

ORIGINAL ARTICLE

Could familial Mediterranean fever gene mutations be related to PFAPA syndrome?

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Abstract

Background: The cause and pathophysiology of PFAPA syndrome is unknown. The aim of this study was to determine all MEFV gene variants relevant to familial Mediterranean fever in children with PFAPA syndrome.

Methods: All MEFV gene variants were analyzed in patients with PFAPA syndrome. All patients were evaluated using the Gaslini scoring system. Serum immunoglobulin levels were also determined upon admission.

Results: We evaluated 64 patients with PFAPA syndrome. The median age at diagnosis was 37.5 (min–max: 6–96) months, and the percentage of male patients was 55.0%. The Gaslini diagnostic score for periodic fever was high in 81.0% of the patients. An MEFV gene mutation was found in 42 (66.0%) children. Mostly, heterozygous or compound heterozygous variants of the MEFV gene were found. Two patients were homozygous for R202Q. MEFV gene mutations were not detected in 22 (34.0%) patients. No significant differences in clinical or laboratory findings were observed between the two groups ($p > 0.05$), and there were no significant differences in period and duration of the fever episodes ($p > 0.05$). The fever of all 47 patients (100.0%) who received prednisolone during the episodes decreased within hours and did not recur. Eighteen of the patients using prednisolone underwent prophylaxis with colchicine, and the fever episodes of 9/18 (50.0%) patients using colchicine decreased within months.

Conclusions: Most patients presenting with PFAPA syndrome have heterozygous MEFV gene mutations. Whether carrying a heterozygous MEFV gene is the primary cause of this syndrome requires further investigation.

Periodic fever syndromes are a group of autoinflammatory conditions that share similar symptoms and are characterized by recurrent, unprovoked inflammatory processes in the absence of infection (1). Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome was first described in 1987 by Marshall et al. (2). The prognosis of this disease is better than those of other autoinflammatory diseases (3), and it is probably the most common cause of recurrent fever in children (4). However, the cause and pathophysiology of PFAPA syndrome is still unknown.

The familial Mediterranean fever (MEFV) gene, located on chromosome 16p13.3, is comprised of ten exons and it encodes pyrin, a protein involved in the regulation of apoptosis and inflammation. Over 80 mutations have been identified so far (5). Four missense mutations (M680I, M694V, M694I, and V726A) in exon 10 and one (E148Q) in exon 2 are the most common mutations in the Turkish

population (6). A few recent studies have reported that heterozygous variants of the MEFV gene were found in patients with PFAPA syndrome (1, 3, 7).

The aim of this study was to evaluate MEFV gene mutations in patients with PFAPA syndrome using the Gaslini diagnostic score (8).

Methods

Study population

Sixty-four children diagnosed with PFAPA syndrome between January 2011 and January 2014 who were followed up at our pediatric immunology and allergy department were included in this study retrospectively. Demographic data, disease duration, physical examination findings, erythrocyte sedimentation rates

(ESR), C-reactive protein (CRP), white blood cells (WBC), absolute lymphocyte counts (ALC), absolute neutrophil counts (ANC), and serum immunoglobulin (Ig) levels were evaluated during the attacks. The diagnosis of PFAPA syndrome was determined using previously established modified clinical criteria (9). PFAPA syndrome is characterized by episodes of fever lasting 3–6 days, with a recurrence every 3–8 weeks, and is associated with at least one of the three main signs: aphthous stomatitis, cervical adenitis, or pharyngitis. Disease onset is usually before 5 years of age and it generally resolves by adolescence. Patients are asymptomatic between episodes and show normal growth and development. Diagnosis is established on the basis of clinical criteria and on the exclusion of other possible causes of recurrent fever (2, 10). The patients in this study were divided into two groups: MEFV gene positive and MEFV gene negative.

Definition of hypogammaglobulinemia

The inclusion criterion was decreased serum levels of one or more major Ig isotypes upon presentation, defined as at least two standard deviations below the age-defined norms for healthy Turkish children (11). Patients receiving drugs (e.g., glucocorticoids, captopril, carbamazepine, phenytoin) that could lead to hypogammaglobulinemia were excluded from the study (12).

Detection of MEFV gene mutations

Each sample was screened by direct sequencing for mutations located in exons 2, 3, 5, and 10 of the MEFV gene. Genomic DNA was extracted from ethylenediamine tetraacetic acid (EDTA) anticoagulated whole blood samples using a Genomic DNA Purification Kit (Invitrogen, Carlsbad, CA, USA). Following selective amplification of exons 2, 3, 5, and 10 with specific primers (primer sequences available upon request), polymerase chain reaction products were run in a 2% agarose gel containing ethidium bromide and were visualized under UV light using an imaging system (Syngene InGenius, Cambridge, UK). Next, sequencing was performed using a BigDye Terminator v3.1 Cycle Sequencing Kit and an ABI 3500XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 15.0 (SPSS, Chicago, IL, USA). All data are expressed as median, mean $\pm$ standard deviation, or percentages. A chi-square test, a Mann–Whitney *U*-test, and Student's *t*-test were used, and values of $p < 0.05$ were accepted as statistically significant.

Ethical disclosure

Ethics committee approval was granted by decision no. OMU KAEK 2014/646 dated April 24, 2014 by the Ondokuz Mayıs University Ethics Committee of Medical Research.

Results

Sixty-four patients (35 boys and 29 girls) diagnosed with PFAPA syndrome were followed up in our clinic. While the median age of the patients at diagnosis was 37.5 months (min–max: 6–96 months), the median age of onset of symptoms was 18 months (min–max, 2–36 months). The Gaslini diagnostic score for periodic fever was high in 81% of the patients. In all the patients who received prednisolone during these episodes (47/64), the fever decreased within hours and did not recur. Thirty-two of these patients were from the MEFV-positive group, and 15 patients were from the MEFV-negative group. Eighteen of the patients with MEFV mutation who were given prednisolone underwent prophylaxis with colchicine. Nine (50.0%) of those patients responded to colchicine, and the episodes of fever decreased within months. Demographic data of the patients are summarized in Table 1. No significant differences in clinical or laboratory findings were observed between the MEFV-positive group and the MEFV-negative group ($p > 0.05$). The period and duration of the episodes also did not differ significantly between the two groups ($p > 0.05$) (Table 2). MEFV gene mutations were positive in 42 (65.6%) patients. Mostly, heterozygous or compound heterozygous variants of the MEFV gene (14 R202Q, 7 M694V/R202Q, 3 E148Q, 2 V726A, 2 M680I, 1 E148Q/D486D, 1 E148Q/R501R, 1 R202Q/L694V, 1 P369S/R408Q, 1 R202Q/M694V/M680I, 1 R202Q/M694V/E148Q, 1 R202Q/V726A, 1 T726I/T309R, 1

Table 1 Demographic and clinical data of patients with PFAPA syndrome

Variables	n (%)
Age at diagnosis (median, min–max), month	37.5 (6–96)
Age at onset (median, min–max), month	18 (2–36)
Male	35 (54.7)
Consanguinity	5 (7.8)
Gaslini risk score, high	52 (81.3)
MEFV variant	42 (65.6)
Interval between attack (median, min–max), week	2 (2–5)
Attack duration (median, min–max), day	4 (2–7)
Pharyngitis	64 (100.0)
Fever ($\geq 39^\circ\text{C}$)	54 (84.4)
Fever (38.5–39°C)	10 (15.6)
Aphthae	48 (75.0)
Abdominal pain	33 (51.6)
Musculoskeletal pain	27 (42.2)
Cervical lymphadenopathy	27 (42.2)
Diarrhea	18 (28.1)
Constipation	7 (10.9)
Response to colchicine prophylaxis	9/18 (50.0)
Response to prednisolone during attack	47/47 (100.0)
Response to tonsillectomy	4/4 (100.0)
Hypogammaglobulinemia	8 (12.5)
IgG deficiency	5 (7.8)
IgA deficiency	3 (4.7)
IgM deficiency	3 (4.7)
Total	64 (100.0)

Table 2 Comparisons of PFAPA patients according to the presence of MEFV mutation

	MEFV variants n = 42 n (%)	No MEFV variants n = 22 n (%)	p
Male*	21 (50.0)	14 (63.6)	0.437
Age at diagnosis (mean, s.d.), month‡	39.0 ± 24.6	44.8 ± 20.2	0.349
Age at onset (mean, s.d.), month‡	17.6 ± 10.3	19.8 ± 8.6	0.394
Gaslini risk score, high*	34 (81.0)	19 (86.4)	0.735
Consanguinity*	4 (9.5)	1 (4.5)	0.652
Interval between attacks (median, min–max), week†	2 (2–5)	2 (2–5)	0.880
Attack duration (median, min–max), day†	4.5 (3–7)	4 (2–7)	0.994
Aphthae*	31 (73.8)	17 (77.3)	1.000
Cervical lymphadenopathy*	17 (40.5)	10 (45.5)	0.907
Abdominal pain*	20 (47.6)	13 (59.1)	0.543
Musculoskeletal pain*	17 (40.5)	10 (45.5)	0.907
Diarrhea*	9 (21.4)	9 (40.9)	0.176
Fever (≥39°C)*	33 (78.6)	21 (95.5)	0.144
Hypogammaglobulinemia*	7 (16.7)	1 (4.5)	0.245
IgG deficiency*	4 (9.5)	1 (4.5)	0.652
IgA deficiency*	3 (7.1)	0 (0.0)	0.545
IgM deficiency*	3 (7.1)	0 (0.0)	0.545
CRP (mg/dl), median (min–max)†	21 (3–172)	13 (3–224)	0.297
ESR (mm/h), median (min–max)‡	35.3 ± 18.7	28.9 ± 18.4	0.196
ANC (/mm ³), median (min–max)†	4225 (1000–18,000)	4390 (1650–16,500)	0.697
ALC (/mm ³), median (min–max)†	3415 (1080–11,250)	3355 (890–5980)	0.292
WBC (/mm ³), median (min–max)†	8725 (3680–24,510)	9310 (3970–20,800)	0.949

s.d., standard deviation.

*chi-square test.

†Mann–Whitney *U*-test.‡Student's *t*-test.

A744S, 1 M694V, 1 E148Q/P369S/R408Q, and 1 M680I/V726A) were found. Two patients were homozygous for R202Q. No MEFV gene mutations were detected in the remaining 22 patients (34.3%). The MEFV gene variants of the 42 patients are shown in Table 3.

Discussion

MEFV gene mutations are associated with the activation of the interleukin (IL)-1 β pathway (13). Variants have been investigated in several types of inflammatory conditions, such as Behcet's disease, Crohn's disease, ulcerative colitis, Henoch–Schönlein purpura, and the coincidence of familial Mediterranean fever (FMF). These studies have revealed an increased incidence of the genes involved in FMF in patients with these autoinflammatory diseases, as well as an increased severity in the symptoms of each disease (14–18).

Recently, the role of MEFV gene mutations in PFAPA syndrome has been a topic of investigation. A few studies have reported an incidence rate of 27–65% MEFV mutations in this patient population (1, 3, 7); the ratio of MEFV gene mutations was 66% in our study. The ratio of MEFV gene mutations is about 20% in the normal Turkish population (19), indicating that MEFV gene mutations are more frequent in patients with

Table 3 MEFV mutations of patients with PFAPA syndrome

MEFV variants	Patients n = 64 n (%)
R202Q Het	14 (19.4)
M694V/R202Q CH	7 (9.8)
E148Q Het	3 (4.2)
V726A Het	2 (2.8)
R202Q Hom	2 (2.8)
M680I Het	2 (2.8)
E148Q/R501R CH	1 (1.4)
R202Q/L694V CH	1 (1.4)
P369S/R408Q CH	1 (1.4)
R202Q/V726A CH	1 (1.4)
T726I/T309R CH	1 (1.4)
A744S Het	1 (1.4)
R202Q/M694V/E148Q CH	1 (1.4)
E148Q/D486D CH	1 (1.4)
M694V Het	1 (1.4)
R202Q/M694V/M680I CH	1 (1.4)
E148Q/P369S/R408Q CH	1 (1.4)
M680I/V726A CH	1 (1.4)
Wilde type	22 (34.3)

Het, heterozygote, Hom, homozygote, CH, compound heterozygote.

PFAPA syndrome. Kolly et al. (4) found the rate of MEFV mutation-positive rates to be 4/15 (26.2%) in patients with PFAPA syndrome, which is considerably lower than the results of our study. However, in the study of Kolly et al., only the second and tenth exons of the MEFV gene were examined, while we examined the second, third, fifth, and tenth exons.

Tanauchi et al. found that patients with PFAPA syndrome had a higher rate of E148Q-L110P and P369S R408Q variants compared to healthy individuals, suggesting that mutations might trigger PFAPA syndrome. They also reported that some MEFV mutations might affect the PFAPA phenotype (3). In our study, while there was no E148Q-L110P mutation, a P369-R408Q mutation was detected in one patient. These findings undermine this assertion and suggest that mutations might vary by ethnic origin or geographic region.

Different studies have reported different results regarding the clinical features of PFAPA syndrome and its association with MEFV gene mutations. While it has been reported in the literature that PFAPA syndrome can start after 5 years of age (20), the symptoms of all of the patients in our study started prior to 5 years of age. In the current study, all of the patients had fever symptoms; however, 15.6% of the patients experienced fever between 38.5 and 39.0°C during their attacks. According to Berkun et al., PFAPA episodes in carriers of MEFV variants were shorter compared to those of patients without MEFV variants. In addition, the regular cyclic pattern of attacks and the occurrence of oral aphthae were lower in MEFV variant-positive patients than in patients without MEFV variants (21). Taniuchi et al. found that the only affected variable was the duration of PFAPA episodes: The duration was shorter in the variant-positive group than in the variant-negative group. In their conclusion, Taniuchi et al. (3) suggested that these results show that the MEFV gene might not affect the onset of some autoinflammatory diseases, but it is likely to modify the intensity and the displayed phenotype in terms of disease symptoms. In our study, there were no significant differences in clinical and laboratory findings, frequency pattern, or duration of episodes between the MEFV mutation-positive and MEFV mutation-negative groups.

Compared with the literature, the rate of cervical adenopathy was found to be lower in the present study, while abdominal pain symptoms were found to be similar (22). When cervical adenopathy and abdominal pain were assessed together, the rate of abdominal pain was found to be 16/27 (59.2%) in patients with cervical adenopathy and 17/37 (45.9%) in patients without cervical adenopathy. The lower rate of abdominal pain in patients with cervical adenopathy, along with other symptoms, led us to reject a diagnosis of FMF.

In the literature, there are a limited number of studies assessing serum Ig values in patients with PFAPA syndrome (23). Because our patients were admitted with a complaint of recurrent fever, their serum Ig levels were checked during the immunological assessment for differential diagnosis, and hypogammaglobulinemia was found in eight (12.5%) of our patients with PFAPA syndrome. Five of these patients recovered and were considered to have transient hypogammaglobulinemia; however, their periodic fever attacks

continued after they recovered from the hypogammaglobulinemia. The remaining three patients were considered to have unclassified hypogammaglobulinemia, as their low immunoglobulin levels continued.

Familial Mediterranean fever should be considered as part of the differential diagnosis of PFAPA. Padeh et al. studied a group of Israeli children with recurrent fever and noted that FMF could potentially be misdiagnosed as PFAPA. This is particularly true in regions of the world where FMF is common. However, FMF can be differentiated from PFAPA because FMF patients do not respond to prednisone/prednisolone (24). FMF is common in Turkey, but it is difficult to distinguish between FMF and PFAPA syndrome. In addition, it is very difficult to discern whether PFAPA syndrome is a clinical manifestation of a heterozygous MEFV mutation. In the current study, 18 patients who presented with signs of PFAPA were given both prednisolone and colchicine. All of these patients responded completely to prednisolone during the attacks, and their fever decreased within hours. The patients were warned to avoid using antipyretics during fever episodes and to only apply ice in addition to prednisolone. Colchicine treatment was started only in patients who were found to be MEFV mutation positive. The response to colchicine differed from patient to patient, with half of the patients achieving a good response to colchicine. The fever episodes decreased over the course of a few months with the use of colchicine. While some of the patients reached partial response, five of the 18 patients (27.7%) did not respond at all. Some patients only responded to prednisolone during the episodes and were not given colchicine. Therefore, there is no way of knowing whether those patients would have responded to colchicine. If heterozygous MEFV mutations manifest clinically in the form of PFAPA syndrome, how should PFAPA syndrome patients without mutations be evaluated? It is important to note that MEFV mutations are not detected in 15–20% of patients with FMF (25).

In a recent study from our country, the rate of heterozygote R202 mutation in the healthy Turkish population was found to be 33.8%, while the rate of homozygote R202 mutation was found to be 0.0% (26). In our study, R202Q mutation was found in 16/64 patients (25.0%). When this mutation is assessed alone, it does not seem higher than in the normal population. In our study, the R202Q was the most common mutation. Fourteen patients had heterozygous and two had homozygous R202Q mutations. It was shown in a recent study that R202Q mutations have both homozygous and heterozygous clinical manifestations (27). The mean age of Turkish patients with R202Q mutations was higher in the study of Çomak et al. than in our study. The most common symptoms were abdominal pain, fever, arthralgia/myalgia, arthritis, chest pain, and erysipelas-like erythema. In our study, we found that patients with R202Q mutations might present with PFAPA syndrome during the preschool years. When given prednisolone, the fever episodes of all of our patients decreased within hours. Four of the patients who responded to prednisolone therapy also received colchicine. Episodes of fever in those patients decreased within months.

The ratios of M694V-R202Q and E148Q mutations were also high in our study. E148Q has been determined to be a polymorphism by some authors (28), and some clinical studies have observed clinical heterogeneity and a high frequency of symptoms in patients with E148Q mutations (29). In the current study, there were three patients with an E148Q mutation. Two of those patients were given prednisolone during their attacks, and they achieved complete response.

Colchicine prophylaxis was also started in one of those two patients, and an obvious decrease in the number of attacks was observed.

In conclusion, most patients presenting with PFAPA syndrome have heterozygous MEFV gene mutations. Whether carrying a heterozygous MEFV gene is the primary cause of this syndrome requires further investigation.

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