Neurological Face of Familial Mediterranean Fever

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ABSTRACT

Objective: Familial Mediterranean fever is a systemic inflammatory disease characterized by recurrent attacks in the form of fever and inflammation of serous membranes. We aimed to search for neurological signs and symptoms of children with familial Mediterranean fever.

Materials and Methods: Medical records database from 2010 to 2020 was screened retrospectively. In total, 625 children with familial Mediterranean fever were included in the study. Neurological symptoms and associated factors were searched.

Results: The mean age at onset of familial Mediterranean fever symptoms and time to diagnosis was calculated as 5.12 ± 3.51 years and 7.27 ± 3.9 years, respectively. The neurological symptoms were present in 142 (23.5%) patients. Headache was the most common symptom. During follow-up, different neurologic diseases were diagnosed in 40 familial Mediterranean fever patients and epilepsy was the most frequent disease. The coexistent disease was present in 49.9% of children with familial Mediterranean fever. Juvenile idiopathic arthritis was found to be a risk factor for the neurologic symptom (P < .05). The frequency of neurological symptoms was higher in patients with E148Q mutation (P < .012).

Conclusion: The results of the present study revealed that patients with familial Mediterranean fever can present with various central nervous system manifestations. A multidisciplinary approach must be considered in the treatment of these children.

Keywords: Familial Mediterranean fever, children, brain, neurology

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive, auto-inflammatory disease. It is characterized by recurrent fever and inflammation of serous membranes. Although it occurs worldwide, it is most frequent in the population of the Mediterranean region. Familial Mediterranean fever’s prevalence varies from 1: 500 to 1: 1000 in endemic countries with the highest reported prevalence of 1:395 from the central Anatolia region. Considering disease prevalence and population size, Turkey has the highest number of FMF patients in the world followed by Israel and Armenia. It is caused by a mutation in the Mediterranean fever (MEFV) gene, located on the short arm of the 16th chromosome. The most frequently identified mutations occur as M694V, M680I, E148Q, and V726A. Kilic et al reported that the most common mutation in children in our country with FMF was M694V. The diagnosis of FMF is based on the clinical features of the patient and genetic tests may be needed to confirm the diagnosis. Attacks of FMF are caused by dysregulation of the pyrin inflammasome, which leads to constitutive hypersecretion of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 with intermittent exacerbations.

Familial Mediterranean fever is a multisystemic disease, and fever and abdominal pain are the main complaints of patients. Familial Mediterranean fever attacks usually start from early childhood, and 80%-90% of patients become symptomatic before the age of 5.
20 years. Different neurological signs and symptoms have been reported in children with FMF in different case series. Canpolat et al reported that headache was the most frequent neurological finding in Turkish children with FMF. Epilepsy, febrile seizure, multiple sclerosis, and pseudotumor cerebri have been reported in patients. The exact pathophysiology of the neurological manifestation of FMF is unclear. The present study aimed to search for neurological signs and symptoms in pediatric FMF patients. We further aimed to search relationship between genetic mutation type and neurological signs and symptoms.

MATERIALS AND METHODS

In the present study, we retrospectively reviewed medical records of FMF patients who were followed up between January 2010 and January 2020 at the Department of Pediatrics, Faculty of Medicine, Eskisehir Osmangazi University.

Data Collection

All patients were examined by the pediatric nephrology department and diagnosed according to Yalcinkaya-Ozen’s criteria. Clinical manifestations, demographic data, family history, laboratory studies, and genetic analysis of MEFV mutations were obtained from patient charts at the first visit. At subsequent visits, clinical and laboratory parameters were evaluated. Follow-up visits were scheduled at 3-12-month intervals depending on clinical status. During each visit, the patients’ clinical features, response to colchicine therapy, and compliance were recorded. Patients who suffer from neurological signs and symptoms were examined and evaluated by pediatric neurologists.

For the study protocol, the patient’s age, gender, age at diagnosis of FMF, age at onset of neurological complaints, drugs used, and coexisting diseases were all retrospectively recorded.

The study was approved by the Eskisehir Osmangazi University Ethical Committee (No: 2020/17).

Genetic Analysis

Mutation analysis was performed from peripheral blood samples according to standard procedures by polymerized chain reaction technique. Exons 2, 3, 5, and 10 were examined, and M694V, M694I, M694L, M680I, F479L, E148Q, S675N, M680L, R717S, V722M, I192del, K695R, K695M, V726A, A744S, R761H, P369S, H478Y, G6978E, T681I, I720M mutations were investigated. Mutations were classified as homozygotic, heterozygotic, and compound.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Inc., Chicago, Ill, United States). Descriptive statistics were shown in mean ± standard deviation and frequency format. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of continuous variables between the groups. The parameters with normal distribution were compared by Student’s t-test, whereas those without normal distribution were evaluated by the Mann–Whitney U-test. Monte Carlo simulation was used while performing the chi-square analysis in the cross-table, in which the distribution of the presence or absence of neurological symptoms according to mutations was examined (95% CI of 10 000 trials).

RESULTS

Demographic Parameters and Clinical Features of Patients

A total of 625 pediatric FMF patients (320 girls and 305 boys) were included in the study. The female to male ratio was calculated as 1.04. The mean age at the onset of FMF symptoms was 5.12 ± 3.51 years. Nearly half of children (44.7%) were diagnosed at an age between 5 and 10 years, and the mean age at diagnosis of FMF was calculated as 7.27 ± 3.9 years. The ratios of parenteral consanguinity and family history of FMF were found to be 9.7% and 39.5%, respectively.

Patient records showed that the majority of patients experienced 1 or 2 attacks per month (46.8%). The duration of attacks was between 24 and 48 hours for 234 children. Medical records showed that genetic analysis had been performed on 610 children, and the most common mutation type was the M694V mutation (51.5%). All patients have been treated with colchicine. When the patients’ compliance with colchicine treatment was checked, it was shown that 86.8% of them were using the drug regularly. In addition to colchicine, 19.8% of the patients were found to be treated with drugs other than colchicine (methotrexate, steroids, hydroxychloroquine, azathioprine, etanercept, anakinra, and mesalazine). Medical records of patients showed that the co-existing disease was present in 49.9% of children (Table 1).

Neurological Manifestations of Patients

The neurological symptoms were present in 142 (23.5%) patients (Table 2).

The results revealed that parenteral consanguinity and family history of FMF does not affect the frequency of neurologic symptoms. However, in children diagnosed younger than 5 years old, neurologic manifestations are statistically less frequent than others (Table 3) (P < .05).

Headache was the most common symptom, and it was accompanied by secondary other neurological disorders in 10 patients.

Table 1. Co-existing Diseases of FMF Patients

| Disease                      | n (%) |
|------------------------------|-------|
| Urinary disorders            | 60 (9.6) |
| Hematological disorders      | 50 (8) |
| Gastrointestinal disorders   | 42 (6.7) |
| Endocrine disorders          | 34 (5.4) |
| Allergic disorders           | 27 (4.3) |
| Henoch–Schönlein purpura     | 25 (4) |
| Juvenile idiopathic arthritis| 20 (3.2) |
| Metabolic disorders          | 17 (2.7) |
| Cardiac disorders            | 10 (1.6) |
| Acute rheumatic fever         | 6 (0.9) |
| Behçet’s disease             | 6 (0.9) |
| Other disorders              | 21 (3.3) |

*Some patients have more than 1 co-existing disease.

FMF, familial Mediterranean fever.
Migraine and chronic daily headaches were diagnosed in 27 and 18 children, respectively. Headache was also presented as a symptom of the case with idiopathic intracranial hypertension. The type of syncope was vasovagal in all cases. The origin of vertigo was central for 4 children with stroke and cerebral vasculitis. Fifty patients suffered from myalgia. However, none of them were diagnosed with protracted febrile myalgia.

During follow-up, different neurologic diseases were diagnosed in 40 FMF patients and epilepsy was the most frequent disease. The neurologic diseases are presented in Table 4.

Epilepsy was the most frequent neurologic disease. Except for 4 children, epileptic seizures were idiopathic in 10 patients. The seizures were focal in symptomatic epilepsies.

The magnetic resonance imaging (MRI) revealed pathologic neuroimaging findings in 14 patients. Acute ischemic infarct in the brain region supplied by the left middle cerebral artery was detected in stroke cases. Non-specific signal changes and arachnoid cysts were noticed in 8 and 2 children, respectively. The 2 cases with cerebral vasculitis were diagnosed by MRI findings.

**DISCUSSION**

Although FMF is a systemic disease, neurological manifestations might be present.10,11 The present study aimed to search the neurological signs and symptoms of a large group of children with FMF.

Our results revealed that 142 (23.5%) children experienced neurological symptoms. A previous study reported that the prevalence of neurological manifestations in pediatric cases was 12.8%.14 In a recent study, Biro et al15 compared the neurological complaints of children with FMF and their healthy siblings and it was found that neurological manifestations were more prevalent in cases. As compatible with our results, in a study conducted in our country, Canpolat et al16 searched neurological signs and symptoms in 104 children and reported the prevalence of neurological manifestations as 21.5% in the study group.

Headache was the most common neurological complaint of children in the present research and was detected in 11.5% of the study group. A study from Turkey reported a much higher frequency of headaches among pediatric FMF patients.17 This result was compatible with the literature.10,18,19 Salehzadeh et al17 reported that the most common neurological manifestation was a headache in 47.26% of patients; 64.1% of those were persistent and 35.9% had a recurrent nature. They also revealed that negative results for MEFV gene mutations had a significantly different frequency of headaches. Headache is a common symptom in children with other chronic diseases such as juvenile idiopathic arthritis,11 systemic lupus erythematosus,20 juvenile idiopathic arthritis with uveitis21 and juvenile idiopathic arthritis with psoriasis.22

It was found that the coexistence of juvenile idiopathic arthritis is a risk factor for neurologic manifestations (P < .05).

| Table 2. Neurological Symptoms of Patients |
|------------------------------------------|
| **Symptoms** | **n** (%) | **Negative, n (%)** |
| Headache | 72 (11.52) | 14 (17.1) |
| Myalgia | 50 (8.00) | 16 (2.56) |
| Vertigo and dizziness | 38 (6.08) | 2 (0.32) |
| Sensation disorders | 26 (4.16) | 1 (0.16) |
| Syncope | 22 (3.52) | 10 (1.60) |
| Muscle weakness | 16 (2.56) | 7 (1.12) |
| Visual disorders | 16 (2.56) | 2 (0.32) |
| Psychosocial disorders | 11 (1.76) | 2 (0.32) |
| Neurocognitive functional disorders | 10 (1.60) | 7 (1.12) |
| Movement disorders | 7 (1.12) | 1 (0.16) |
| Auditory disorders | 2 (0.32) | 1 (0.16) |
| Others | 7 (1.12) | 1 (0.16) |

*Some patients presented more than 1 symptom.*

| Table 3. The Age of Diagnosis and Neurologic Symptoms |
|------------------------------------------|
| **Age of Diagnosis** | **Neurologic Symptom Positive, n (%)** | **Neurologic Symptom Negative, n (%)** | **P** (95% CI) |
| <5 years | 31 (17.2) | 149 (82.8) | .037 (.030-.041) |
| 5-10 years | 67 (26.6) | 185 (73.4) | .037 (.030-.041) |
| >10 years | 37 (27.8) | 96 (72.2) | .037 (.030-.041) |

*Percentages of rows. **Pearson chi-square statistical probability value in cross-table analysis with Monte Carlo simulation.

| Table 4. Neurologic Diseases in Children with FMF |
|------------------------------------------|
| **Disease** | **n (%)** |
| Epilepsy | 16 (2.56) |
| Febrile seizure | 6 (0.96) |
| Aseptic/viral meningitis | 2 (0.32) |
| Cerebral vasculitis | 2 (0.32) |
| Cerebrovascular event | 2 (0.32) |
| Transverse myelitis | 1 (0.16) |
| Idiopathic intracranial hypertension | 1 (0.16) |
| Others | 10 (1.6) |

FMF, familial Mediterranean fever.

| Table 5. The Relation Between Mutation Type and Neurologic Symptoms |
|------------------------------------------|
| **Mutation Type** | **Neurologic Symptom Positive, n (%)** | **Neurologic Symptom Negative, n (%)** | **P** (95% CI) |
| M694V | 50 (16.3) | 257 (83.7) | .012 (.009-.014) |
| E148Q | 46 (30.9) | 103 (69.1) | .012 (.009-.014) |
| V726A | 14 (17.1) | 68 (82.9) | .012 (.009-.014) |
| R202Q | 11 (14.7) | 64 (85.3) | .012 (.009-.014) |
| M680I | 15 (22.7) | 51 (77.3) | .012 (.009-.014) |
| P369S | 6 (18.8) | 26 (81.2) | .012 (.009-.014) |
| K695R | 6 (28.6) | 15 (71.4) | .012 (.009-.014) |

*Percentages of rows. **Pearson chi-square statistical probability value in cross-table analysis with Monte Carlo simulation.
as celiac and rheumatic diseases. Chronic inflammation and a lower pain threshold in these children may play a role in the pathophysiology of headache.

The prevalence of epilepsy in Turkey was reported as 0.8%. Epilepsy was identified in 16/625 (2.56%) of the general FMF population in the present study. Canpolat et al. detected epilepsy in 5.8% of children with FMF. Among 2300 children with FMF, epilepsy was reported in 0.5% of them. Although the cellular and molecular mechanisms of epileptogenesis are unclear, focal or systemic dysregulated inflammatory processes might result in abnormal neural connectivity and the hyperexcitable neuronal network that mediates the onset of epilepsy. Chronic inflammation might have a role in the coexistence of epilepsy and FMF. In some patients, anti-epileptic drugs (AED) fail to control seizures.

Gentiloni et al. described a patient unresponsive to AED. Subsequently, the patient was diagnosed with FMF, and seizures were controlled after the administration of colchicine. The prevalence of febrile seizures (FS) is 2%-5% in the general pediatric population. Febrile seizures in children with FMF were more prevalent compared to healthy children. Both FS and FMF share common molecular pathways such as increased production of IL-1β.

A study done on children with simple FS revealed that 68% of children were heterozygotes for any mutation and M694V was the most common type of mutation. The risk of FS increased by 2.9-fold in FMF patients compared to the general population.

Idiopathic intracranial hypertension is a neurological disorder characterized by signs and symptoms of increased intracranial pressure in the absence of infection, vascular abnormality, or a space-occupying lesion. One patient was diagnosed with idiopathic intracranial hypertension (pseudotumor cerebri) and presented with papilledema. Idiopathic intracranial hypertension comorbid with FMF has been described in the literature. The exact explanation of this association is unclear yet.

Vertigo and dizziness were detected in 38 (6.08%) children. Salehzadeh et al. reported that 26.7% of their case series had suffered from vertigo in a study done with both adults and children. The nature of vertigo is subjective. Therefore, children in the present research might have been able to describe vertigo verbally.

Hearing loss or auditory disorders are described in pediatric FMF cases. Cochlear involvement occurs in FMF. Two children experienced hearing impairment in our study group. Unfortunately, we could not get any information about the prognosis of hearing loss in these children.

Cerebrovascular events have been rarely reported in FMF patients. Kalyoncu et al. reported that only 7 cases experienced stroke among 3034 adult patients. In another study done in adults, no stroke case was reported. In the present study, 2 children had a stroke. This result is quite high compared to adults. It is unclear whether FMF can be considered a risk factor for stroke is still to be answered; however, some associated diseases with FMF, particularly systemic vasculitis, may involve the central nervous system (CNS) and present CNS vascular disorders such as stroke and ischemia.

Canpolat et al. reported that M694V was the most frequent mutation (49.0% in the overall cohort), but it was more frequently detected in 59.0% of patients with neurological involvement. In contrast to them, we detected a lower frequency of neurologic manifestations in patients with M94V mutation. In a case series study, the headache was present in 47.26% of cases and it was more common in M694V mutation-negative patients. The high frequency of common neurologic symptoms in FMF patients with negative MEFV gene mutations could emphasize the partial protection and/or modifying role of this mutation in the appearance of these symptoms. Although there is no genotype-phenotype correlation, Cekin et al. reported that patients having E148Q or V726A mutant allele showed fewer clinical FMF symptoms in their case series.

At present, the frequency of consanguinity between parents and family history of FMF was found to be 9.7% and 39.5%, respectively. Although no effect of these parameters on the prevalence of neurologic manifestations was reported, these rates are lower than previously reported. Comorbidity is defined as the presence of 1 or more additional disorders to the existing disease. Rheumatologic disorders are common in FMF cases. Our results revealed that half of the study group had associated diseases and 3.5% of children had associated juvenile idiopathic arthritis (JIA). A recent study reported a similar rate of JIA in children with FMF. However, in a large case series conducted on both adult and pediatric cases, Peynircioglu et al. reported that 1.55% of FMF cases had JIA. The statistical analysis showed that it is an important risk factor for neurologic signs and symptoms. It is uncertain whether JIA is a risk factor for FMF because FMF and JIA association could be an over conclusion.

The main limitation of the present study is that the patients were evaluated retrospectively. Therefore, minor neurologic signs and symptoms might be underestimated and might not be recorded in the patient’s medical files.

In conclusion, neurologic manifestations are more common in FMF patients than in the general population. This could affect the prognosis of pediatric FMF cases. As a result, during routine follow-up visits, clinicians must be suspicious of any neurologic symptoms. Prospective, case-control research could support clarifying the pathophysiology of FMF neurologic signs and symptoms.

Ethics Committee Approval: The study was approved by the Eskisehir Osmangazi University Ethical Committee (Approval No: 2020/17).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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