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Original Article

Is colchicine more effective to prevent periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis episodes in Mediterranean fever gene variants?

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Abstract ***Background*:** Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is the most frequent repetitive fever syndrome in childhood. It is characterized by fever episodes lasting for approximately 3–6 days, once every 3–8 weeks.

***Methods*:** Clinical and laboratory data for PFAPA syndrome patients between January 2010 and December 2014 followed up at a tertiary pediatric care hospital were reviewed.

***Results*:** Four hundred children (256 male, 144 female; mean age at diagnosis, 4.2 ± 2.2 years), were enrolled in the study. During the episodes, mean leukocyte number was high (12 725/mm^3) with predominant neutrophils. The mean number of monocytes was 1256/mm^3, and 90.2% had monocytosis. Serum amyloid A and C-reactive protein were high in 84.6% and in 77.8% of the patients, respectively. Mediterranean fever (*MEFV*) gene heterozygous mutation was identified in 57 of the 231 patients (24.7%) in whom genetic analysis had been performed. The most frequent mutation was heterozygous M694V (10%, n = 23). Extension of between-episode interval following prophylaxis was noted in 85% of those on regular colchicine treatment (n = 303). In the colchicine group, between-episode interval was prolonged from 18.8 ± 7.9 days (before colchicine treatment) to 49.5 ± 17.6 days on prophylactic colchicine therapy; also, prophylactic treatment was more effective in reducing episode frequency in patients with *MEFV gene* variant (n = 54, 96%) than in those without (n = 122, 80%; P = 0.003).

***Conclusions*:** This study has involved the largest number of PFAPA syndrome patients in the literature. It is particularly important to assess and to demonstrate the high rate of response to colchicine prophylaxis in PFAPA syndrome patients, especially those with *MEFV* variant. On blood screening, neutrophilia associated with monocytosis and low procalcitonin could contribute to diagnosis.

Key words child, colchicine, *MEFV*, periodic fever, PFAPA syndrome.

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a polygenic/multifactorial autoinflammatory disorder of unknown etiology, first described by Marshall *et al.*[1] in 1987. This syndrome is characterized by periodically recurring episodes of high fever accompanied by symptoms of at least one of the following: aphthous stomatitis, pharyngitis, and/or cervical lymph node enlargement.

Children with PFAPA syndrome have episodes of fever, each lasting 3–6 days, usually 3–8 weeks apart. The most frequent accompanying sign is erythematous or exudative pharyngitis, cervical lymphadenopathy, with swollen and tender lymph nodes, and oral aphthosis. The clinical picture may be further exacerbated by headache, abdominal pain, nausea, vomiting, chills, malaise, myalgia, and arthralgia.[2–4] Symptoms dramatically reduce within 2–4 h following a single dose of prednisolone (1–2 mg/kg/day), which may also be used as a diagnostic criterion.[5]

The aims of this study were therefore to clarify the clinical clues that will facilitate the identification of PFAPA, which is a clinical diagnosis, and to investigate the efficacy and safety of colchicine prophylaxis in a large cohort. Additionally, we also investigated the effects of Mediterranean fever (*MEFV*) gene mutations on the severity of clinical PFAPA findings.

Methods

Clinical and laboratory data of 400 consecutive patients with PFAPA syndrome followed up at the Department of Pediatric Immunology and Rheumatology, Uludag University Faculty of Medicine, were collected from the medical records retrospectively. All participants included in the study fulfilled the Padeh *et al.*[6] clinical criteria for PFAPA syndrome. Demographic data, complete blood count, absolute monocyte count

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(AMC), absolute neutrophil count (ANC), serum immunoglobulins (Ig), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA), C-reactive protein (CRP), fibrinogen and procalcitonin were documented during the episodes. *MEFV gene* analysis was performed in 231 of the 400 PFAPA patients. The patients were started on colchicine for 12 consecutive months (<5 years of age, 0.5 mg/day; 5–10 years of age, 1 mg/day; >10 years of age, 1.5 mg/day).

The clinical response to colchicine prophylaxis was determined as interval prolongation of episodes. The study was approved by the Uludag University Faculty of Medicine Ethics Committee.

Statistical analysis

NCSS 2007 (Number Cruncher Statistical System, Kaysville, UT, USA) was used for the statistical analysis. In addition, the descriptive variables (mean, SD, median, frequency and ratio) with non-normal distribution were compared between the groups using Mann–Whitney *U*-test. Qualitative variables were compared using Pearson chi-squared test and Fisher's exact test. The confidence interval was determined as 95%, and $P < 0.05$ was accepted as significant.

Results

Four hundred patients (boys, $n = 256$, 64%; girls, $n = 144$, 36%) with PFAPA syndrome were included in this study. While the mean age of onset of symptoms was 2 ± 1.5 years (median, 1.5 years; range, 0.2–3 years), mean age at diagnosis was 4.2 ± 2.2 years (median, 4 years; range, 0.75–8 years). A family history of PFAPA (i.e. parents and siblings) was present in 31.3% of cases; parental consanguinity was identified in 12.3%; and 36.5% of patients were school aged. The clinical findings noted during PFAPA episodes consisted of pharyngitis, oral aphthous ulcers, cervical lymphadenopathy, headache, abdominal pain, joint pain and other symptoms; all of the patients had high fever during every episode (Table 1). SAA, CRP, fibrinogen and ESR were high in 84.6%, 77.8%, 50% and 46.2% of patients, respectively. Gender or school attendance was not found to affect the frequency of the episodes ($P > 0.05$).

Table 1 Clinical characteristics of PFAPA episodes

Symptoms	*n*	%
Fever	400	100
Pharyngitis	394	98.5
Cervical lymphadenopathy	270	67.5
Abdominal pain	161	40.2
Oral aphthous ulcers	157	39.3
Arthralgia	151	37.7
Headache	148	37.0
Myalgia	81	20.1
Skin rash	44	11
Conjunctivitis	20	5

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis.

A total of 356 patients (89%) had been receiving regular prophylactic colchicine treatment. Forty-four patients (11%) did not receive prophylactic treatment due to the side-effects of colchicine, or unwillingness to have daily therapy. Extension of episode interval following prophylaxis was noted in 85% of those on regular colchicine treatment ($n = 303$). In the colchicine group, the between-episode duration was significantly prolonged from 18.8 ± 7.9 before colchicine therapy to 49.5 ± 17.6 days on prophylactic colchicine therapy ($P = 0.001$), although mean age was similar between those who did and did not use colchicine (4.1 ± 2 years vs 4.5 ± 3.2 years, respectively). No side-effect was observed except mild diarrhea during colchicine treatment.

MEFV gene mutation analysis

The *MEFV gene* mutation status was investigated in 231 patients: in total 57 (24.7%) were found to have a heterozygous mutation in *MEFV gene*. The most frequent mutation was heterozygous M694V (10%, $n = 23$) and the second was heterozygous R202Q mutation (4.3%, $n = 10$). The other mutations were heterozygous E148Q (3%, $n = 7$), heterozygous V726A (2.5%, $n = 6$), heterozygous K695R (2.1%, $n = 5$), heterozygous M680I (1.7%, $n = 4$), heterozygous R761R (0.4%, $n = 1$) and heterozygous A744S (0.4%, $n = 1$).

Of the 231 patients with *MEFV gene* analysis, distributions of symptoms during episodes including pharyngitis, oral aphthous ulcers, cervical lymphadenopathy, headache, abdominal pain and arthralgia did not differ significantly between the heterozygous and non-heterozygous patients.

Patients were classified into three groups according to *MEFV gene* mutation status: group 1, most common disease-associated pathogenic *MEFV gene* variants: M694V, V726A, M680I, and M694I; group 2, other *MEFV gene* variants with unknown significance: K695R, E148Q and so on; and group 3, no mutation. Mean patient age in groups 1, 2 and 3 was 4.4 ± 2.1, 4.1 ± 1.7 and 4.2 ± 2 years, respectively ($P = 0.89$). The mean time interval between two consecutive attacks was similar between the three groups (group 1, 18 ± 13.2 days; group 2, 17.2 ± 8.3 days; group 3, 19 ± 8.2 days; $P = 0.75$). Mean attack duration was 3.2 ± 1 days in group 1, 3.4 ± 1.2 days in group 2 and 3.3 ± 1.1 days in group 3 ($P = 0.54$). There were no differences between the groups in terms of age and gender. IgG and A in group 2 were significantly higher than in the other groups. There was no significant correlation in the other clinical and laboratory characteristics between the groups (Tables 2 and 3).

A total of 96% of patients with *MEFV gene* variant responded to colchicine prophylaxis ($n = 54$), but in the group negative for *MEFV* gene mutation only 80% ($n = 122$) of those on colchicine treatment ($n = 153$) responded. Therefore, prophylactic treatment was more effective in reducing episode frequency in the *MEFV gene* variant group ($P = 0.003$).

Table 2 PFAPA symptoms vs *MEFV* mutation

	Group 1 (n = 33)		Group 2 (n = 24)		Group 3 (n = 174)		P-value
	n	%	n	%	n	%	
Family history	12	36.3	8	33.3	56	32.1	0.89
Parent consanguinity	6	18.1	4	16.6	17	9.7	0.28
Colchicine prophylaxis	33	100	23	95.8	153	87.9	0.06
Symptoms							
Fever	33	100	24	100	174	100	
Pharyngitis	28	84.8	18	75.0	136	78.2	0.61
Abdominal pain	18	54.5	7	29.1	82	47.1	0.15
Oral aphthous ulcers	21	63.6	14	58.3	115	66	0.75
Arthralgia	11	33.3	6	25.0	76	43.7	0.14
Headache	4	16.7	10	30.3	66	37.9	0.10
Myalgia	10	30.3	6	25	50	28.7	0.7
Skin rash	4	12.1	2	8.3	20	11.4	0.12
Conjunctivitis	2	6	–	–	10	5.7	0.13

MEFV, Mediterranean fever; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis.

Mean AMC during episodes increased significantly compared with the non-episode period (during episodes, 1268.8 ± 440/mm^3; between episodes, 673.6 ± 287/mm^3; $P < 0.001$). During the episodes, procalcitonin was normal in 288 out of 296 patient (97.3%) and fibrinogen was high in 162 out of 324 patient (50%).

Clinical response to prednisolone (1 mg/kg/day) during the episodes occurred at between 0 and 10 h (mean, 3.6 ± 2.3 h). A total of 92.8% of all patients received steroid therapy during the episodes, and the prevalence of tonsillectomy was 1% (n = 4).

Discussion

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome is the most common autoinflammatory syndrome in children due to the lack of evidence of autoimmune or infectious causes.[7] PFAPA is considered as an autoinflammatory disease, but the exact pathogenesis or genetic background remains unclear. In the present study, there were more male than female patients (246/144), similar to previous studies.[4,6] This disease has an early onset (usually before the age of 5 years) and in general it completely resolves before adulthood.[7] In the present study, the mean age at onset was 2 years, and the mean duration of the episodes was 3.3 days. In a recently published study comparing PFAPA patients from Turkey and the USA, the Turkish patients had symptom onset at a younger age and shorter duration of fever episodes during attacks compared with the US patients.[8] The authors concluded that epigenetic and environmental factors might modify the phenotypic features of PFAPA.

Although it is generally considered a sporadic disease, frequent occurrence in members of the same family and emergence of common genetic mutations (*NLRP3*, *MEFV*, *TNFRSF1A*, *MVK*, *AIM$_2$*) in the periodic fever syndrome

Table 3 Laboratory data vs *MEFV gene* mutation

	Group 1 n = 33 Mean ± SD	Group 2 n = 24 Mean ± SD	Group 3 n = 174 Mean ± SD	P-value
Leukocytes (/mm^3)	13 525.8 ± 5,745.0	11 245.4 ± 3,981.5	13 076.6 ± 4,561.7	0.96
Hemoglobin (g/dL)	11.9 ± 0.9	11.8 ± 0.8	11.7 ± 0.9	0.54
Platelets (/mm^3)	285 151.5 ± 65 171.5	275 166.7 ± 74 670.1	281 540.2 ± 83 528.7	0.99
ANC (/mm^3)	8,084.5 ± 3,916.9	7,152.1 ± 3,680.6	7,495.0 ± 3,673.4	0.81
AMC (/mm^3)	1,203.3 ± 459.1	1,263.3 ± 404.3	1,259.3 ± 406.5	0.88
ALC (/mm^3)	2,750.0 ± 1,193.2	2,925.4 ± 1,685.9	2,569.1 ± 1,277.0	0.81
CRP (mg/dL)	2.5 ± 2.6	2.8 ± 3.1	2.8 ± 2.6	0.88
Serum amyloid A (mg/L)	187.9 ± 215.7	248.8 ± 151.7	312.6 ± 332.1	0.11
Fibrinogen (mg/dL)	382.7 ± 157.4	378.0 ± 141.9	435.7 ± 122.5	0.23
ESR (mm/h)	23.6 ± 12.5	22.0 ± 10.5	24.7 ± 18.5	0.98
IgG (mg/dL)	850.4 ± 250.3	1,135.5 ± 215.1	907.1 ± 265.9	0.005
IgA (mg/dL)	107.6 ± 76.7	149.5 ± 56.8	101.9 ± 60.0	0.001
IgM (mg/dL)	109.7 ± 56.3	106.3 ± 50.8	96.1 ± 34.3	0.36

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; MEFV, Mediterranean fever.

spectrum suggest a probable genetic transmission of PFAPA syndrome.[7,9–12] In the present study, the prevalence of positive family history (parents and siblings) was 31.2%, but there was no finding indicative of autosomal dominant inheritance.

The PFAPA syndrome may arise from malfunction in the control of inflammation, due to mutations in inflammasome-related proteins indirectly leading to abnormal inflammasome activation. Possible involvement of *MEFV gene* mutations associated with the activation of the interleukin (IL)-1β dependent innate inflammatory response might be involved in PFAPA.[11] To date, more than 200 mutations have been reported in *MEFV gene*.[13] *MEFV gene* mutation frequency in the healthy population varies according to country.[13–18] In a screening study conducted in the healthy Turkish population by the Turkish Familial Mediterranean Fever (FMF) Study Group, the prevalence of *MEFV gene* carriers was 20%, and the most common *MEFV gene* mutations were E148Q (12%), M680I (5%), M694V (3%) and V726A (2%).[18,19] Additionally, in a recent study from Turkey the prevalence of heterozygous R202Q mutation in a healthy Turkish population was 33.8%.[20] The prevalence of *MEFV gene* mutations is between 8% and 66% in PFAPA patients in various studies.[7,12] Dagan *et al.*[9] identified M694V (15.7%) as the most common mutation in PFAPA patients, followed by A726V (8%) and E148Q (3.5%). Celiksoy *et al.*[12] reported a high prevalence of *MEFV gene* variants (66%), mostly R202Q mutation, in PFAPA syndrome patients.

In the present study, *MEFV gene* mutation was investigated in 231 patients, 24.7% of whom ($n = 57$) were positive for heterozygosity. The most frequent mutation was M694V heterozygosity in 23 patients (10%), followed by R202Q heterozygosity in 10 patients (4.3%). Heterozygous M694V mutation was the most common variant in PFAPA patients in both the Dagan *et al.* and the present series.

Batu *et al.*[8] found no differences between PFAPA patients with and without *MEFV gene* variants in terms of demographics, clinical data and laboratory parameters. Although there was no association between the presence of *MEFV gene* mutation and age at onset or symptom severity, serum IgG and IgA in group 2 patients were higher than in the other two groups. During the fever episodes, pharyngitis was present in most of the patients (98.5%), and cervical adenitis and aphthous stomatitis were present in 67.5% and in 39.3% of patients, respectively, similar to other studies.[21,22] Inflammatory parameters are elevated during febrile episodes in PFAPA patients.[23] Kolly *et al.*[11] also showed that fever episodes are characterized by increased neutrophil and monocyte count, although AMC was not significantly increased compared with the afebrile period in that study. They also showed that stimulated circulating mononuclear cells secreted significantly more IL-1β during attacks, suggesting that IL-1β production by monocytes is dysregulated in PFAPA syndrome. Monocytes carry various receptors to track environmental changes. Antigen processing and presentation to T cells involve active contribution by the monocytes. Besides leukocytosis and neutrophilia, 90.2% of the present patients had monocytosis during episodes. We therefore consider that AMC during febrile episodes may be included in the diagnostic criteria for PFAPA syndrome.

Erythrocyte sedimentation rate, SAA and CRP were raised during febrile attacks, similar to previous studies.[11,23–25] Procalcitonin concentration does not increase with the increase of other acute-phase reactants during attacks, which identifies this protein as a possible useful marker for differentiating PFAPA syndrome from infection. During the PFAPA episodes, 97.3% in 296 evaluated patients of the present patients had normal serum procalcitonin (data not shown). Fibrinogen was high in approximately 50% of 324 evaluated patients of cases. This high level during attack did not differ significantly between *MEFV gene* heterozygous and non-heterozygous PFAPA patients.

With regard to serum Ig, 9% of 332 patients had low IgG, IgA and IgM. When age group and the presence of antibody response were analyzed, the patients were diagnosed as having transient hypogammaglobulinemia of infancy.

Colchicine is a phenanthrene derivative of plant origin, and its anti-inflammatory effect is generated by binding to tubulins, thereby blocking the assembly and polymerization of microtubules. Microtubules, key components of the cytoskeleton, are involved in various cellular processes including maintenance of cell shape, intracellular trafficking, cytokine and chemokine secretion, cell migration, and regulation of ion channels and cell division. The therapeutic use of colchicine has been well documented in gout, FMF and Behçet disease.[19,26] The cause remains obscure but overexpression of inflammasome-related genes and increase in IL-1β during attacks in PFAPA suggest an autoinflammatory mechanism. Similarly to FMF, T-helper (Th)1 activation is responsive to IL-1 blockade. The rationale for colchicine prophylaxis in the present study was based on the clinical and laboratory similarities between these two very common autoinflammatory disorders in Turkey. It has been considered as an effective prophylaxis, rather than as treatment for the periodic attacks in PFAPA syndrome, in a small number of studies with a limited number of patients.[6,27,28] Tasher *et al.*[28] reported that colchicine treatment increased the between-episode interval in eight out of nine patients. Between-episode interval was significantly increased following colchicine treatment, from an average of 1.7 to 8.4 weeks. In the present study, extension of episode interval following prophylaxis was identified in 85% of those ($n = 303$) on regular colchicine treatment. The between-episode duration in the colchicine group was significantly prolonged from 18.8 ± 7.9 to 49.5 ± 17.6 days on prophylactic colchicine therapy ($P = 0.001$).

When the response to colchicine prophylaxis was evaluated in the patients with and without *MEFV gene* mutation, 33 patients were non-responders, 31 of whom (93.9%) were negative for *MEFV gene* mutation. In the patients with *MEFV gene* mutation, only two did not respond to colchicine. The clinical picture of the attacks in the *MEFV gene* variant patients was more compatible with PFAPA than FMF. In the literature, the clinical symptoms in patients with *MEFV gene* variants were exacerbated in periodic fever syndrome, and in autoimmune diseases such as Behcet's disease and rheumatoid arthritis.[29–31]

Although no association was detected between the severity of symptoms and the presence of *MEFV gene* mutations in the present study, colchicine prophylaxis was more effective in reducing the frequency of episodes in PFAPA patients with *MEFV gene* variant.

The role of tonsillectomy in PFAPA syndrome is controversial. In a meta-analysis of 15 studies on this subject, 149 PFAPA syndrome patients underwent tonsillectomy, 83% of whom were in remission.[32] Tonsillectomy alone or tonsillectomy plus adenoidectomy remains a highly efficacious treatment for PFAPA, but given that PFAPA syndrome is a self-limiting disease, surgery should be reserved for prophylactic treatment-refractory cases. Four of the present patients underwent tonsillectomy and periodic episodes resolved immediately in all.

Prednisolone is the most common first-line drug in the treatment of episodes, but it does not prevent recurrence and may even increase the frequency. Therefore, colchicine, a well-recognized drug with a high safety profile, is a good option for reducing the frequency of episodes and avoiding the side-effects of prednisolone, especially in those with *MEFV gene* variant.

PFAPA syndrome resolves spontaneously and tonsillectomy does not seem to be a valid option in all PFAPA patients with or without *MEFV gene* variant.

In conclusion, PFAPA syndrome is a very frequent disease of childhood. Pediatricians should keep PFAPA syndrome in mind before prescribing antibiotics when they encounter patients with recurrent fever episodes and pharyngitis, especially when the laboratory data indicate monocytosis associated with neutrophilia and normal serum procalcitonin. Colchicine was effective in decreasing the frequency of fever episodes. But the clinical response to colchicine prophylaxis was better in *MEFV gene* carriers. Tonsillectomy should be reserved only for treatment-refractory individuals.

Limitations

This was a clinical study and the data were collected retrospectively.

Disclosure

The authors declare no conflict of interest.

Author contributions

G.M. and K.S.S. designed the study; G.M., C.S. and K.S.S. collected and analyzed data and wrote the manuscript. All authors read and approved the final manuscript.

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