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# Increased Frequency of Febrile Seizures in Two Periodic Fever Syndromes: Familial Mediterranean Fever and PFAPA Syndrome

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## What is already known on this topic?

- *Familial Mediterranean Fever (FMF) is an autoinflammatory disease and studies have shown that the frequency of febrile seizure increases in FMF.*

## What this study adds no this topic?

- *Patients with Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome had an increased frequency of febrile seizures than general population.*
- *This increased frequency of febrile seizure in both periodic fever syndromes seems to be a result of recurrent fever, rather than a neurologic involvement of the underlying disease.*

## ABSTRACT

**Objective:** Our aim in this study is to reveal the frequency of febrile seizures in patients with Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome and to compare it to normal population.

**Materials and Methods:** Patients with Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome, who were diagnosed according to Turkish pediatric Familial Mediterranean Fever diagnostic criteria and Marshall criteria, were enrolled to the study. A form containing questions about febrile seizures history was prepared for Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome patients. Demographic data and febrile seizures history of Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis patients were obtained by calling the parents by phone. Familial Mediterranean Fever patients were randomly selected during their routine follow-up. The frequency of febrile seizures in both disease groups was compared with the prevalence of previous febrile seizures studies in the general population in Turkey.

**Results:** A total of 417 Familial Mediterranean Fever and 152 Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis subjects were recruited to the study. The frequency of febrile seizures in Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome was similar (8.4% vs. 8.6%; $P > .05$). The frequency of febrile seizures in Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome patients was found to be significantly higher than the frequency in general population (8.4% vs. 4.4%) [$P < .0001$, OR: 1.99 (CI: 1.4-2.8)]; (8.6% vs. 4.4%) [$P < .01$, OR: 2.03 (CI: 1.1-3.6)], respectively.

**Conclusion:** The frequency of febrile seizures in patients with Familial Mediterranean Fever and Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis syndrome was found to be significantly higher than in the general population. This increased frequency of febrile seizures in both periodic syndromes seems to be a result of recurrent fever.

**Keywords:** Familial Mediterranean Fever (FMF), Periodic Fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis (PFAPA) syndrome, febrile seizure, childhood

## INTRODUCTION

A febrile seizure (FS) is defined by International League Against Epilepsy as a convulsion associated with a febrile infection other than central nervous system infection, electrolyte disturbance, trauma, intoxication, or metabolic disorder. It is typical to occur between 1 month and 6 years of age.[1-3] Febrile seizures are classified as simple and complex, thus trying to predict the risk of developing epilepsy prospectively. Simple FS are generally defined

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as convulsions with no focal signs and lasting less than 15 minutes. The long-term adverse effects of simple FS have not been reported, but are still of great concern to parents.

Considering the possibility that methodological differences may be an underlying cause, the differences can be better understood in terms of the prevalence of FS in the world. The FS is the most common childhood seizure disorder, although geographical, genetic predispositions, and socioeconomic differences factors affect its incidence and prevalence. The prevalence was found to be 4.3% and 4.8%, in two separate studies conducted among large populations in our country recently.[4,5] Additionally, the prevalence has been reported as 2-5% in the United States and Europe and 6-9% in Japan.[6-8]

The most frequently seen periodic fever syndromes in Turkey are periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome, and Familial Mediterranean Fever (FMF).[9-12] There is a lack of data regarding the frequency of FS in periodic fever syndromes. Our aim in this study is to reveal the frequency of FS in patients with FMF and PFAPA syndrome and to compare it to a normal population.

## MATERIALS AND METHODS

### Study Population and Study Design

Patients with FMF and PFAPA syndrome, who were diagnosed according to Turkish pediatric FMF diagnostic criteria[13] and Marshall criteria for PFAPA syndrome,[14] were enrolled in the study. Patients with a history of major neurological diseases (cerebral palsy, neuromuscular diseases, stroke etc.) other than FS were excluded. FMF patients who met the study criteria and were accepted to participate in the study and were admitted to the hospital within certain periods (January 2017 to June 2017) were randomized. All patients who were followed up for PFAPA syndrome and accepted to participate in the study were included in the study by phone call.

### Patient Group

A form containing questions about FS history was prepared for FMF and PFAPA syndrome patients. The contents of the form were as follows: A FS history, age of first FS, one or more events within 24 hours, lasting longer than 15 minutes, focal seizure, less than 1 year old at first seizure, electroencephalographic (EEG) features, usage of antiepileptic drugs, family history of FS or epilepsy, and consanguineous marriage. Demographic and FS history of PFAPA syndrome patients were obtained during the telephone conversation with parents. Telephone interviews with parents of PFAPA patients were conducted by HK and EP. Familial Mediterranean Fever patients were randomly selected during their normal routine follow-up, questions on these forms were asked and notes were taken, one by one. Past medical history of all subjects from postnatal 6 months to 6 years of age were assessed in terms of FS. Apart from the questions recorded in the form, additional questions were asked to FMF patients with a history of FS. Thus, simple or complex FS and antiepileptic drug use histories were determined and recorded. The ethical protocol of the study was approved by the institutional review board of the Cerrahpasa Medical School (2017-394036).

### Statistical Analysis

The analysis was mainly descriptive. Interquartile range (IQR), mean and standard deviation were calculated. Categorical variables were compared with the chi-square test. Odds ratio (OR) and risk factors were evaluated with OR and a 95% CI. Analyzes were evaluated with the Statistical Package for Social Sciences, version 20.0 software (SPSS Inc.; Chicago,IL, USA) and statistically significant value was accepted as $P < .05$.

## RESULTS

### Demographic Features of Patients

A total of 417 FMF and 152 PFAPA syndrome subjects were recruited to the study with a female frequency of 49.9% and 42.8%, respectively. The mean age of the FMF and PFAPA syndrome patients at study time was 12.4 ± 4.5 years and 5.3 ± 2.1 years, respectively. The mean age at disease onset was 5.1 ± 3.8 (IQR: 2-7) years in the FMF group, whereas it was 21±16.5 months (IQR: 10-30) in the PFAPA syndrome group.

### Characteristics of the Patient Group

The frequency of FS in FMF (n = 35) and PFAPA syndrome (n = 13) was similar (8.4% vs. 8.6%). Among the subjects with FS, 42.9% (n = 15) in the FMF group and 30.8% (n = 4) in the PFAPA group underwent EEG. The EEG result of all subjects was reported to be normal. While 8 subjects with FS (22.9%) in the FMF group required anticonvulsant therapy, 2 patients (15.4%) in the PFAPA syndrome group used anticonvulsant treatment. Among the PFAPA syndrome subjects with FS (n = 13), 53.9% (n = 7) underwent tonsillectomy. Thereafter, 85.7% (n = 6) of the patients with tonsillectomy never experienced an FS. Febrile seizure characteristics in PFAPA and FMF patients are given in Table 1.

### Comparison of Groups

The prevalence of FS in both disease groups was compared with the prevalence of the general population found in previous large Turkish studies.[4,5] In order to determine the frequency of FS in the general population in Turkey, articles published in pubmed in the last five years were searched. Two separate studies with the frequency of FS in the general population in Turkey were found (the frequency of FS was 4.3% vs. 4.8%, respectively). The frequency of FS in the general population was recalculated by combining these two study pools. The frequency of pooled FS in the general population was calculated as follows: The total number of subjects (n=15548) was calculated by adding the total number of subjects participating in

**Table 1.** Febrile Seizure Characteristics in PFAPA Syndrome and FMF Patients

| | Age at First FS Year (Min-Max) | Seizure Under 1-Year Old of Age | More Than One Seizure in 24 hours | FS Longer Than 15 Minutes | Anticonvulsant Usage | Family History of FS |
|---|---|---|---|---|---|---|
| **FMF** (n = 35) | 2 (0.5-5.5) | 6 (17.1%) | 5 (14.2%) | 5 (14.2%) | 7 (20.0%) | 12 (34.2%) |
| **PFAPA** (n = 13) | 1.5 (0.6-4.0) | 4 (30.7%) | 0 | 1 (7.6%) | 2 (15.3%) | 4 (30.7%) |

FS, febrile seizures; FMF, familial Mediterranean fever; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis.

both studies. The total number of subjects diagnosed with FS (n = 638) was determined by adding the number of subjects diagnosed with FS in both studies. The pooled frequency was found by dividing the total number of patients diagnosed with FS to the total number of subjects (638/15548= 4.4%).

The frequency of FS in FMF patients (8.4%) was significantly higher than that observed in the studies of Atesoglu et al (4.8%; [$P < .001$, OR: 1.64 (CI: 1.1-2.4)]) and Canpolat et al (4.3%; [$P < .001$, OR: 1.86 (CI: 1.3-2.6)]), both of which investigated the prevalence of FS in two different regions of Turkey. In addition, the frequency of FS in PFAPA patients (8.6%) was also significantly higher than that observed in the studies of Atesoglu et al (4.8%; [$P < .05$, OR: 1.85 (CI: 1.03-3.34)]) and Canpolat et al (4.3%; [$P = .01$, OR: 2.10 (CI: 1.2-3.7)]).

Comparison of the frequency of pooled FS in the general population and study patients is as follows: The frequency of FS in FMF patients was significantly higher than the frequency in the general population (8.4% vs 4.4%) [$P < .0001$, OR: 1.99 (CI: 1.4-2.8)]. The frequency of FS in PFAPA syndrome patients was significantly higher than the frequency in the general population (8.6% vs. 4.4%) [$P < .01$, OR: 2.03 (CI: 1.1-3.6)]. However, the frequency of FS in FMF did not differ from the patients with PFAPA syndrome (8.4% vs. 8.6%, $P > .05$).

## DISCUSSION

In this study, the frequency of FS was determined in patients with FMF and PFAPA syndrome, known as periodic fever syndromes. As a result, the frequency of FS was found to be much higher in periodic fever syndromes than in the general population in Turkey. The frequency of FS in our country was determined in two separate studies conducted recently. In one of the studies conducted with a large population (n=10742), telephone interviews were conducted with the relatives of the patients who were determined by questionnaires and reported to have FS. The total prevalence of FS in Kayseri was found to be 4.3%.[4] In another study conducted with a large population (n=3806) in the province of Izmir, the prevalence of FS was found to be approximately as 4.8%.[5] The fact that these studies were carried out recently makes valuable in terms of showing the socioeconomic and cultural similarity between the study groups.

The incidence of febrile convulsions in Caucasians has been reported as 2% to 5%.[3,6] The frequency has been slightly higher in Asian population: 8% to 10%.[8,15] Although the prevalence of FS in Turkey was not clearly reported before 2018, prevalence rates of 4.5% and 3.5% were reported in two separate studies. The mentioned study was placed in Izmir province and performed in cross-sectional manner, with using the cluster sampling method in 2018.[5] The study population has been selected from the primary schools randomly and parents responded to the survey. The other study has been performed in the Kayseri provide, with the same methodology in the same year.[4] Furthermore, more details for children with history of febrile convulsions were obtained by the telephone conversation with parents. In those studies, the frequency of febrile convulsions was reported as 4.8% and 4.3%. Data obtained from both studies were like those from West European countries.[3]

Neurological complications are rarely seen during the course of FMF. It has been reported that neurological findings such as aseptic meningitis, pseudotumor cerebri, and headache may occur during recurrent polyserositis attacks.[16] FMF attacks are often accompanied by fever, suggesting an increased risk of FS. In a recent study of 97 patients with FMF, 13 patients were found to have a history of FS, which was reported to be significantly higher than in the general population.[17] In another recent study, the frequency of FS in FMF patients was found to be 9%.[16] Likewise, in the present study, the frequency of FS was found to be higher in patients with FMF than in the normal population. It can be suggested that this increase in frequency develops as a result of high fever during attacks in individuals with a genetic predisposition to FS, rather than being a neurological complication of FMF. In support of this prediction, patients with a diagnosis of FPAPA syndrome were also included in the study as a positive control group. The high frequency of FS in patients with a diagnosis of PFAPA syndrome also supports our results. The increase in the frequency of FS in both patient groups may suggest that the main reason is the increase in the frequency of fever, rather than a neurological complication.

PFAPA syndrome is a condition of unknown etiology, which is frequently observed in early childhood (below 5 years of age), presents with periodic fever, pharyngitis, oral aphthae, and cervical lymphadenopathy.[14,18] Body temperature usually rises up to 39-40,5 °C during attacks that are within the regularity of the clockwork. Although fever is typical during PFAPA syndrome attacks, the association of FS has not been investigated to date. In the present study, the fact that patients with PFAPA syndrome were exposed to fever attacks much more frequently than children in the normal population may explain the higher frequency of FS in this patient group. In patients with PFAPA syndrome, a frameshift variant in the CARD8 gene was found more frequently than in controls. The related variant causes loss of function in CARD8, resulting in an increase in NLRP3 function and caspase 1 activation.[19] In support of this prediction, Anakinra administration was effective in suppressing disease flares during long-term follow-up in a small cohort of glucocorticoid-resistant PFAPA syndrome patients.[20,21] Although active IL-1β increased by this mechanism explains the occurrence of fever in the pathogenesis of PFAPA syndrome, the results need to be clarified with larger cohorts.

Fever is the shared clinical feature of FS in patients with FMF and PFAPA syndrome. No single gene defect has been implicated in FS. A multifactorial genetic predisposition is responsible for FS, but most children with have no family history and therefore genetic testing is not routinely recommended. In this sense, interleukin 1 (IL-1) is the most important cytokine in the pathogenesis of fever, which is the common clinical feature of FS and autoinflammatory disease such as FMF. Caspase-1, which metabolizes pro-IL- to IL-1, is activated by a protein called pyrin, which is encoded by the MEFV gene.[22,23] Overproduction of IL-1, one of the endogenous pyrogens that cause fever, may be a cause that predisposes patients to FS in FMF patients and, although not yet fully elucidated, in PFAPA syndrome patients.

The immune system is regulated by pro-inflammatory and anti-inflammatory cytokines which are reported due to be increased during the infection. The etiology of febrile convulsion is multifactorial, including immune, inflammatory, cytokine and genetic factors that have common role. Proinflammatory

cytokines such as IL-1b, TNF-a, and IL-6 are responsible for the inflammatory response, including fever. The role of inflammatory mediators in the pathogenesis of febrile convulsions has been demonstrated in experimental studied. It is obvious that febrile convulsions develop during the febrile phase of patients which implicates the common mechanisms included in development of fever and febrile convulsions. Previous studies reported that plasma IL-1b levels were significantly higher in FS patients compared with the control group.

Although the history of FS has been carefully evaluated by an experienced pediatric neurologist, the retrospective nature of the study and data collection via telephone interview with parents raises the possibility of misunderstandings and recall bias, which represents the limitation of our study. Another limitation is that studies determining the frequency of FS in the normal population were conducted in different cities.

As a result, the frequency of FS in patients with FMF and PFAPA syndrome was found to be significantly higher than in the general population, in this study. The recurrent fever, which is the main shared manifestation of these two diseases, is possibly a trigger for FS. This increased frequency of FS in both periodic syndromes appears to be a consequence of recurrent fever. Although it does not seem to be related to the neurological involvement of the underlying disease, this result should be supported by prospective studies.

**Ethics Committee Approval:** This study was approved by Ethics committee of İstanbul University-Cerrahpaşa, (Approval No: 2017-394036).

**Informed Consent:** Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

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