Official Journal of the European Paediatric Neurology Society

Original article

Febrile seizures in children with familial Mediterranean fever: Coincidence or association?

Elif Çomak [a,*], *Özlem Tüfekçi* [b], *Fatih Kılıçbay* [c], *Emel Isıyel* [a], *Ali Haydar Sever* [c], *Ayça Aslanger* [d], *Barış Ekici* [e]

[a] *Pediatric Nephrology and Rheumatology, Derince Training and Research Hospital, Kocaeli, Turkey*
[b] *Pediatric Hematology, Derince Training and Research Hospital, Kocaeli, Turkey*
[c] *Pediatrics, Derince Training and Research Hospital, Kocaeli, Turkey*
[d] *Medical Genetics, Derince Training and Research Hospital, Kocaeli, Turkey*
[e] *Pediatric Neurology, Derince Training and Research Hospital, Kocaeli, Turkey*

ARTICLE INFO

Article history:
Received 22 December 2014
Received in revised form
4 May 2015
Accepted 9 May 2015

Keywords:
Familial Mediterranean fever
Children
Febrile seizure

ABSTRACT

Background: Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent bouts of fever and polyserositis and caused by MEditerranean FeVer gene (MEFV) mutations. Given the febrile characteristics of the disease one would expect higher frequency of febrile seizure in this group of pediatric patients.

Objectives: To evaluate the frequency of febrile seizure and related factors in patients with FMF.

Methods: The children with the diagnosis of FMF were enrolled in the study. Information including clinical features, type of mutation and the history of febrile seizure were all noted.

Results: A total of 97 patients, 43 (44.3%) girls with a median age of 7.93 ± 4.05 years (2–16) and a median follow-up period of 20.65 ± 24.33 months (6–135) were included in the study. The frequency of febrile seizure in children with FMF was found as 13.4%, which is higher than the general population [$p = 0.04$, OR: 2.9 (95% CI: 1.0–8.5)]. The allele frequency of exon 2 mutations in MEFV genes was higher in the patients with febrile seizure ($p = 0.03$). Frequency of FMF related clinical findings (fever, abdominal pain, arthralgia/myalgia, arthritis, chest pain and erysipelas-like erythema) was similar between the two groups. However, frequency of headache was higher in the patients with febrile seizure ($p = 0.014$).

Conclusion: The frequency of febrile seizure in children with FMF was found to be higher than the general population. Although this finding may be related to high fever during FMF attacks in individuals with genetic propensity of febrile seizure, it may also be a neurologic complication of FMF.

Abbreviations: CI, confidence interval; OR, odds ratio; OMIM, online Mendelian inheritance in man; EEG, electroencephalogram; FMF, familial Mediterranean fever; MEFV, Mediterranean fever gene.

* *Corresponding author*. Kocaeli Derince Training and Research Hospital, Department of Pediatric Nephrology and Rheumatology, 41900 Derince, Kocaeli, Turkey. Tel.: +90 262 317800; fax: +90 262 2335540.
E-mail address: elif_comak@hotmail.com (E. Çomak).

http://dx.doi.org/10.1016/j.ejpn.2015.05.004

1. Introduction

Familial Mediterranean fever (FMF, OMIM 249100) is an autosomal recessive disease characterized by self-limited recurrent episodes of fever and serositis. The disease is caused by mutations in the Mediterranean Fever gene (MEFV, OMIM 608107), which is composed of 10 exons and encodes a protein consisting of 781 amino acids protein named pyrin, serving as a negative regulatory protein of inflammation.[1]

Neurologic manifestations of FMF are rare and are still not clearly defined.[2,3] So far, some neurological disorders that might be relevant to FMF have been reported as sinus vein thrombosis,[4] pseudotumour cerebri,[5] optic neuritis,[6] central nervous system (CNS) complications of systemic vasculitidis (Henoch–Schonlein purpura (HSP)),[7] polyarteritis nodosa (PAN),[8] Behcet's disease (BD)[9] demyelinating lesions[3] and multiple sclerosis.[10] However little information is available regarding the presence of febrile seizures in children with FMF.[11,12] Febrile seizure is the most common seizure disorder in childhood. The prevalence and incidence of febrile seizure vary by geographic location. The incidence has been reported as 2–5% in the United States and Europe 1% in China, 2% in Taiwan, 8% in Japan and 14% in Guam.[13,14] Different studies from Turkey reported the incidence rate of febrile seizures as 2.57%, 3.2% and 4.48%.[15–17] Given the febrile characteristics of the FMF attacks, one would expect higher frequency of febrile seizure in this group of pediatric patients. The aims of this study were to evaluate the frequency of febrile seizures in children with FMF and also to examine whether there is an association between MEFV mutations types and febrile seizures in FMF.

2. Methods and material

2.1. Participants and procedures

The children with FMF who visited our outpatient clinic between January 2014 and July 2014 were enrolled. This cross-sectional study is conducted by same physicians during outpatient clinic visits. Caregivers of children were questioned whether the child had febrile convulsions diagnosed by a doctor?" If the answer was "Yes," age at onset of first seizure, duration of seizures, body temperature, and type of seizure were requested. Episodes of febrile seizures that occurred between the ages of 6 and 60 months were all noted. Information including demographic findings, clinical features, type of MEFV mutation, family history of FMF were collected from patients' medical records.

2.2. Definition

Febrile seizures are subdivided into 2 categories: simple and complex. A simple febrile seizure is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-h period. A complex febrile seizure is more prolonged (>15 min), is focal, and/or recurs within 24 h.[13]

The diagnosis of FMF was determined according to the criteria described by Livneh et al.[18] All children were of Turkish origin, from the different regions of Turkey. Ethics committee approval was obtained.

2.3. Genetic evaluation

Peripheral venous blood was collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes, and DNA was extracted from lymphocytes by standard methods. All patients were screened for the mutations located in exons 2, 3, 5 and 10 of the MEFV gene by direct sequencing.

2.4. Statistical analysis

Analysis was mainly descriptive, calculating mean and standard deviations. A chi-square test or Fisher's exact test was used to compare categorical variables, and odds ratio (OR) and 95% confidence interval (CI) were used for the assessment of risk factors. Mann–Whitney *U* tests was performed to compare group results. Analyses were performed with SPSS software, version 16.0 (Chicago, IL) and p value less than 0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

A total of 97 patients, 43 (44.3%) girls with a median age of 7.93 ± 4.05 years (2–16) and a median follow-up period of 20.65 ± 24.33 months (6–135) were included in the study. Twenty one patients (21.6%) had parental consanguinity and 49 patients (50.5%) had family history of FMF. Twenty seven patients (27.8%) were homozygous, 37 patients (38.1%) were compound heterozygous and 33 patients (34.1%) were heterozygous for MEFV gene (Table 1). A total of 13 children (13.4%) had history of febrile seizure. Of those, 6 had recurrent febrile seizure episodes (46.1%). One patient experienced 5 febrile seizure episodes at different times. The seizures were all simple febrile seizures in nature. The median time for febrile seizures was median 23 months (7–48 months), which was before the diagnosis of FMF. The febrile seizure incidence in different region of Turkey was reported as 2.57%, 4.48% and 3.2%.[15–17] When the frequency of febrile seizure in the general population is accepted as 5%, the frequency of febrile seizures was found to be significantly higher than that of the general population in FMF patients(13.4 vs 5%) [$p = 0.04$, OR: 2.9 (CI: 1.0–8.5)].

3.2. MEFV gene mutations in patients with febrile seizures

There was no difference between febrile seizure positive and negative patients regarding the allele frequency of MEFV mutations (80.7 vs 83.9%, $p = 0.77$). On the other hand, analysis of the frequency of exon 2 and exon 10 mutations between two groups revealed a higher frequency of exon 2 in febrile seizure