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Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome: A Single-Center Experience

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What is already known on this topic?

- *PFAPA syndrome is one of the most common periodic fever syndromes in children.*
- *There is no consensus in treatment of PFAPA syndrome.*
- *Collaborative studies and cumulative knowledge about the disease are needed.*

What this study adds on this topic?

- *Apart from cardinal signs, abdominal pain, myalgia, and headache may also be seen in PFAPA syndrome.*
- *Colchicine may be a good alternative for episode prophylaxis in PFAPA syndrome.*
- *The frequency of cervical adenitis is higher in males.*

ABSTRACT

Objective: The purpose of this study is to share our experience about clinical findings, natural course, and treatment response rates of a large cohort of patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome.

Materials and Methods: Medical records of patients who were diagnosed with PFAPA syndrome between January 2010 and May 2021 at Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty pediatric rheumatology department were reviewed retrospectively.

Results: A total of 607 patients (females: 277, males: 330) with PFAPA syndrome were included. The median duration of episodes was 3 (1-15; interquartile range (IQR) 3-5) days, and the median interval between episodes was 20 days (5-120; IQR 15-30). The median age at the last attack and median disease duration were 66 (24-168; IQR 48-84) months and 40 (4-132; IQR 27.5-60) months, respectively. Fever (100%) was the most common clinical finding, followed by pharyngitis/exudative tonsillitis in 594 (97.9%), aphthous stomatitis in 308 (50.7%), cervical lymphadenopathy in 278 (45.8%), abdominal pain in 249 (41%), and arthralgia in 228 (37.6%) of the patients. Among the clinical findings, there was no statistical difference according to gender, except for cervical lymphadenitis being higher in males ($P < .001$). Of the patients who were given steroids during attacks, 94.6% were responsive. Colchicine was effective in 93 (63.7%) patients. The disease episodes ceased in 313 (95.4%) of patients who had tonsillectomy/adenoidectomy.

Conclusions: Clinicians should be alert for additional symptoms such as abdominal pain, arthralgia, and headache apart from the cardinal signs. Although tonsillectomy is highly effective, its use is controversial. Colchicine may be a good alternative for prophylaxis.

Keywords: PFAPA, pharyngitis, aphthous, stomatitis, periodic fever, course

INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, an autoinflammatory disease with unknown etiology, was first reported in 1987.[1] The episodes of the disease which last 3-7 days and reoccur every 3-8 weeks usually start before the age of 5 and are usually accompanied by at least one of the following: cervical adenitis, pharyngitis, and aphthous stomatitis.[2,3] Although the disease is commonly seen in childhood and resolves before the adolescent period, there is an increasing number of studies reporting the adult-onset PFAPA syndrome.[4]

In spite of the fact that the disease is known for many years, there are still lots of unsolved points about its etiopathogenesis and genetic background. The disease belongs to a group of autoinflammatory disorders which are associated with hyperactivity of innate immunity and unprovoked episodes of hyperinflammation.[2,3] Although the genetic bases of

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most of these autoinflammatory diseases are well-known, no causative/predisposing gene mutation has been established so far despite the increasing number of studies reporting familial aggregation in PFAPA syndrome and suggesting a possible genetic basis.[5-7] Another unmet need in PFAPA syndrome is the absence of evidence-based treatment recommendations which causes treatment approaches to depend on expert opinion and vary highly between the clinics.[8] Therefore, there is obviously a need for collaborative studies and cumulative knowledge about the disease for solving these points.

The purpose of this retrospective cohort study is to share our experience with clinical findings, natural course, and treatment response rates of a large cohort of PFAPA patients.

METHODS

The medical records of patients who were diagnosed with PFAPA syndrome between January 2010 and May 2021 at Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty pediatric rheumatology department were reviewed, respectively. In total, 607 patients with PFAPA syndrome who agreed to participate were enrolled in the study, and demographic features, clinical findings, treatments used, and treatment response for each medication were noted. The diagnosis of PFAPA syndrome was made based on modified Marshall's criteria by a pediatric rheumatologist.[9] The family history of familial Mediterranean fever (FMF) or PFAPA was considered as positive if there is an individual with FMF or PFAPA among the first- or second-degree relatives of the patients. Steroid responsiveness was defined as the disease episode ceasing within 6 hours after a single dose steroid administration during the disease attack. The patients whose disease episodes ended or became less frequent after colchicine treatment were considered as "colchicine responsive." The disease was considered to be ceased if the patient did not experience an attack for at least 1 year.

Statistics

Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for performing the statistical analyses. For assessing the distribution of the variables, the Kolmogorov–Smirnov test and/or Shapiro–Wilk test were used. While categorical variables were given as numbers (percentages), the continuous variables with normal distribution were represented as mean ± SD. The continuous variables without normal distribution were given as median (minimum-maximum; IQR 25th-75th percentiles). For comparing the categorical variables between groups, the chi-square test was used. The comparison of continuous variables was made by using the Mann–Whitney *U* test. The *P* value < .05 was considered significant.

Ethics

Istanbul University-Cerrahpasa Institutional Review Board reviewed and approved the protocol of the study (29430533-903.99-167385). Verbal and written informed consent was obtained from participants.

RESULTS

Demographic Features

A total of 607 patients (females: 277, males: 330) with PFAPA syndrome were included in the study. The median age at the time of the study, at disease onset, and at diagnosis were 8.5 (1.8-21.1; IQR 6.2-10.8) years, 18 (1-60; IQR 11-30) months, and 36 (12-180; IQR 24-51) months, respectively. The duration of episodes was 3 (1-15; IQR 3-5) days, and the median interval between episodes was 20 (5-120; IQR 15-30) days. In total, 36.4% (97/266) of the patients who did not undergo tonsillectomy/adenoidectomy, episodes ceased during the follow-up. Among these patients, the median age at the last attack and median disease duration were 66 (24-168; IQR 48-84) months and 40 (4-132; IQR 27.5-60) months, respectively. Family history of PFAPA syndrome, tonsillectomy, and FMF was detected in 29.7% (180), 47% (285), and 15.2% (96) of the patients, respectively. No difference was found for age at the time of the study, at disease onset, and at diagnosis and duration of episodes between females and males (for all $P > .05$).

Clinical Findings

Fever was the most common clinical finding and was reported in 607 (100%) patients, followed by pharyngitis/exudative tonsillitis in 594 (97.9%), aphthous stomatitis in 308 (50.7%), cervical lymphadenopathy in 278 (45.8%), abdominal pain in 249 (41%), arthralgia in 228 (37.6%), nausea in 150 (24.7%), headache in 90 (14.8%), rashes in 79 (13%), myalgia in 64 (10.5%), diarrhea in 58 (9.6%), chest pain in 31 (5.1%), and arthritis in 21 (3.5%) of the patients. Among the clinical findings, there was no statistical difference according to gender, except for cervical lymphadenitis being higher in males ($P < .001$). The frequencies of the clinical findings of patients and the comparison according to gender are shown in Figure 1.

Treatment Approaches

In total, 477 (94.6%) of 505 (83.2%) patients who were given steroids during attacks were responsive. Colchicine treatment was tried in 146 (24.1%) patients with PFAPA syndrome and 93 (63.7%) of them were responsive. Tonsillectomy/adenoidectomy had been performed on 328 (54%) patients during the follow-up and the disease episodes ceased in 313 (95.4%) of them (Figure 2). No statistical difference was found according to the response rates for each treatment option between females and males (for all $P > .05$).

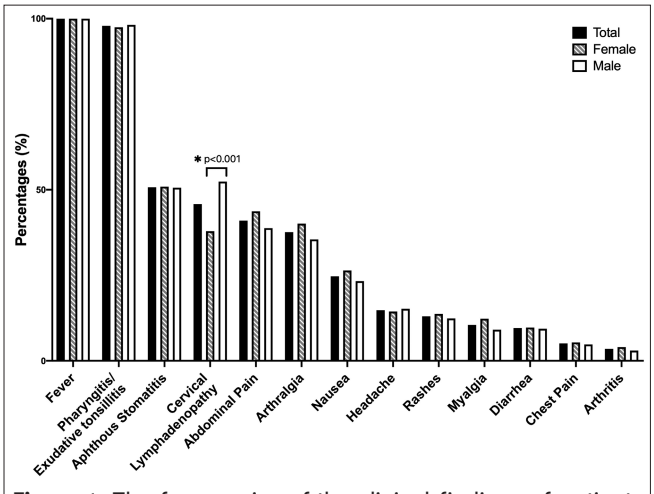

Figure 1. The frequencies of the clinical findings of patients and comparison according to gender.

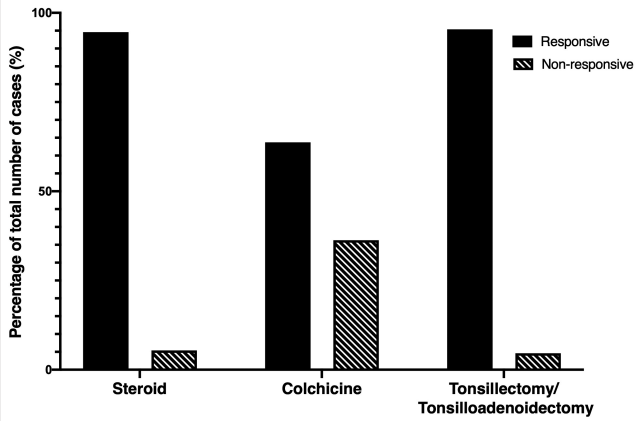

Figure 2. Treatment approaches and response rates.

Demographic features and clinical findings of patients of recent study and main PFAPA cohorts reported were summarized in Table 1,[5,10-18] and the comparisons of the demographic features and clinical findings of the patients according to gender were shown in Table 2.

DISCUSSION

In this retrospective cohort study, we report our experience with clinical findings, natural course, and treatment response rates of a large cohort of PFAPA patients from one of the biggest referral centers in Turkey. To our best knowledge, this is the biggest PFAPA cohort reported so far, and we believe that the results of the study may extend the clinicians' understanding of the phenotype of the disease and may help clinicians for decision-making process about the management of their patients.

In our study population, consistent with the literature, males were the majority (54.4%).[10-18] The median age at disease onset (18 months), median episode duration (3 days), and median symptom-free interval (20 days) were also in accordance with the previous studies.[5,10-18] There is an ongoing debate about the necessity of the age cut-off as a criterion for the classification of PFAPA syndrome. Although the onset of the disease before the age of 5 is a mandatory criterion according to the modified Marshall's criteria, there is an increasing number of papers reporting adult-onset PFAPA syndrome.[4,19] Hofer et al.[12] reported that 10% of their patients that were classified as PFAPA patients based on expert opinion had disease onset after 5 years of age and the patients with late-onset disease showed similar clinical features compared with patients with disease onset before 5 years of age. Based on these findings, the authors suggested that age is not a reason for exclusion.[12] As we used modified Marshall's criteria[9] for diagnosing patients, there were no patients with disease onset after 5 years of age in our cohort.

As expected, pharyngitis/exudative tonsillitis (97.9%), aphthous stomatitis (50.7%), and cervical lymphadenopathy (45.8%) were the most common clinical findings after fever (100%) in our cohort. As it can be seen in Table 1, these three cardinal symptoms were the most commonly reported ones among patients with PFAPA syndrome in nearly all published cohorts.[5,10-18] Interestingly, patients also reported various clinical symptoms apart from cardinal findings of the disease such as abdominal pain (41%), arthralgia (37.6%), nausea/vomiting (24.7%), headache (14.8%), rashes (13%), myalgia (10.5%), diarrhea (9.6%), chest pain (5.1%), and arthritis (3.5%). Most of these clinical findings were also reported among patients with PFAPA syndrome in various studies.[5,10-18] In one of these studies, Hofer et al.[12] speculated that these additional clinical findings may be due to the increased systemic inflammation or awareness of these children about the clinical symptoms. It should be noted that these additional clinical symptoms may cause diagnostic difficulties and misdiagnoses. As fever episodes and abdominal pain, which was reported in 41% of our patients, are also classical findings of the FMF, these two diseases may be confused with each other. Adrovic et al.,[3] in their study discussing the shared features and differences of FMF and PFAPA syndrome, stated that these two conditions have several common points causing diagnostic difficulties and suggested that the ethnicity of the patients, the regularity of the disease episodes, and the presence of the upper respiratory system-related symptoms may be useful for differential diagnosis.

One of the novel findings of the recent study was cervical lymphadenitis being higher in males ($P < .001$). The frequencies of the remaining clinical findings, the response rate to each treatment, age at disease onset and at diagnosis, and duration of episodes were similar between females and males. There are only a few studies assessing the difference of the disease phenotype between genders in the literature. Gunes et al.[10] reported that there was no difference between genders for the frequency of disease episodes. In two different studies, it was shown that sex ratio was similar between family history-positive and -negative patients with PFAPA syndrome[6] and between patients responding or not.[13]

Although PFAPA syndrome is a self-limited disease, it is obvious that it has certain negative effects on the quality of life of the patients and their families. As previously mentioned, there is no consensus about the management of the disease, and the treatment approaches usually depend on expert opinion and are highly variable between the clinics. Although it is well known that corticosteroids are exceedingly effective in ending fever episodes, it does not prevent further episodes.[2] In addition, it is shown that corticosteroids shorten the symptom-free periods and hence increase the frequency of the episodes in some of the patients.[20] In accordance with the literature, most of our patients (94.6%) were responsive to steroids.[5,10-18]

Colchicine, a blocker of the assembly and polymerization of microtubules, is one of the main treatment options for preventing episodes of PFAPA syndrome. In a randomized-controlled study, it was shown to be effective in decreasing the episodes.[21] In our daily practice, we discuss all of the treatment options in detail with every patient diagnosed with PFAPA syndrome and their families. Although there is no consensus for indications of colchicine treatment in PFAPA syndrome, in general, we suggest it to patients with frequent disease episodes who have excessive need for steroid treatment and who do not want to have tonsillectomy, regardless of their Mediterranean fever gene (MEFV) status. Consistent with the studies reporting the efficacy on decreasing the episodes of the colchicine treatment in 45.5-85% of PFAPA patients, 63.7% of our patients were responsive to colchicine.[10,11,14,15,18,22] In contrast to the

Table 1. Demographic Features and Clinical Findings of Patients of the Recent Study and Main PFAPA Cohorts Included More Than 50 Patients

	Recent Study	Güneş et al.[10]	Amarilyo et al.[11]	Hofer et al.[12]	Vigo et al.[13]	Aviel et al.[14]	Batu et al.[15]	Berkun et al.[16]	Perko et al.[17]	Manhtiram et al.[5]	Çeliksoy et al.[18]
Number of patients	607	400	303	301	275	270	131	124	81	80	64
Gender (males, %)	54.4	64	60.4	53.4	58.9	60	64.7	57	63	47	54.7
Age at disease onset	18 (1-60) months	2 ± 1.5 years	2.9 ± 1.8 years	20.4 (1.2-144) months	27.9 (6-148) months	3 ± 1.9 years	21 (2-159) months	2.9 ± 2 years	2.1 (0.1-6.5) years	20.1 months	18 (2-36) months
Duration of fever (days)	3 (1-15)	-	4.2 ± 1.9‡	4 (1-10)	4 (3-7)	4.1 ± 1.8	4 (1.5-8)	3.8 ± 1.7§	4.2 (2-11)	4.5	4 (2-7)
Time interval between fever episodes	20 (5-120) days	-	3.5 ± 1.9 weeks‡	28 (7-84) days	3.5 (2-8) weeks	3.7 ± 2.2 weeks	26 (10-49) days	4.1 ± 3 weeks§	4 weeks (14-60 days)	27.7 days	2 (2-5) weeks
Family history of PFAPA syndrome†† (%)	29.7	31.1	24.3‡	3.6	30.5	13	33.5‡‡‡	-	-	23	-
Family history of FMF† (%)	15.2	-	22.7‡	2.6	-	17‡‡	6.1	35.5	-	-	-
Family history of tonsillectomy	47	-	22.8‡	ns	-	31	-	-	56 (first degree)	-	-
Clinical findings (%)											
Pharyngitis	97.9	98.5	95.5‡	90	69.8	ns	96.2	100	98	84	100
Aphthous stomatitis	50.7	39.3	37.5‡	57	30.2	35.2	42.7	33.8	56	59	75
Lymphadenopathy	45.8	67.5	51.1‡	78	47.6	47	53.4	ns	94	70	42.2
Arthralgia	37.6	37.7	15.9‡	30	14.5	19.3	25.1	ns	31	30	ns
Arthritis	3.5	ns	ns	3	ns	ns	ns	ns	ns	20	ns
Abdominal pain	41	40.2	54.5‡	45	16.4	55.2	45.8	74.1	51	50	51.6
Chest pain	5.1	ns	ns	ns	ns	ns	ns	5.5	ns	ns	ns
Diarrhea	9.6	ns	ns	16	ns	ns	10.6	ns	22	ns	28.1
Myalgia	10.5	20.1	25.6‡	20	ns	27	ns	41.9	ns	39	42.2
Headache	14.8	37	ns	29	5.7	ns	16.7	24.4	ns	55	ns
Nausea/vomiting	24.7	ns	ns	11	12.4	ns	21.3	ns	41	38	ns
Rashes	13	11	ns	13	5.1	ns	5.3	ns	12	ns	ns
Response to steroids (%)	94.6	ns	86.5‡	63 (full); 32 (partial)	75.3 (full); 22.9 (partial)	98.9‡‡	98.7	100	100	95	100
Response to colchicine (%)	63.7	85	78‡	ns	ns	63‡‡	45.5	0	ns	ns	50
Response to tonsillectomy (%)	95.4	ns	76‡	ns	65.9	ns	94.3	42.8	93	70 (full); 15 (partial)	100

†Familial Mediterranean fever; ††periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome; ‡data of patients with Mediterranean descent (n = 178); ‡‡data of pure PFAPA patients group (n = 218; PFAPA/FMF group not included); ‡‡‡recurrent pharyngitis; §data of patients with Mediterranean fever gene mutation (*n* = 65); ns, not specified.

Table 2. The Comparison of the Demographic Features and Clinical Findings of the Patients According to Gender

	Females (n = 277)	Males (n = 330)	*P*
Median age at the time of study (years)	8.28 (6.2-10.6)	8.64 (6.3-10.8)	.43[a]
Median age at disease onset (months)	18 (11-30)	18 (11-36)	.37[a]
Median age at diagnosis (months)	36 (24-50)	36 (24-53)	.58[a]
Median duration of episodes (days)	3 (3-5)	4 (3-5)	.34[a]
Median intervals between episodes (days)	15 (15-30)	20 (14.5-30)	.76[a]
Pharyngitis, n (%)	270 (97.8)	324 (98.2)	.75[b]
Aphthous stomatitis, n (%)	141 (50.9)	167 (50.6)	.94[b]
Lymphadenopathy, n (%)	105 (37.9)	173 (52.7)	<.001[b]
Arthralgia, n (%)	111 (40.1)	117 (35.5)	.24[b]
Arthritis, n (%)	11 (4)	10 (3)	.52[b]
Abdominal pain, n (%)	121 (43.7)	128 (38.9)	.23[b]
Chest pain, n (%)	15 (5.4)	16 (4.9)	.75[b]
Diarrhea, n (%)	27 (9.8)	31 (9.4)	.88[b]
Myalgia, n (%)	34 (12.3)	30 (9.1)	.21[b]
Headache, n (%)	40 (14.5)	50 (15.2)	.80[b]
Nausea/vomiting, n (%)	73 (26.4)	77 (23.3)	.39[b]
Rashes, n (%)	38 (13.8)	41 (12.4)	.62[b]
Response to steroid, n (%)[†]	216 (95.2)	261 (94.9)	.90[b]
Response to colchicine, n (%)[††]	42 (57.5)	51 (69.9)	.12[b]
Response to tonsillectomy/adenoidectomy, n (%)[†††]	143 (97.9)	170 (93.4)	.05[b]

The patients whose data were not available were excluded from the related analyses. [†]Only the patients who were tried steroid treatment and whose data were available were included (n = 502; females: 227, males: 275). [††]Only the patients who were tried colchicine treatment were included (n = 146; females: 73, males: 73). [†††]Only the patients who has tonsillectomy/adenoidectomy were included (n = 328; females:146, males:182). [a]Mann–Whitney *U* test; [b]Chi-square test.

previous studies, Berkun et al.[16] stated that none of their PFAPA patients who tried colchicine were responsive. The remarkable difference between the rates of colchicine-responsive PFAPA patients reported in the studies and the fact that the high responsiveness rates were generally from communities around the Mediterranean made the effect of underlying MEFV mutations on the effectiveness of colchicine treatment a matter of interest. Pehlivan et al.[23] reported that the rate of colchicine responders among PFAPA patients carrying MEFV mutations was higher than patients without. Similar results about the effect of underlying MEFV mutations on the response rate to colchicine treatment in patients with PFAPA syndrome were also found in different studies.[10,14,22] Supporting the prior findings, Amarilyo et al.,[11] in their study evaluating the relationship between ethnicity and PFAPA syndrome, reported that the colchicine-responsive patients among patients of Mediterranean descent were higher than in patients with multi-ethnic descent. In contrast to earlier findings, there are studies in the literature suggesting similar rates of colchicine responders between patients carrying MEFV mutations and patients without MEFV mutations.[15,24] The discrepancies between studies evaluating the effect of MEFV variants on the colchicine response rate in PFAPA syndrome may be due to the difference between the classification criteria used in the studies or the differences between the definition of colchicine responsiveness.

Although tonsillectomy is shown to be highly effective in PFAPA syndrome, its role in the management of PFAPA syndrome is controversial.[25] Consistent with the response rate to tonsillectomy (42.8-100%) reported in the literature, 95.4% of our patients were responsive to tonsillectomy (5, 10-18). In 2014, Vigo et al.[13] stated that the percentage of the patients responding to tonsillectomy was comparable with the rate of patients responding to medical treatment and speculated that tonsillectomy was not superior to medical treatment. As PFAPA syndrome is a self-limited condition with spontaneous resolution and tonsillectomy is a surgical procedure with potential complications, all of the management/treatment options should be discussed in detail with the families before a decision is made.

Of the patients who did not undergo tonsillectomy/adenoidectomy, and whose episodes ceased during the follow-up, the median age at the last attack and median disease duration were 66 months and 40 months, respectively. There are only a few studies reporting the natural course of PFAPA syndrome in the literature. In accord with our results, Vigo et al.[13] stated that the mean age at clinical remission and the mean disease duration of the patients who went into clinical remission were 66.1 months and 39.9 months, respectively. In another study, Berkun et al.[16] reported that the mean disease duration was 5.0 years and the mean age at attacks cessation was 8.7 years in their PFAPA patients with MEFV mutations. In addition, the authors found that there was a significant difference for neither disease duration nor age at attacks cessation between patients with and without MEFV mutations.[16] In one of our group's previous studies on the natural course of the PFAPA syndrome, our group showed that later age of disease onset, positive family history for PFAPA syndrome, and the absence of headache may be predictors for resolution of PFAPA syndrome within 4 years after the onset.[26]

Although PFAPA syndrome is widely accepted as a sporadic disorder, there is an increasing number of papers reporting familial aggregation in PFAPA syndrome and suggesting a suspected genetic component.[5,6,27] A positive family history of PFAPA syndrome was reported as 3.6-45.5% in the

literature.[5,6,10,12-14] Consistent with the previous studies, positive family history was found in 29.9% of our patients. It should be noted that familial aggregation is not certain evidence for genetic transmission, it may also be related to common environmental exposures among family members. There is obviously a need for further studies to investigate the possible genetic background of the disease.

The main limitations of the study were it's having retrospective design and it's being conducted in a region endemic for FMF. It is shown in several studies that underlying MEFV mutations may have a modifier effect on disease phenotype and may interfere with the treatment response.[10,15,16,18,23,24] In addition, the sensitivity of the classification criteria may remain low in regions endemic for FMF.[28] Therefore, further studies from different geographic regions are needed for documenting differences in the disease characteristics between the patients from different regions.

In conclusion, in this retrospective study, we share our experience about clinical findings, natural course, and treatment response rates of a large cohort of PFAPA patients. Clinicians should be alert for additional clinical findings such as abdominal pain, arthralgia, and headache apart from the cardinal signs of the disease. Although tonsillectomy is highly effective in PFAPA syndrome, its use in the management of the disease is controversial. Colchicine may be a good alternative for episode prophylaxis especially in endemic regions for FMF. Further studies from different regions of the world are needed for expanding our understanding of the disease phenotype.

Ethical Committee Approval: Ethics committee aproval was received from the Istanbul University-Cerrahpasa (29430533-903.99-167385).

Informed Consent: Verbal and written informed consent was obtained from the participants who participated to this study.

Peer Review: Externally peer-reviewed.

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