Neurological Manifestations in Familial Mediterranean Fever: a Genotype-Phenotype Correlation Study

Background and Aims: Familial Mediterranean Fever (FMF) is a periodic auto-inflammatory disease with an autosomal recessive hereditary pattern. The aim of this study is to explain the spectrum of possible neurological manifestations and its genotype-phenotype correlation in patients with familial Mediterranean fever.

Methods: In this case series study, data of 311 FMF patients at the FMF Registration Center in Iran (<http://www.fmfran.ir/>) was studied. Patient’s information was entered into a researcher designed questionnaire. Data were analyzed by SPSS software.

Results: The mean age of the 181 male and 130 female patients was 23.01 years, ranging from 3–78 years old. Twelve common MEFV gene analyses were performed in 311 patients, with mutated results in 187 (60.1%) patients. The most common neurological manifestations were headache in 47.26%; 64.1% of those were persistent and 35.9% had a recurrent nature. Other neurological manifestations were vertigo (83 patients, 26.7%), paresthesia (72 patients, 23.2%), tremor (53 patients, 17%), disorientation (40 patients, 12.9%), breath-holding (23 patients, 7.4%), migraine (19 patients, 6.1%), syncope (8 patients, 2.6%), epilepsy (7 patients, 2.3%), febrile seizure (4 patients, 1%), and ataxia (5 patients, 1.6%). There were no cases of stroke or metabolic disorders among these patients.

Conclusion: The prevalence of epilepsy among FMF patients was significantly higher than the general population. FMF patients with negative results for MEFV gene mutations had significant frequency of headache, paresthesia, breath-holding, and ataxia.

Keywords: familial mediterranean fever, MEFV gene, epilepsy, migraine, headache, breathe holding, paresthesia

Introduction

Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease with autosomal recessive inheritance. FMF is characterized by recurrent fever and inflammation of serous membranes, leading to abdominal pain, chest pain, and joint inflammation, and its classic feature includes self-limiting periods of fever and serositis.1

Clinical manifestations of the disease usually occur during the first decade of life in more than 80% of patients, and in 90% of the patients the disease began before 20 years of age.2,3 FMF is common among Mediterranean populations (Jews, Arabs, Turks, and Armenians).1 The highest prevalence of the disease among the “Sephardic Jews” and the Armenians has been reported. In the Middle East its prevalence is one in 100–2,000 people, according to different studies.3

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The disease frequency in young age groups is low.\(^4\) Males are slightly more involved than females, with a prevalence rate of 1.5–2-times.\(^5\) The Mediterranean fever gene (MEFV), the causative agent of FMF, is located on the short arm (p) of chromosome 16 at position 13.3 (16p 13.3) and encode a protein called pyrin (or marenosmin) which suppresses the inflammatory response.\(^6\),\(^7\)

Two MEFV gene mutations confirms the genetically diagnosis of FMF. Moreover, with regards to genotype-phenotype correlation, some data reported that patients carrying heterozygous mutations showed a more severe disease when compared both to subjects carrying homozygous and compound heterozygous mutations.\(^8\)

Patients carrying MEFV mutations can also display aspecific clinical manifestations as well as significant changes in disease behavior over time.

Although FMF is a polyserositis disease, there is also central nervous system (CNS) involvement and many neurological associated symptoms. Aseptic meningitis, headache, demyelinating lesions, and pseudo tumor cerebri have been reported in patients with FMF. The neurological manifestations of disease are listed in Table 1, including persistent and/or episodic symptoms associated with febrile attacks.\(^9\)

It is not included following four distinct types of musculoskeletal pain (myalgia) syndrome as known neuromuscular involvement of FMF: as a constitutional symptom, as an additional type of FMF, exertion leg pain, and protracted febrile myalgia syndrome.\(^10\)

Recently, FMF has been reported as a common autoinflammatory disease from the northwest of Iran, with its own phenotype genotype features. The most common MEFV gene mutations in FMF patients are M694V (20.9%), V726A (12.7%), E148Q (10.7%), M680I (10.3%), and M694I (2.1%), respectively,\(^11\),\(^12\) whilst 25% of the healthy and general population in this area showed different MEFV gene alleles, as follows: E148Q (18.3%), P396S (3.1%), V726A (2.2%), features in heterozygote form.\(^13\),\(^14\)

The aim of this study is to assess the clinical findings of FMF patients who presented with neurological findings due to CNS involvement. This study explains common neurological symptoms in these patients, which, based on some reports, have different frequencies and presentation compared with the general population regarding their MEFV gene mutations and phenotype-genotype correlations.

### Materials and Methods

This is a case series study. The data of 311 FMF under-controlled patients, who were diagnosed based on Tel-Hashomer criteria at the rheumatologic clinic and FMF Registration Center (http://www.fmffiran.ir), were collected.

Demographic information of patients, such as age, race, gender, and their neurological findings, which have been confirmed by adult or pediatric neurologist, were collected. 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 complaint with the Helsinki Declaration and was approved by the local Ethics Committee under number IR.ARUMS.REC.1396.95. Written Informed consent was obtained from all the participants and/or their parents.

### Statistical Analysis

Analysis was mainly descriptive, calculating mean and frequency derivatives using SPSS version 20.

A 2-sided P-value<0.05 was considered statistically significant.

### Results

#### Demographic Findings

This study included 181 (58.2%) males and 130 (41.8%) females (M/F=1.4). The mean age of the patients was 23.01±15.5 years. The youngest patient was 2 years old and the oldest one was 78 years old. The mean age of the male and female patients was 23.87 and 21.82 years, respectively.

#### Neurologic Findings

The neurological manifestations among the patients showed headache as the most common symptom in 147 (47.26%) patients, 64.1% of them had persistent ache, 35.9% recurrent headache, 6.1% showed classic migraine, and 10% had tension and cluster type headaches.

Other neurological manifestations were vertigo (83, 26.7%), paresthesia (72, 23.2%), tremor (53, 17%),

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**Table 1 Neurological Manifestation in FMF**

| PRES                          | Ataxia                   |
|-------------------------------|--------------------------|
| Cerebro-vascular disease      | Headache                 |
| Demyelinating diseases        | Tremor                   |
| Seizure and febrile seizure   | Breath holding           |
| Focal paresis                 | Syncope                  |
| Visual disease                | Meningitis recurrent\(^10\),\(^11\) |
| Vertigo                       | Pseudo tumor cerebral\(^12\) |
disorder, migraine (19, 6.1%), syncope (8, 2.6%), epilepsy (7, 2.3%), ataxia (5, 1.6%), and febrile seizure (4, 1.2%).

There were no stroke or metabolic disorders among patients. One female patient suffered from a MS-like disorder.

Genetic Findings
As shown in Table 2, two groups of FMF patients with positive (12 common pathogenic variants alleles) and negative results for MEFV gene mutations had significantly different frequencies of headache, paresthesia, breath-holding, and ataxia. These manifestations were significantly higher than patients without mutations.

Regarding seizures, although their frequency was higher than patients with MEFV mutations, this difference is not meaningful ($P=0.537$).

Discussion
Gedalia and Zamir$^{18}$ reported that, out of 101 children with FMF, 13 children (12.9%) had headache during acute fever attacks. In the Uluduz et al$^{19}$ study, 32.9% of FMF patients had tension headache. A severe type of headache in the form of FMF-like recurring meningitis has also been reported by Feld et al.$^{20}$ Our study showed that the prevalence of headache in FMF patients is 47.26% and it is significantly more common in MEFV allele’s negative patients.

A recent study by Canpolat et al$^{21}$ of 22 children with FMF showed neurological findings included headache in 16 patients (72.7%), epilepsy in six patients (27.3%), pseudotumor cerebri in two patients (9.1%), multiple sclerosis in one patient (4.5%), and tremor in one patient (4.5%). The most common MEFV gene mutation in these patients was M694V (40.9%).

Three Israeli FMF patients with seizure were reported in 1993, which was the first report of seizure and FMF association.$^{18}$ In general, our recent data has not shown a strong relationship between FMF and epilepsy. The prevalence of the epilepsy in FMF patients is 2.3%, however, in comparison with the prevalence of epilepsy in the general population of the Mediterranean region, 0.4–1.2%$^{22}$ it seems, this is interestingly twice the rate of the general population.

The frequency of febrile seizure (FS) in the general population is estimated between 2–5%,$^{23}$ while, in our study, the frequency of FS in FMF patients was lower than the normal range, although Comak et al$^{24}$ showed children with FMF had a higher rate of FS than the general population. These contradictory results consider multiple factors in the pathogenesis of FS such as environmental and ethnic backgrounds.

There was not any case of metabolic disorders among our patients. In the Kiykim et al$^{25}$ study in 174 FMF patients, only two cases of fatty acid oxidation deficiency were observed.

The relationship between FMF and stroke has not been completely studied and it is limited to a case report in children. Seven cases of stroke were reported in 3,034 patients with FMF in Kalyoncu et al$^{9}$ study. Although these patients also had other risk factors, this indicates a high prevalence compared to the general population rates (0.2% vs 0.005–0.015 in adults older than 50 years), whether FMF can be considered as a risk factor for stroke is still to be answered; however, some associated disease with FMF, particularly systemic vasculitis, may involve CNS and presents CNS vascular disorders such as stroke and ischemia.$^{26}$

There have been some case reports about the coexistence of familial Mediterranean fever and posterior reversible leukoencephalopathy (PRES); however, there was, not any co-existence of stork and PRES in our study.

The frequency of breath holding as an autonomic dysfunction in this study was 7.4%, which is higher than the general population (4–5%).$^{27}$ In this study, 23.2% of patients had paresthesia, which was similar to the result of Salehzadeh et al$^{15}$ report 22%, whereas in Kalyoncu et al’s$^{9}$ work from 18 patients with FMF who had neurological symptoms, 11.1% had paresthesia.

An interesting study by Witt et al$^{28}$ showed that the sign and symptoms of autonomic dysfunction are more prevalent in FMF patients than in age- and gender-matched healthy controls.

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**Table 2 Neurological Manifestations of Patients Regarding MEFV**

| Symptom                  | MEFV+ No (%) | MEFV- No (%) | Total No (%) | $P$-value |
|--------------------------|-------------|-------------|--------------|---------|
| Symptom                  |             |             |              |         |
| Headache                 | 69 (36.89)  | 78 (69.90)  | 147 (47.26)  | 0.041   |
| Vertigo                  | 50 (26.7)   | 33 (26.6)   | 83 (26.7)    | 0.975   |
| Paresthesia              | 36 (19.3)   | 36 (29)     | 72 (22.3)    | 0.045   |
| Tremor                   | 27 (14.4)   | 26 (21)     | 53 (17)      | 0.134   |
| Disorientation           | 21 (11.2)   | 19 (15.3)   | 40 (12.9)    | 0.291   |
| Breath holding           | 9 (4.8)     | 14 (11.3)   | 23 (7.4)     | 0.033   |
| Syncope                  | 4 (2.1)     | 4 (3.2)     | 8 (2.6)      | 0.553   |
| Epilepsy (seizure)       | 5 (2.7)     | 2 (1.6)     | 7 (2.3)      | 0.537   |
| Ataxia                   | 1 (0.5)     | 4 (3.2)     | 5 (1.6)      | 0.064   |
| Total                    | 187         | 124         | 311          |         |

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Of these, 35.9% had recurrent headache and 6.1% showed classic migraine, whilst in the study of Uluduz et al., 29.5% of FMF patients had migraine. On the basis of MEFV gene alleles, headache as a general symptom was meaningfully more common in MEFV negative patients.

In our study, 26.7% had vertigo and there is not any difference in frequency of vertigo between MEFV gene negative and positive patients.

The other neurological manifestations such as tremor (17%), disorientation (12.9%), and syncope (2.6%) showed a similar frequency between MEFV gene negative and positive patients.

Ataxia has been shown in 1.6% of patients, and meaningfully it was more common in MEFV gene negative patients.

The high frequency of four common neurologic symptoms in FMF patients (headache, paresthesia, breath holding, and ataxia) with negative MEFV gene mutations could be emphasized the partial protection and or modifying role of this mutation in appearance of these symptoms.

One patient in our study had multiple sclerosis (MS) like disorder with M694V heterozygous pattern. Although it has been shown that MS is more common in FMF than in the general population, however; it does not have any effect on the course of the disease.

There was no case of recurrent meningitis, known as mollaret meningitis, among these patients.

The main limitation of this study is that the patients were evaluated retrospectively, and we did not separate pediatric from adult patients.

Conclusion
The frequency of seizure among FMF patients is significantly higher than the general population. Headache, paresthesia, breath holding, and ataxia are more common in the MEFV gene mutations negative group.

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

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Author Contributions
F.S. and A.A. work at the rheumatology clinic and planned the study and diagnosed the FMF patients. F.A. worked on the neurologic manifestations of patients and wrote the final copy. R.N. wrote the draft copy of the manuscript. M.M. collected all data for the manuscript. All authors contributed to data analysis, drafting or revising the article, 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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