


Coexisting Diseases in Patients with Familial Mediterranean Fever

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Background and Aims: Familial Mediterranean fever (FMF) is a prototype of autoinflammatory disease and mainly associated with *MEFV* gene mutations. This single-center study as an experience represents FMF-coexisting disease in the FMF registration database.

Methods: Four hundred patients who had FMF based on clinical criteria (Tel-Hashomer) and/or *MEFV* mutations enrolled the study. Twelve most common *MEFV* mutations (P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H, E148Q) were analyzed if needed by the reverse hybridization assay. Any co-existing disease had been confirmed by a related subspecialist. All data were analyzed by a simple analytical method.

Results: Fifty-seven (14%) patients had associated disease, 32 patients were male and 24 patients were under 10 years old. They included 92 *MEFV* variant alleles and only in five patients there were not any mutations. The most common variant alleles were *M694V* (36%), *E148Q* (22%), *V726A* (17%), *M680I* (1%) and *M694I* (0.07%) respectively. Rheumatologic disorders were the most common coexisting disease, then followed by gastrointestinal and neurological disorders. Some rare diseases such as TTP, growth hormone deficiency, multiple sclerosis, idiopathic ascites, Leiden factor V deficiency and Felty syndrome have been detected. Homozygote mutations of (*M694V-M694V*) were associated with idiopathic ascites, orchitis and pericarditis.

Conclusion: Coexisting disease in patients with FMF is presented with positive *MEFV* gene mutations particularly with these five common variant alleles: *M694V*, *E148Q*, *V726A*, *M680I*, and *M694I*. The commonly associated diseases are rheumatologic, gastrointestinal and CNS disorders.

Keywords: familial mediterranean fever, MEFV mutation, FMF-coexisting disease

Introduction

FMF is an autoinflammatory and autosomal recessive disease mainly affecting ethnic groups living around the Mediterranean Sea: Jews, Armenians, Turks, Arabs,¹ with a prevalence ranging from 1/200 to 1/1000.²

Early manifestations have usually appeared by the first decade and are characterized by recurrent, self-limiting attacks of polyserositis and fever. Serositis is presented by abdominal and chest pain as peritonitis or pleuritis, and, with less frequency pericarditis and recurrent painful orchitis can be seen.³

Arthritis in periodic and nondestructive form or persistent with chronic destructive pattern usually in large joints may occur. Severe prolonged myalgia or myositis due to vasculitis is seen.^{4,5} Frequency of attacks is variable and asymptomatic periods that last also a few years have been reported. Laboratory evaluation shows positive

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results of acute-phase reactant that may be detected more-over in asymptomatic periods, particularly serum amyloid A.^{6,7}

Until 1998, the diagnosis of FMF was based on clinical criteria alone. The Tel Hashomer criteria generally form the basis of the clinical diagnosis. These criteria contain three major (recurrent febrile episodes accompanied by serositis; amyloidosis of AA type; favorable response to colchicine) and three minor criteria (FMF in first-degree relatives; erysipelas like erythema; recurrent febrile episodes); for diagnosis of FMF, it needs two major or one major plus two minor criteria.⁸ In 1992, the gene responsible for FMF, (MEDITERRANEAN FEVER) *MEFV*, was found on the short arm of chromosome 16.⁹ Five years later, the *MEFV* gene locus was discovered that encode the protein named marenostin or pyrin.¹⁰ This protein probably has an important role in the downregulation of inflammation in innate immune response.

In populations with a high FMF, prevalence 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 who fulfilled clinical criteria in Mediterranean origin,¹¹ while it was much lower in patients from non-Mediterranean areas (10%).¹²

Although until the last decade, 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 with a main effect on the course and severity of the disease.¹³

Coexistence of FMF with rheumatoid and autoimmune conditions like seronegative spondyloarthritis (SpA)¹⁴ Bechet's disease¹⁵ rheumatoid arthritis (RA)¹⁶ Sjögren's syndrome,¹⁷ Juvenile idiopathic arthritis,^{18,19} inflammatory bowel disease (IBD)²⁰ and polyarteritis nodosa (PAN)²¹ have been reported.

In this study, we aimed to evaluate the frequency of comorbid disorders in a large FMF cohort of FMF registration center with relatively long follow-up duration. Additionally, we aimed to assess the association between FMF and other co-existed diseases and conditions with genotype-phenotype correlation survey. (WWW.FMFIRAN.IR)

Methods

Study Population

This is a case series study. The data of 400 FMF patients, who were diagnosed based on Tel- Hashomer criteria at

the rheumatologic clinics of Bouali Hospital and from FMF Registration Center database (<http://www.fmfiran.ir>) were collected.

Demographic information of patients, such as age, race, gender, and their extra FMF disease, which have been confirmed by adult or pediatric subspecialist were collected.

MEFG Gene Analysis Study

Blood samples were screened for the 12 common pathogenic variants (E148Q, P369S, F479L, I692del, M680I (G/C), M680I (G/A), M694V, M694I, K695R, V726A, A 744S and R 761H) according to manufacturer's instructions (FMF Strip Assay, Vienna lab, Vienna, Austria). The study is compliant with the Helsinki Declaration and was approved by the local Ethics.

Ethical and Legal Aspect

Committee under number IR.ARUMS. REC.1396.95. Written Informed consent was obtained from all the participants and/or their parents.

Comorbidity Diagnosis

Among them, 57 patients had associated disease that had been confirmed by related subspecialist and clinic of the hospital.

Statistical Analysis

Analysis was mainly descriptive, we have done all the statistical analyses with IBM SPSS 20 program (SPSS Inc., Chicago, IL, USA). Categorical variables were reported as numbers and percentages. Fisher's exact test was used when the sample size was small (expected cell sizes < 5). The statistical significance defined as p value < 0.05.

Results

Among the patients, 57 (14%) had associated disease other than FMF manifestations. Thirty-two patients were male and 24 patients were under 10 years old. **Tables 1** and **2** show the patient's profile as inflammatory and non-inflammatory conditions.

There were 92 *MEFV* gene mutations. The most common were M694V (36%), 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,

Table 1 Autoinflammatory and Autoimmune Disorders Co-Existed

No.	Age	Sex	MEFV Gen. Mutations	Co-Exist Condition
Autoinflammatory 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
11	15	F	Wt/Wt	PAN
12	40	M	M694V- M694V	RA+ Felty syndrome
13	14	M	M694V-R202Q	JSpA
14	14	M	M694V- M694V	JSpA
15	4	M	M694V-R202Q	JSpA
Organic-specific autoimmune disease				
16	7	F	E148Q-V726A	(IBD) Ulcerative colitis
17	38	M	M680I-Wt (?)	(IBD) Crohn Disease
18	10	M	Wt (?) -Wt (?)	Alopecia totalis
19	37	F	Wt (?) -Wt (?)	Multiple Sclerosis (MS)
20	11	M	E148Q-P369S	Celiac
21	21	M	R761H-V726A	TTP (Thrombotic Thrombocytopenic Purpura)
Systemic vasculitis				
22	5	F	E148Q- Wt (?)	(IgAV) Henoch-Schönlein purpura
23	7	F	E148Q-V726A	Behcet Disease
24	29	M	M694V- E148Q	Protracted febrile myalgia syndrome (PFMS)
25	20	M	M680I-V726A	(IgAV) Henoch-Schönlein purpura
Non-clarified associated serositis				
26	12	M	M694V- V726A	Pleuritis (Recurrent Idiopathic/FMF related)
27	13	M	M694V- M694V	Pericarditis (Recurrent Idiopathic/FMF related)
28	49	F	M694V-M694V	Ascites (Idiopathic/FMF related)
29	46	F	M694V-M694V	Ascites (Idiopathic/FMF related)
30	23	M	M694V-M694V	Orchitis (Idiopathic recurrent/FMF related)

Vasculitis), followed by gastrointestinal GI (Peptic ulcer, cholelithiasis) and CNS (migraine, seizure) disorder. Some rare diseases such as thrombotic thrombocytopenic

Table 2 Non-Inflammatory Coexisting Disorders

No.	Age	Sex	MEFV Gen. Mutations	Co-Exist Condition
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

purpura TTP, growth hormone deficiency, multiple sclerosis MS, ascites 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. These homozygote mutations (M694V-M694V) were associated with idiopathic ascites, orchitis and pericarditis. There were three cases of JSpA and one case of Felty syndrome and one patient with childhood PAN. There was not a meaningful association between MEFV mutations and non-inflammatory disease. (P value 0.05%)

Discussion

Vasculitis

Vasculitis is found at a higher incidence in FMF patients than in the unaffected population.¹³ In our series, we had just two cases of IgA-V (0.5%) with positive *MEFV* mutations, while HSP has been reported in 3% even to 11% of FMF patients. Occult FMF cases were identified from Israel, commonly in children with IgA-V.²²

PAN also occurs more commonly in patients with FMF usually with a younger age of onset.²³ We detected one case of PAN among the patients however with negative *MEFV* mutations. The prevalence of PAN in FMF patients is about 1% (24). Hypertension and nephritis are more likely to occur in PAN than in FMF-PAN patients.²⁵ It seems that PAN is less severe in FMF patients.²⁶ In patients with PAN-FMF, the prevalence of antistreptolysin O antibody elevation is high.²⁷ Data are insufficient to determine whether this disorder is more common in FMF patients than in the general population.²⁸

Arthritis

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. This collection contains three cases of Juvenile Spondylo-Arthropathy (JSpA) and one case of RA with neutropenia as a Felty syndrome; in our knowledge FMF association with Felty syndrome has not been reported already. 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 of FMF. The authors concluded those FMF groups were febrile with short duration arthritis, positive family history of FMF and *MEFV* mutations with good response to colchicine.²⁹ We reported a rare form of relapsing arthritis as palindromic rheumatism that had been related to *MEFV* gene mutations without apparent FMF manifestation.³⁰

Serositis

In our study, there was a patient with recurrent febrile chest pain as the only manifestation of FMF and combined *MEFV* mutations (M694V-V726A). Pleuritis can rarely present as the sole manifestation of FMF. As a rule in patients with paroxysmal febrile chest pain, especially in the Mediterranean area, FMF should be considered.³

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.³¹ In our series, there was one case with the same problem and M694V-M694V mutation analysis.

Skin Disease

In our series, there was not any especial skin disease except a case of alopecia totalis without *MEFV* gene mutation, but recurrent urticarial has been reported as a rare manifestation of FMF. Alonso et al described a patient with recurrent urticarial and final diagnosis of FMF.³²

Neurological Disease

Neurological involvement has been reported and it varies from headache to aseptic meningitis. Meningitis can occur rarely in FMF as Mollaret meningitis. In each of the reported cases, the patients' attacks of recurrent aseptic meningitis resolved after treatment with colchicine.^{33–35} We reported recently neurological manifestation of familial Mediterranean fever as a separate study.³⁶ FMF-associated central nervous system (CNS) involvement includes demyelinating lesions, stroke, and posterior reversible leukoencephalopathy syndrome (PRES). Different studies showed that MS patients with *MEFV* mutations seem to develop a more progressive disease and it seems that *MEFV* mutations may increase the risk of MS progression.^{37–39}

Inflammatory Disorder

In this work, there is a Bechet child with E148Q-V726A mutation analysis. An increased frequency of *MEFV* mutations has been reported in individuals with Bechet disease. FMF carriers with Bechet disease have been found to have an increased risk for venous thrombosis.⁴⁰ Both FMF and Bechet disease are observed all around the Mediterranean area. From different studies,^{41–43} BD patients have a higher frequency of *MEFV* mutations than controls, and this high prevalence provides a further argument to support the role of *MEFV* mutations in the manifestation of different inflammatory disorders other than FMF.⁴⁴

This study contains two cases of IBD with E148Q-V726A mutations as Ulcerative Colitis (UC) and M680I-Wt (?) in Crohn disease (CD). Some studies have found an increased frequency of *MEFV* mutations in patients with UC.²⁰ Other studies have found that CD seems to be more

prevalent in FMF patients.^{45,46} *MEFV* gene mutations may act as modifiers and affecting the expression of IBD.¹³

Patients with FMF certainly have an exaggerated response to streptococcal antigens and may be more prone to the late complications of streptococcal infection.²⁰ 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 poststreptococcal glomerulonephritis and acute rheumatoid fever, have been reported in patients with FMF.⁴⁷

Non-Inflammatory Diseases

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

Here, we represent a patient with celiac disease coexisted with FMF and E148Q-P369S mutations. FMF and celiac disease (CD) may show different genetic and environmental factors as well as certain clinical features;⁴⁸ however, the association between CD and FMF remains controversial.

Two sisters had idiopathic ascites and FMF with homozygote mutations as M694V-M694V. A female patient with FMF who developed chronic ascites has been reported by Ureten et al. She was a compound heterozygote for the mutations M694V and M680I, and after dose adjustment of colchicine, the amount of ascites decreased.⁴⁹ There was one patient with recurrent orchitis and M694V-M694V mutations, although acute scrotum is rarely seen as a complication of FMF.⁵⁰

Miscellaneous Disorder

Patients with growth hormone deficiency, TTP, Leiden Factor deficiency and retinitis pigmentosa and Felty syndrome were additional and probably unreported association in this study. We have discussed about the *MEFV* gene and PFAPA in a distinct article.⁵¹ However, here we report six FMF patients with co-existed PFAPA. In all of these patients, *MEFV* mutations are positive and one of them had compound heterozygote mutations (R761H-M694I). In half of these patients, FMF had been developed earlier than PFAPA.

Initially, we thought these patients are colchicine-resistant FMF, but more workup and closed observation with good response to a single dose of prednisolone during attacks revealed their co-existed PFAPA. On the basis of

this finding particularly in young patients with colchicine resistant FMF, we recommend the probability of PFAPA as a possible associated condition.

In a recently published study by Yildiz,⁵² they showed that frequency of certain inflammatory conditions such as juvenile idiopathic arthritis, juvenile spondyloarthropathies, Henoch–Schönlein purpura, uveitis and inflammatory bowel disease was increased in their pediatric FMF patients; in contrary, asthma was less commonly detected in compared to general prevalence. The results of their study are relatively similar to our findings; however, in our experience uveitis is not a feature of FMF patients.⁵³

The most important limitation of our study is the lack of a healthy control group in which we can compare the frequencies of the diseases. The other limitation was including adult and pediatric population in the same study.

Conclusion

Associated diseases in FMF usually are presented in patients with positive *MEFV* gene mutations particularly with these five mutations M694V, E148Q, V726A, M680I, and M694I. Rheumatologic, gastrointestinal and CNS disorders are common co-existed disease.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees.

Author Contributions

FS and AE work at the rheumatology clinic and planned the study and diagnosis of the FMF patients. AE wrote the final copy. FS wrote the draft copy of the manuscript. All authors made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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