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FAMILIAL MEDITERRANEAN FEVER COEXISTED DISEASES AND CONDITIONS A CASE SERIES STUDY

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ABSTRACT

FMF is an auto inflammatory disease mainly associated with MEFV gene mutations. Until recently, the MEFV gene was considered to be responsible only for FMF. However, it is now known that it can also be associated with other clinical conditions. This study represents FMF-associated disease among our FMF clinic patients. 400 patients who had FMF based on the clinical and or MEFV gene study enrolled to study. Patients if needed were analyzed for the 12 most common MEFV mutations (P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H, E148Q) by a reverse hybridization assay. Any co-existed disease was confirmed by related subspecialist team. Among the patients Fifty two (13%) had associated disease.28 patients were male and 23 patients were under ten years old. Five patients had no MEFV mutations and overall, there were 82 MEFV gene mutations. The most common were M694V (30%), E148Q (22%), V726A (17%), M680I (1%) and M694I (0.07%) respectively. Rheumatologic disorders were the most common co-exist disease, then followed by GI and CNS disorder. Some rare disease such as TTP, Growth hormone deficiency, MS, ascitis and leiden factor V deficiency have been shown. This homozygote mutations (M694V-M694V) were associated with ascitis, orchitis and pericarditis. Associated disease in FMF usually presents in patients with MEFV gene mutations particularly with these five mutations M694V, E148Q, V726A, M680I, and M694I. Rheumatologic, gastrointestinal and CNS disorders are common co-existed disease.

INTRODUCTION

FMF is an autosomal recessive disease mainly affecting ethnic groups living around the Mediterranean Sea: Jews, Armenians, Turks, Arabs, and Druse [1] with a prevalence ranging from 1/200 to 1/1000. [2]

First manifestations have usually appeared by 4 years of age and are characterized by recurrent, self-limiting attacks of fever and polyserositis. Serositis presents as abdominal and chest pain. [3]

Arthritis of the large joints and, less frequently, pericarditis and painful scrotal swelling or epididymitis can be found. Chronic destructive arthritis and severe prolonged myalgia or myositis due to vasculitis may occur [4, 5].Frequency of attacks is highly variable and asymptomatic periods that last a few years have been reported. Laboratory evaluation shows an acute phase response that can persist in asymptomatic periods [6, 7]
Until 1998, the diagnosis of FMF was based on clinical grounds alone. The Tel Hashomer criteria form the basis of the clinical diagnosis.[8]

In 1992, the gene responsible for FMF, MEFV, was found to reside on the short arm of chromosome 16. [9]Five years later, the MEFV gene locus was discovered that encode the protein named pyrin.[10] This protein probably has an important role in the down regulation of inflammation.

In populations with a high FMF prevalence (Jewish, Armenian, Arab, Turkish) clinical criteria have a high specificity of 95–99% for the presence of genetically

confirmed FMF, but sensitivity is much lower. In a recent study, FMF was genetically confirmed in 60% of patients that fulfilled clinical criteria in Mediterranean origin, while was much lower in patients from other areas (10%) [11].

Patients with Mediterranean ancestry that fulfill FMF criteria but negative results for one or two MEFV mutations are usually considered as 'clinical' FMF. [12].

Until recently, the MEFV gene was considered to be responsible only for FMF. However, it is now known that it can also be associated with other clinical conditions. Additionally, various atypical presentations have been reported in which the clinical features were not typical of FMF but with positive results of MEFV gene mutations, and which, in many cases, resulted initially in misdiagnoses. [13]

Coexistence of FMF with rheumatoid and autoimmune conditions like Sjögren's syndrome. [14]seronegative spondyloarthropathy [15] Behcet's disease [16] juvenile idiopathic arthritis [17, 18] rheumatoid arthritis(RA) [19] and inflammatory bowel disease (IBD)have been reported.

It is also possible that mutations in the MEFV gene could be an additional susceptibility genetic factor in certain other disorders and it may participate in the manifestation of inflammatory disorders other than FMF. [13]

This study represents associated and co-exist disease and atypical conditions with FMF patients in our FMF Clinic. (WWW.FMFIRAN.IR)

METHODS

400 patients who had FMF based on the clinical Tel – Hashomer criteria and or MEFV gene study enrolled to this study at FMF clinic in northwest of IRAN (Ardabil). Among them fifty two patients had associated disease that had been confirmed by related clinic and subspecialist. The patients were investigated for 12 known common FMF mutations by a reverse hybridization assay (FMF Strip Assay, Vienna lab, Vienna, Austria) according to the instructions provided by the manufacturer. About 10 ml of peripheral blood was used for extracting DNA by boiling – based method. In a first step, exons 2, 3, 5 and 10 were amplified for each patient in a single, multiplex PCR, with primers supplied by the noted RDB kit. The thermocycling program of amplification was 35 cycles including (94c for 15 sec,58c for 45 sec, and 72c for 45 sec) and a final extension at 72 c for 7 min. Agarose electrophoresis revealed the accuracy of amplification by detecting four amplified DNA fragments including 206, 236, 295 and 318 bp. Biotinylated PCR products were selectively hybridized to a test strip presenting a parallel array of allele-specific oligonucleotide Probes. Thereby the twelve common mutations E148Q in exon 2, P369S in exon 3, F479L in exon 5 and M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H in exon 10 were determined.

Statistical analysis was performed using SPSS V 15.0, and P value 0.05 was accepted as statistically significant if needed.

RESULTS

Among the patients Fifty two (13%) had associated disease and atypical manifestations.28 patients were male and 23 patients were under ten years old. Five patients had no MEFV gene mutations. Table.1and 2

There were 82 MEFV gene mutations. The most common were M694V (30%), E148Q (22%), V726A (17%), M680I (1%) and M694I (0.07%) respectively and other mutations (R761H, P369S, A744S, M694L, R202Q) were the rest.

Rheumatologic disorders were the most common co-exist disease, (Arthritis, PFAPA, Vasculitis), followed by GI (Peptic ulcer, cholelithiasis) and CNS (migraine, seizure ,MS) disorder. Some rare disease such as TTP, Growth hormone deficiency, MS, ascitis and leiden factor V deficiency and retinitis pigmentosa have been shown. JIA had M680I- V726A mutations and in RA M694V-M680I or V726A mutations have been shown. This homozygote mutations (M694V-M694V) were associated with idiopathic ascitis, orchitis and pericarditis. There was not meaningful association between MEFV mutations and some specific disease.

Table 1. Autoinflammatory, Inflammatory, Autoimmune and Vasculitis Disorders and conditions co-existed in our patients

No.	Age	Sex	MEFV Gen. Mutations	Co-Exist condition
Auto inflammatory conditions				
1	7	M	M680I-Wt (?)	PFAPA
2	18	M	M694V- Wt (?)	PFAPA
3	6	F	M694V- Wt (?)	PFAPA
4	5	F	E148Q- Wt (?)	PFAPA
5	9	F	V726A -Wt (?)	PFAPA
6	11	M	R761H-M694I	PFAPA
Inflammatory joints disease				
7	14	F	M680I- V726A	JIA (Oligo A.)
8	45	M	M680I- M694V	RA
9	16	F	M680I- V726A	JIA (Oligo A.)

10	19	F	M694V- V726A	RA
Organic-specific autoimmune disease				
11	7	F	E148Q-V726A	(IBD) UlCerative colitis
12	38	M	M680I-Wt (?)	(IBD) Crohn Disease
13	10	M	Wt (?)-Wt (?)	Alopecia totalis
14	37	F	Wt (?)-Wt (?)	Multiple Sclerosis(MS)
15	11	M	E148Q-P369S	Celiac
16	21	M	R761H-V726A	TTP (Thrombotic Thrombocytopenic Purpura)
Systemic Vasculitis				
17	5	F	E148Q- Wt (?)	(IgAV) Henoch–Schönlein purpura
18	7	F	E148Q-V726A	Behcet Disease
19	29	M	M694V- E148Q	Protracted febrile myalgia syndrome (PFMS)
20	20	M	M680I-V726A	(IgAV) Henoch–Schönlein purpura
Non-clarified associated serositis				
21	12	M	M694V- V726A	Pleuritis (Recurent Idiopathic /FMF related)
22	13	M	M694V- M694V	Pericarditis (Recurent Idiopathic/FMF related)
23	49	F	M694V-M694V	Ascites (Idiopathic /FMF related)
24	46	F	M694V- M694V	Ascites (Idiopathic /FMF related)
25	23	M	M694V-M694V	Orchitis(Idiopathic recurrent /FMF related)

Table 2. Non-inflammatory conditions found in our patients

No.	age	sex	MEFV Gen. Mutations	Co-Exist conditions
Hematologic, Hormonal ,Metabolic conditions				
26	12	F	E148Q- Wt (?)	Thalassemia
27	8	F	E148Q-M694V	Thalassemia
28	43	M	Wt (?)-Wt (?)	Hyperlipidemia
29	45	F	M694V- Wt (?)	Infertility(Idiopathic)
30	9	F	M694V-M680I	Growth hormone deficiency
31	45	M	M680I- M694V	LIDEN Factor Deficiency
32	21	M	R761H-V726A	Pancytopenia
33	41	F	E148Q- V726A	Hypothyroidism(Idiopathic)
34	25	F	M694L-R202Q	Retinitis pigmentosa
Common non inflammatory disease/Conditions				
35	22	F	E148Q- P369S	Peptic Ulcer Disease
36	8	F	E148Q-M694V	Peptic Ulcer Disease
37	41	M	Wt (?)- Wt (?)	Peptic Ulcer Disease
38	13	M	Wt (?)- Wt (?)	Peptic Ulcer Disease
39	47	F	M694I- V726A	Peptic Ulcer Disease
40	10	F	E148Q- P369S	*Cholelithiasis*
41	9	M	E148Q- P369S	*Cholelithiasis*
42	11	M	M694I- M694I	*Cholelithiasis*
43	7	M	M680I- V726A	*Cholelithiasis*
44	12	F	E148Q- Wt (?)	*Migraine*
45	8	F	A744S- Wt (?)	*Migraine*
46	11	M	E148Q- Wt (?)	*Migraine*
47	15	F	M694V- Wt (?)	Seizure(idiopathic)
48	11	M	R761H-M694I	seizure(idiopathic)
49	8	M	M694V- V726A	Seizure(idiopathic)
50	5	M	E148Q-A744S	Vesicoureteral Reflux
51	5	M	E148Q-A744S	Gastroesophageal Reflux
52	12	F	E148Q- Wt (?)	Congenital Cardiac Anomaly

DISCUSSION

Vasculitides are found in FMF patients at a higher incidence than in the unaffected population. [20]Three forms of systemic vasculitis have been described to occur in FMF": polyarteritis nodosa (PAN), microscopic polyangiitis and IgA vasculitis (IgAV) formerly named Henoch Schonlein purpura (HSP). [21, 22]

In our series we had two cases of (IgAV) (0.5%) with MEFV mutations in both of them; while HSP have been reported in3% even to 11% of FMF patients [23] Occult FMF cases were identified in a series of children with (IgAV) from Israel. The (IgAV) incidence in the general population is 20/100,000 aged < 17 years (24), and in one study in FMF patients varies from 2.6% to 3.6 %[25]

PAN also occurs more commonly in patients with FMF with a younger age of onset. [26] We could not detect any case of PAN among the patients. The prevalence of PAN in FMF patients is about 1% (27) Hypertension and nephritis are more likely to occur in PAN than in FMF-PAN patients. [28] Data from evolutionary studies also gives the impression that PAN is less severe in FMF patients. [29]As in patients with PAN-FMF, the prevalence of antistreptolysin O antibody elevation is high [30].Data are insufficient to determine whether these disorders are more common in FMF patients than in the general population. [31].

We had two cases of JIA with Oligo- type and same mutations (M680I- V726A) in both and two cases of RA which showed combined heterozygote mutations. Recurrent monoarthritis can be the sole manifestation of FMF; in such cases, the true diagnosis may not be established for some time. Lidar et al. conducted a study to clinically and genetically characterize patients with FMF in whom arthritis constituted the only manifestation .The authors concluded those FMF groups were febrile with short duration arthritis, positive family history of FMF and mutation analysis, and good response to colchicines. [32]. Ayaz et al. screened 35 children with the diagnosis of systemic onset juvenile idiopathic arthritis (SoJIA) for 12 MEFV mutations. The overall mutation frequency of patients was 14.28 %,[33]

In our study there was a patient with recurrent febrile chest pain as the only manifestation of FMF and combined MEFV mutation (M694V- V726A). Pleuritis can rarely present as the sole manifestation of FMF. As a rule in patients with paroxysmal febrile attacks and chest pain, especially if they originate from the eastern Mediterranean area, FMF should be considered [13]

Recurrent pericarditis, though rare, can present as the single manifestation of FMF. Okutur et al. described a 25-year-old Turkish woman who presented with recurrent pericarditis of no obvious cause [34].In our series there was one case with same problem and M694V- M694V mutation analysis.

In our series there was not any especial skin disease except a case of alopecia without MEFV gene mutation, but recurrent urticaria has been reported as a rare manifestation of FMF. Alonso et al. described a patient referred for recurrent urticaria and final diagnosis of FMF [35].

Neurological involvement is rare but has been reported and varies from headache to aseptic meningitis. Meningitis can occur rarely in FMF. In each of the reported cases, the patients' attacks of recurrent aseptic meningitis resolved after treatment with colchicine. [36, 37, 38, and 39]

FMF-associated central nervous system (CNS) involvement includes demyelinating lesions, stroke, and posterior reversible leukoencephalopathy syndrome (PRES). Approximately 70% of patients had the homozygote M694V mutation. Neurologic involvement is rare but serious in FMF. [40]

This study represents three cases of migraine and three cases of seizure disorder with at least one MEFV gene mutation in.

We had one MS patient who did not show MEFV gene mutations. More recent study found that MS patients with MEFV mutations seem to develop a more progressive disease and on the other hand MEFV mutations may increase the risk of MS development. [41, 42]

In this work, there is a Behcet child with E148Q-V726A mutations analysis. An increased frequency of MEFV mutations has been found in individuals with Behcet disease. FMF carriers with Behcet disease have been found to have an increased risk for venous thrombosis. [43] Both FMF and Behcet disease are observed all around the Mediterranean basin, but Behcet disease clusters along the ancient Silk Road [44]

From different studies [45, 46, 47, and 48] BD patients have a higher frequency of MEFV mutations than controls, and that this high prevalence provides a further argument to support the proposal that MEFV mutations may participate in the manifestation of inflammatory disorders other than FMF. [48].

This study contains two cases of IBD with E148Q-V726A mutations in Ulcerative Colitis (UC) and M680I-Wt (?) in Crohn disease (CD). Some studies have found an increased frequency of MEFV mutations in patients with UC, and this may suggest a possible modifying effect of MEFV in the disease process. [20]Other studies have found that CD seems to be more prevalent in FMF and presents later than in patients without FMF. [49, 50]MEFV gene mutations may act as modifiers, affecting the expression of IBD. [13]

Although there was not any cases in our patients, Streptococcus associated diseases with the presence of high levels of antistreptolysin O (ASO) antibodies and streptococcus-associated diseases, such as acute post-streptococcal glomerulonephritis and acute rheumatoid fever have been reported in patients with FMF. [51]Patients with FMF certainly have an exaggerated response to streptococcal antigens and may be more prone to the late complications of streptococcal infection. [20]

In this work there were four cases of peptic ulcer disease (PUD) and four patients with cholelithiasis (CL), which in most of PUD and all CL there was combined heterozygote mutations.(table. 2)

Here we represent one patient with celiac disease and FMF with E148Q-P369S mutations. FMF and celiac disease (CD) may share genetic and epigenetic factors as well as certain clinical features [52] however; association between FMF and CD remains controversial.

Two sisters with idiopathic ascitis and FMF were in this study with similar MEFV gene mutations, M694V-M694V. A female patient with FMF who developed chronic ascites has been reported recently by Ureten et al. She was a compound heterozygote for the mutations M694Vand M680I, and after dose adjustment of colchicine, the amount of ascites decreased [53]

There was one patient with recurrent orchitis and M694V-M694V mutations, although acute scrotum is rarely seen as a complication of FMF [54].

Patients with growth hormone deficiency, TTP, Leiden Factor deficiency and retinitis pigmentosa were additional and probably unreported association in this study. We have discussed about the MEFV gene and PFAPA in distinct article(in press); however, here we report six FMF patients with co-existed PFAPA. In these entire patients MEFV gene mutations are positive and one of them had compound heterozygote mutations (R761H-M694I).In half of these patients PFAPA presented firstly, and in the others FMF developed earlier than PFAPA. Initially we thought these patients are colchicine resistant FMF, but more work up and closed observation with good response to single dose prednisolon during attacks revealed their co-existed PFAPA. On the basis of this finding particularly in young patients with colchicine resistant FMF, we recommend co-existed PFAPA as a possible condition.

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