease onset (months)	95.51 ± 53.77
Age at FMF diagnosis (months)	95.03 ± 48.08
Age at associated disease diagnosis (months)	101.29 ± 53.77
Attack frequency before colchicine (/year)	15.87 ± 14.73
Attack frequency after colchicine (/year)	3.56 ± 7.42
Clinical findings of FMF	
Fever	58 (75.3)
Abdominal pain	62 (80.5)
Chest pain	23 (29.9)
Arthritis	51 (66.2)
Arthralgia	49 (63.6)
ELE	13 (16.9)
Leg pain	36 (46.8)
Heel pain	26 (33.8)
Presence of two mutations (n = 73)	54 (74)
M694V positivity (n = 73)	59 (80.8)
M694V homozygosity (n = 73)	32 (43.8)
Final colchicine dosage (mg/m^2/d)	1.01 ± 0.24

FMF, Familial Mediterranean fever; ELE, Erysipelas like erythema.

Table 2. FMF-associated diseases

Associated diseases	n = 600 (%)
Vasculitis	30 (5)
JIA	21 (3.5)
IBD	7 (1.16)
Sacroiliitis (isolated)	5 (0.83)
Asthma	4 (0.66)
ARF	3 (0.5)
Behçet disease	1 (0.16)
SLE	1 (0.16)
Optic neuritis	1 (0.16)
Membranoproliferatif glomerulonephritis	1 (0.16)
C1q nephropathy	1 (0.16)
Migraine	1 (0.16)
Hereditary spherocytosis	1 (0.16)

Discussion

This study confirmed that considerable number of patients with FMF had accompanying diseases during the childhood period. Especially, certain inflammatory disorders including vasculitis, chronic arthritis and IBD were more frequently detected in our FMF patients.

The major role of pyrin is the (up or down) regulation of caspase-1 activation, and the inflammatory phenotypes of FMF are induced by IL-1β and NF-κB, which are abnormally activated by FMF-associated mutations.[17] Interestingly, it was also shown that obligate carriers of FMF had increased levels of AFRs, confirming the pro-inflammatory phenotype among heterozygous

FMF carriers.[4] This proinflammatory state both in FMF and in asymptomatic carriers of *MEFV* mutations has been suggested to influence the expression of other inflammatory disorders. Diseases that may be associated with FMF were previously evaluated as a part of national multicentric study. Tunca *et al.*[18] detected concomitant diseases in 13.8% (377 of 2716) of adult and pediatric patients. We had also detected other diseases in 12.8% of our study group that only included children. As majority of the patients (74%) developed associated diseases while they were not receiving colchicine therapy we could not interprete whether colchicine therapy may prevent the occurence of associated diseases in these patients.

It was suggested that M694V homozygosity is related with more severe disease and less response to colchicine therapy.[19,20] Interestingly, frequency of homozygous M694V mutation was 44% and M694V allele frequency was 62.3% (91/146) in our study. In the largest series reported from our country, the frequency of homozygous M694V mutation and M694V allele were 28 and 51.4%, respectively.[18] Consequently, it seems that M694V mutation is a susceptibility factor for associated diseases

The most common associated disease was vasculitis (5%) in our cohort. In previous studies, the prevalence of PAN in FMF patients was reported to be about 1% while its prevalence in the general population was 4–6/100.000.[21,22] Although HSP prevalence in the general population varies from 0.05 to 0.8%, its prevalence in FMF patients varies between 2.6 and 7%.[21–23] We also found PAN in 1.5% and HSP in 3.16% of our study population. In recent years, the prevalence of *MEFV* mutations in patients with PAN/HSP without any symptoms of FMF has been investigated and the alterations in the *MEFV* gene were reported as important susceptibility factors for the development of these two vasculitides.[24,25] Although many investigators found an increased frequency of *MEFV* mutations in cohorts of patients with Behçet Disease,[26,27] the possible association between FMF and BD is, however, not as clear as the association between PAN and HSP. We had only one patient with BD in our cohort supporting this weak association during childhood period.

The second most common concomitant disease was JIA (3.5%) in the study group and it was found to be significantly higher than the general population (6.4/10 000 in our country).[28] However, it is hard to put forward a clear association between JIA and FMF. As it is well known, arthritis is a cardinal and common feature of FMF. Although recurrent monoarticular arthritis is the most common type, subacute and chronic arthritis can be found in 5% of FMF patients. The coexistence of FMF, JIA and PsA has rarely been reported in the literature.[29,30] Association of FMF with ankylosing spondylitis (AS) was also described in previous reports and Langevitz et al were the first to suggest that spondyloarthropathy (SpA) be included in the musculoskeletal manifestations of FMF.[31] Prevalence of *MEFV* mutations in patients with JIA/AS without any symptoms of FMF was investigated in also few studies and mutation frequency was found to be higher than the healthy population.[32,33] Tunca *et al.*[18] also detected chronic inflammatory arthritis in 1.3% and seronegative spondylarthritis in 2.3% of patients with FMF. Thus, although chronic arthritis can be a feature of FMF, this study and previous reports suggest that the various JIA subtypes are possibly associated with FMF. Recently, Eshed et al[34] suggested that FMF and spondyloarthritides share a common inflammatory pathogenesis which may be mediated by M694V mutation and that it might predispose to SpA. Moreover, patients with FMF are considered to have an increased risk of isolated sacroiliitis, which was especially reported in adult patients.[35] We had also 5 patients with isolated sacroiliitis and overall 13 (2.17%) patients had sacroiliitis in our cohort including patients with other diseases. Considering the rarity of chronic arthritis especially sacroiliitis in children, our study suggested that FMF particularly M694V genotype is strongly associated with sacroiliitis.

IBD was accepted as a possibly associated disease with FMF. It was detected in 1.16% of our patients. Similarly, Cattan *et al.*[36] evaluated IBD prevalence among 300 patients with FMF and found 3 patients. The authors emphasized high frequency association when compared with the IBD prevalance of 120/100 000 in the general population. Fidder *et al.*[37] identified 7 patients with concomitant CD and FMF among 4978 FMF patients—a higher prevalence than the general Israilian population (50.6/100 000). Although we do not know the IBD prevalance in children in our country, considering the fact that only 25% of all IBD patients were younger than 20 years of age,[38] 1.16% is a significantly high rate. According to our study it seems that this disease is definitely associated with FMF in children.

The frequency of ARF was 0.5% in our study, while Tunca *et al.*[18] detected ARF in 5% of their cohort. However, they reported erroneous diagnosis of ARF in most of their patients and believe that these were true FMF arthritis attacks. Although Tutar *et al.*[39] found approximately four times greater *MEFV* mutation prevalence in patients with rheumatic heart disease than in the normal population in Turkey, our results revealed similar frequencies of ARF in FMF patients and the normal population. We had one patient with systemic lupus erythematosus (SLE) but we thought that it was a coincidence.

The retrospective nature of the study, confinement to a group of Turkish children and the fact that our hospitals are reference centers could be limitations of this study. Multicentric international studies comprising patients from different ethnic populations, including countries where FMF is not frequent are indisputably needed to confirm our findings. On the other hand, recently Ben-Chetrit *et al.*[40] suggested that vasculitis and spondyloarthritides should be considered as an atypical manifestation of FMF rather than a co-existing additional separate clinical entities and renamed them as *MEFV* or pyrin associated diseases. This aproach seems to be reasonable but more studies are needed in this field.

In conclusion, various inflammatory diseases are related with FMF during the childhood period. In countries where FMF is prevalent, clinicians dealing with FMF and other inflammatory diseases should be aware of these associations for prompt management of these patients.

Conflict of interest: None declared.

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