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Prediction of Colchicine Response in Children with Periodic Fever Aphthous Stomatitis Pharyngitis and Cervical Adenitis Syndrome

Periyodik Ateş Aftöz Stomatit Farenjit Servikal Adenit Sendromlu Çocuklarda Kolşisin Yanıtının Belirleyicileri

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Öz

Kolşisin profilaksisi, periyodik ateşli aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromlu hastaların yönetiminde tedavi seçeneklerinden biridir, ancak tedavi yanıtı değişkenlik göstermektedir. Burada kolşisin profilaksisinin etkinliğini ve profilaksiye olumlu yanıtla ilişkili faktörleri araştırmayı amaçladık. Çalışmaya 5 yaşından önce kolşisin tedavisi başlanan PFAPA tanılı hastalar dahil edildi. Profilaktik tedaviye cevap ateşlenme aralıklarındaki değişime göre değerlendirildi ve ateş aralığında> %50 artış olması olumlu yanıt olarak kabul edildi. Olumlu yanıt veren hastalarda ise >3 ay ateşsiz dönem olması tam yanıt olarak kabul edildi. Çalışmaya katılan 41 hasta arasında, 20 (%48.8) hastada olumlu bir yanıt gözlendi ve olumlu yanıt verenler arasında 8 (%19.5) hasta ise tam yanıt verdi. Olumlu yanıt vermeyen diğer hastalardan 9'u (%22) kolşisin profilaksisine yanıtsız olarak değerlendirildi. Kolşisin yanıtının, MEFV mutasyonları ve önceki kortikosteroid kullanımı dahil olmak üzere klinik ve laboratuvar özelliklerle ilişkisi olmamasına rağmen, daha kısa ateş aralıklarının, kolşisine olumlu yanıt verme olasılığını önemli ölçüde artırdığı bulundu. Bu bilgi, PFAPA'lı hastaların tedavisinde terapötik kararlara yardımcı olabilir.

Anahtar Kelimeler: Ateş Aralığı, Kolşisin, PFAPA, Tedavi Yanıtı

Abstract

Colchicine prophylaxis is one of the treatment options in management of patients with periodic fever aphthous stomatitis pharyngitis and cervical adenitis (PFAPA) syndrome, but variability exists in response to the treatment. Here we aimed to investigate the efficacy of colchicine prophylaxis and factors associated with a favorable response. Patients diagnosed with PFAPA in whom colchicine was employed before 5 years old age were included. Response to the prophylaxis was assessed by the change of fever intervals and an increase of fever interval >50% after treatment was accepted as favorable response. Complete response was defined as a fever free interval of > 3 months in patients displayed favorable response. Among 41 patients, a favorable response, was observed in 20 (48.8%) patients, and among favorable responders, 8 (19.5%) patients displayed complete response. Of the remaining patients without a favorable response, 9 (22%) demonstrated no response to colchicine prophylaxis. Despite colchicine response was not associated with clinical and laboratory features including MEFV mutations and previous corticosteroid usage, shorter fever intervals were found to be significantly increased the odds of a favorable response to colchicine, which might aid in therapeutic decisions in management of patients with PFAPA.

Keywords: Fever Intervals, Colchicine, PFAPA, Treatment Response

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is considered to be the most common periodic fever syndrome (1). The disease was first described by Marshall et al. (2) and characterized by an abrupt onset of fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy with spontaneous resolution of fever in 4 to 5 days. Fever episodes occur periodically between 2-8 weeks at early stages and interval of fever episodes might increase with age (3). Also, fever episodes resolve in a significant proportion of patients by age (4,5). Corticosteroid treatment was effective in the cessation of fever but associated with an increased frequency of fever episodes in half of the patients (6). Tonsillectomy might result in the resolution of fever episodes, and colchicine treatment could be used to decrease the frequency of fever episodes (7,8). However, to date, no consensus has been achieved in the management of patients with PFAPA.

In patients with PFAPA, prophylactic colchicine treatment was found to be effective by several studies with varying degrees (8–11). However, most of these studies were conducted in patients with a high frequency of fever episodes and had small sample sizes. Furthermore, no study has investigated the predictors of colchicine response in children with PFAPA. In this study, we aimed to investigate the efficacy of colchicine prophylaxis and factors associated with a favorable response to colchicine treatment in a well-defined cohort of PFAPA patients.

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Material and Method

Medical charts of the children, diagnosed with PFAPA in a reference center between May 2016 and June 2021 were reviewed. Diagnosis of PFAPA was made as an expert opinion in the presence of regularly occurring fever episodes, onset before 5 years of age, associated with either tonsillopharyngitis or cervical lymphadenitis and/or aphthous stomatitis with the absence of clinical

features associated with monogenic autoinflammatory diseases. Patients who did not fulfilled the Eurofever/PRINTO criteria for the diagnosis of PFAPA (12), in whom colchicine was employed after 5 years of age and patients with a previous history of either tonsillectomy or adenoidectomy were excluded. In addition, to minimize bias in the determination of the treatment response, only patients with an observed fever episode at the time of colchicine initiation were included. Because familial Mediterranean fever is endemic in our region, genetic analysis for common MEFV gene mutations was performed in all patients and patients carrying homozygote or compound heterozygote MEFV mutations were also excluded.

Demographic, clinical and laboratory features were extracted from the medical charts of the patients. Response to colchicine was evaluated at the 6th month of treatment and the longest fever free interval between the 3rd and 6th months of treatment was used to evaluate the changes in the interval after colchicine prophylaxis. If a patient was attack free for at least two months at the 6th month of treatment, the first fever episode after the 6th month was also included for the determination of the colchicine response.

Colchicine treatment was started at a dose of 0.5 mg/day and dose adjustments were made in the first three months of treatment by increments of 0.25 mg according to the colchicine response. At the 3rd month of treatment, patients were either under the maximum tolerable dose or the minimum efficient dose of colchicine treatment. None of the patients received a colchicine dose more than 1 mg/day.

As an outcome measure, two distinct descriptions were used. Response to colchicine was evaluated by the increase of fever intervals. Favorable response was defined as an increase of fever intervals > 50% after colchicine initiation (10). Additionally, a definition of a complete response was described as an at least one fever free interval ≥ 3 months (13). Changes of the fever interval within 25% of the interval before treatment or < 7 days were accepted as variation, and changes of the fever intervals within the described variation were considered as nonresponders.

Descriptive statistics were presented as frequency with percentage, mean with standard deviation, or median with interquartile range (IQR). The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Analysis of the continuous variables before and after the initiation of colchicine was performed using the paired sample T-test or Wilcoxon signed rank test. Comparison of the categorical variables was analyzed using Fisher's exact test. Comparison of continuous variables between groups was performed by the students' T test when data were normally distributed or Mann-Whitney-U test when the data were not normally distributed. The Spearman test was used for the correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimum cut-off value of continuous variables associated with colchicine response. Multivariable logistic regression analysis was performed to identify the odds of favorable colchicine response. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM), with a statistical significance set at $p < 0.05$. This study was approved by the local ethical committee.

Results

Medical charts of the 99 children, diagnosed with PFAPA between May 2016 and June 2021, were reviewed. 19 patients, who did not use colchicine, were excluded. Furthermore, 11 patients without an observed fever episode before colchicine initiation and 8 patients, in whom the interval between attacks in the patient history was not consistent with the observed attack interval at the time of the fever episode, were excluded from the study. Among the remaining patients, 4 patients with a homozygote/compound heterozygote MEFV mutation, 6 patients, in whom colchicine was initiated after 5 years of age and, 3 patients, who had a history of tonsillectomy and/or adenoidectomy before initiation of colchicine, were also excluded. Of the remaining patients, 3 were lost on follow-up before the 6th month of colchicine treatment, and 4 patients did not have sufficient data for the determination of the fever episodes after colchicine prophylaxis. A total of 41 patients were included in the data analysis.

Among patients, 31 (75.6%) were male and mean age at the onset of fever episodes was 17.9 months. A family history suggestive of PFAPA was present in 13 (31.7%) of the patients and consanguinity was observed in 4 (9.8%). Tonsillopharyngitis (90.2%) was the most common finding associated with fever episodes, followed by cervical lymphadenopathy (61%) and stomatitis (36.6%). The mean interval between fever episodes was 24.5±5.6 days and the mean duration of fever was 4.5±1.2 days. Mean age at colchicine initiation was 31.3±3.1 months and median time from the onset of fever episodes to colchicine treatment was 12 (IQR: 5 - 18.5) months. Either diagnostic or on-demand corticosteroid therapy was employed in 27 (65.9%) of the patients.

The mean colchicine dose was 0.58±0.17 mg per day and 13 (31.7%) patients experienced treatment side effects associated with a dose increase, in which all of them were gastrointestinal, such as diarrhea and abdominal pain. MEFV mutation analysis was performed in all patients, and a heterozygote mutation was detected in 13 (31.7%) patients. The most common MEFV mutation was the E148Q variant, observed in five patients followed by M694V and M680I in three and two patients

respectively. V726A, A744S and P369S mutations were the other MEFV mutations each detected in one patient.

Favorable response, was observed in 20 (48.8%) patients, and among favorable responders, 8 (19.5%) patients displayed complete response. Of the remaining patients without a favorable response, 9 (22%) demonstrated no response to colchicine prophylaxis. Demographic, clinical and laboratory features, and response to the colchicine treatment are shown in Table 1.

Table 1. Demographical, clinical and laboratory features and characteristics of colchicine treatment in patients with PFAPA syndrome

	n: 41
Demographical features	
Gender (male)	31 (75.6%)
Age at first attack (months)	17.9±10.4
Family history of PFAPA	13 (31.7%)
Consanguinity	4 (9.8%)
Clinical features	
Fever	41 (100%)
Tonsillopharyngitis	37 (90.2%)
Cervical lymphadenopathy	25 (61.0%)
Stomatitis	15 (36.6%)
Abdominal pain	10 (24.4%)
Arthralgia	4 (9.8%)
Headache	2 (4.9%)
Fever interval (days)	24.5±5.6
Duration of fever (days)	4.5±1.2
Treatment features	
Age at colchicine initiation (months)	31.3±3.1
Previous corticosteroid treatment	27 (65.9%)
Duration from onset of fever to colchicine initiation (months)#	12.0 (5.0-18.5)
Colchicine dose (mg/day)	0.58±0.17
Colchicine side effect	13 (31.7%)
Laboratory features	
MEFV mutations	13 (31.7%)
C-reactive protein$^{\Delta}$ (mg/L)	99.9±56.3
ESR$^{\Delta}$ (mm/hr)	37.4±15.8
Serum amyloid A$^{\Delta}$ (mg/L)#	143 (39-209)
Response to the colchicine treatment	
Complete response	8 (19.5%)
Favorable response	20 (48.8%)
No response	9 (22.0%)

Data are presented as mean ± standard deviation, #median (interquartile range) or number (%). PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number, ESR: erythrocyte sedimentation rate. Δ Values in the attack period

Colchicine treatment resulted in a significant increase in the interval between fever episodes (24.5±5.6 days vs. 54.6±26.6 days, p<0.001) and a decrease in the duration of fever (4.5±1.2 days vs. 2.8±1.2 days, p<0.001) in patients with PFAPA. Besides, patients without a favorable response to colchicine also demonstrated a significant increase in the interval between fever episodes (27.5±4.4 days vs. 37.4±7.3 days, p<0.001) and a decrease in the duration of fever (4.3±1.3 days vs. 3.2 ±1.4 days, p=0.001). Despite patients with no response displayed a significantly increased duration between fever episodes, it remained in the described range of variation. Moreover, in patients with no response to colchicine, treatment showed no significant effect on the duration of fever episodes (4.0±1.7 days vs. 3.4±1.7 days, p=0.18). Changes in the interval and the duration of the fever episodes before and after colchicine prophylaxis are shown in Table 2.

When the features of the disease were compared according to the colchicine response, age at onset, gender, family history of PFAPA, clinical manifestations, duration of fever, age at colchicine initiation, acute phase reactants at the time of fever episode and presence of MEFV mutations were not significantly different according to the presence of a favourable response. Besides, the presence of exon-10 mutations was not different between patients with and without favorable response [M680I (2), V726A (1) and A744S (1) in favorable group; M694V (3) in patients without a favorable response]. In addition, a MEFV variation was observed only in 2 patients with complete response (M694V, E148Q). However, patients with a favorable response had a significantly shorter interval between fever episodes before colchicine treatment than patients without a favourable response (21.4±5.2 days vs. 27.5±4.4 days, p: 0.001). A similar association was observed between patients displaying a complete response compared to patients without complete response (20.9±5.5 days vs. 25.4±5.4 days, p=0.001), and between patients with complete response and no response (20.9±5.5 days vs. 28.3±3.3 days, p=0.01). Additionally, none of the features, except fever intervals, were found to be different according to the presence of complete response or between patients with a complete response and those with no response. Comparisons of the features according to the presence of a favorable colchicine response are shown in Table 3.

Correlation analysis revealed a significant moderate negative correlation between the interval of fever episodes before colchicine and the percentage of increase in fever intervals after colchicine (r: -0.612, p<0.001) (Fig. 1). ROC analysis revealed that the interval of fever episodes, longer than 23 days, identified patients without a favorable response to colchicine treatment with a sensitivity of 90% and specificity of 75% (AUC: 0.794, p=0.001) in patients with PFAPA. A univariate logistic regression analysis was performed to examine the odds of a favorable response to colchicine treatment. Among variables tested, only interval between fever episodes <24 days was significantly associated with an increased odd of favorable response to colchicine prophylaxis (OR: 9.6, CI: 2.3 – 39.9, p=0.002). The results of the regression analysis are shown in Table 4.

Table 2. Assessment of the change of the intervals and duration of fever episodes before and after colchicine prophylaxis in children with PFAPA

	Before colchicine	After colchicine	*p* value
All patients with PFAPA (n:41)			
Interval between fever episodes (days)	24.5±5.6	54.6±26.6	<0.001
Duration of fever episodes (days)	4.5±1.2	2.8±1.2	<0.001
Patients with a favorable response (n:20)			
Interval between fever episodes (days)	21.4±5.2	47.1±10.8	<0.001
Duration of fever episodes (days)	4.6±1.1	2.8±0.9	<0.001
Patients without a favorable response (n:21)			
Interval between fever episodes (days)	27.5±4.4	37.4±7.3	<0.001
Duration of fever episodes (days)	4.3±1.3	3.2±1.4	0.001
Patients with no response (n:9)			
Interval between fever episodes (days)	28.3±3.3	32.8±3.5	0.007
Duration of fever episodes (days)	4.0±1.7	3.4±1.7	0.18

Data are presented as mean ± standard deviation. PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number.

Table 3. Comparison of the disease features according to the presence of a favorable colchicine response in children with PFAPA

	Patients with a favorable response n:20	Patients without a favorable response n:21	*p* value
Gender (male)	15 (75.0%)	16 (76.2%)	>0.99
Age at first fever episode (months) [#]	16.5 (12-30)	12 (10-22)	0.19
Consanguinity	3 (15.0%)	1 (4.8%)	0.34
Family history of PFAPA	6 (30.0%)	7 (33.3%)	>0.99
Tonsillopharyngitis	18 (90.0%)	19 (90.5%)	>0.99
Stomatitis	7 (35.0%)	8 (38.1%)	>0.99
Cervical lymphadenopathy	13 (65.0%)	12 (57.1%)	0.75
Abdominal pain	5 (25.0%)	5 (23.8%)	>0.99
Duration of fever (days)	4.8±1.0	4.3±1.3	0.17
Interval between fever episodes (days)	21.4±5.2	27.5±4.4	**0.001**
Previous corticosteroid treatment	14 (70%)	13 (61.9%)	0.74
Age at colchicine initiation (months) [#]	36 (24-42)	25 (18-39)	0.21
Duration from onset to colchicine prophylaxis (months) [#]	12 (4.3-21.3)	11 (6-18.5)	0.63
MEFV gene mutation	6 (30%)	7 (33.3%)	>0.99
C-reactive protein$^{\Delta}$ **(mg/L)** [#]	91 (51-145)	97 (64-126)	0.81
ESR$^{\Delta}$ **(mm/hr)** [#]	38 (24-46)	30 (25-50)	0.89
Serum amyloid A$^{\Delta}$ **(mg/L)** [#]	173 (31-241)	140 (45-199)	0.64

Data are presented as mean ± standard deviation, #median (interquartile range) or number (%). PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number, ESR: erythrocyte sedimentation rate. Δ Values at the fever episode.

Discussion

The results of this study suggest that a shorter interval between fever episodes before colchicine prophylaxis is a predictor of favorable response to prophylaxis in children with PFAPA. Literature knowledge on the efficacy of colchicine prophylaxis in patients with PFAPA supports our findings that colchicine was effective in patients with frequent attacks (8,9,14). However, to the best of our knowledge, no study has reported an association between the frequency of fever episodes and colchicine response. In 2008, Tasher et al. (9) reported for the first time that colchicine treatment might be effective in the prophylaxis of patients with frequent fever episodes. In that study, colchicine treatment resulted in the prolongation of fever episodes in eight of the nine patients and, the mean interval between fever episodes before treatment was 1.7 weeks. Also, in a study from Spain, colchicine was reported to be effective in 13 patients with PFAPA with frequent episodes and a decrease in both duration and number of the episodes were observed (14). In contrast, a study with 20 PFAPA patients shown that colchicine response, described as at least 50% reduction in number of fever episodes, was observed in nine of the patients, and no significant difference was observed in terms of the intervals between fever episodes (10). In an open label prospective study, in which eight of the 18 patients were on colchicine prophylaxis for three months, colchicine treatment was resulted with a decrease in number of the fever episodes. Besides, in patients with colchicine prophylaxis median interval between fever episodes before and after treatment was 17 and 40 days respectively (8). In addition to these knowledges, finding of the no significant difference in fever durations before and after colchicine treatment in non-responders in this study suggests that the effect of colchicine on decreasing the duration of fever episodes is more pronounced in colchicine responders.

Table 4. Logistic regression analysis of features associated with a favorable response to colchicine in children with PFAPA

Features	OR	*Univariate analysis* 95% CI		*p* value
		Lower	Upper	
Onset <12 months age	1.3	0.4	4.6	0.64
Colchicine initiation <24 months age	1.3	0.4	4.7	0.62
Fever duration <4 days	3	0.8	10.7	0.09
Fever interval <24 days	9.6	2.3	39.9	**0.002**
Family history of PFAPA	0.9	0.2	3.2	0.82
MEFV mutation	0.9	0.2	3.2	0.82

OR: odds ratio, CI: confidence interval, PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis.

A consensus management approach is not yet developed for children with PFAPA and research on this topic is limited, mostly due to the benign and self-resolving nature of the disease. Additionally, outcomes measures for the prophylactic approach are not uniformly described. In two prospective trials, the efficacy of prophylaxis was assessed by the decrease of the fever episodes and one described favorable response as twice less fever episode, similar to our description (8,10). More recently, investigators of CARRA suggested outcome measures as complete and partial response (13). In this study, both outcome measures were investigated and unlike the low attainment rate of complete response, favorable response was evident in nearly half of the patients. Since the course of the disease is benign and choice of treatment is often fashioned by the preferences of parents with respect to the quality of life, a favorable response could be as acceptable as complete response.

In a recent study, colchicine was effective in decreasing both physician and parent reported disease activity in 27 patients with PFAPA (15). Our results also suggest that colchicine is effective in the prevention of fever episodes and that resulted in a favorable response in half of the patients. A study from Turkey, which included 356 patients with PFAPA with a mean interval between fever episodes of 18.8 days, reported that 85% of the patients showed an increase in the duration between fever episodes and colchicine response was reported to be more frequently encountered in patients with MEFV mutations (11). In contrast, a study conducted from an endemic region for familial Mediterranean fever (FMF) reported a 19% rate of concomitant FMF diagnosis in patients with PFAPA and did not find a significant difference in colchicine response between patients with and without FMF (16). Although we did not find any association between MEFV mutations and colchicine response, this finding might be due to the limited sample size of our study. We also excluded patients with a homozygote/compound heterozygote MEFV mutation to decrease the bias in determination of the colchicine response in case of concomitant FMF and PFAPA. MEFV mutations were thought to have a modifier effect on the clinical findings of PFAPA with a shorter duration of fever and a lower dose of steroid requirement for the abortion of fever in patients with heterozygote MEFV mutations (17). In contrast, Batu et al. (18) compared the clinical characteristics of patients in two cohorts, one from Turkey and the other from the United States and reported that patients from Turkey were younger and had a shorter duration of fever. In addition, MEFV mutations were not found to be significantly influenced by the disease phenotype in that study (18). Similarly, we did not find any association between colchicine response and MEFV mutations in patients with PFAPA, also our results were not indicative of a modifier effect of MEFV mutations in the disease phenotype.

The use of colchicine for the prophylaxis of fever episodes of PFAPA is mostly based on the experience of patients with FMF (9). In addition to FMF, colchicine has been suggested for treating a varying spectrum of inflammatory disorders, including idiopathic recurrent pericarditis, coronary artery disease, recurrent aphthous stomatitis and Behcet's disease (19,20). The anti-inflammatory and anti-fibrotic effects of colchicine were mainly due to the blockage of assembly and polymerization of microtubules. Microtubules are involved in various cellular processes including intracellular trafficking, cytokine secretion and cell migration. Besides, colchicine concentrates intensively in leukocytes and inhibits neutrophil chemotaxis, adhesion, and recruitment to the site of inflammation (21).

Because of the curative role of tonsillectomy in patients with PFAPA, a triggering role of tonsils in the pathogenesis of the fever episodes has also been suggested (22). Besides, a different subset of lymphocyte population restricted to the tonsils was shown in the tonsils of the patients with PFAPA compared to the tonsils of the patients with obstructive sleep apnea (23). Furthermore, tonsillar microbiota was found to be different in patients with PFAPA and alteration of tonsillar microbiota was implied in the development of fever episodes (24). In a small sample sized study, probiotic supplementation was shown to decrease the frequency of fever episodes in patients with PFAPA (25). Based on this knowledge, variability of the response to colchicine and the association with the interval between fever episodes might be related to a

possible effect of colchicine in sensing the alterations of oral/tonsillar microbiota.

The retrospective nature and patient reported fever episodes were the most notable limitations of this study. In addition, the association of fever intervals with colchicine response might need external validation. Furthermore, selection of the longest interval of the fever episodes to assess the colchicine response might produce bias given the variability of the fever intervals. Another limitation was MEFV testing which might limit the assessment of MEFV mutations in the determination of colchicine response. Although common MEFV mutations were studied in all patients, heterogeneity exists in the number of mutations tested and the number of mutations analyzed differs among patients.

Conclusion

Colchicine prophylaxis resulted in a favorable response in half of the patients. Besides, colchicine shortens the duration of fever, but this effect is less pronounced in nonresponders. Our results suggest that colchicine is more effective in patients with frequent fever episodes and interval of fever episodes shorter than 24 days significantly increase the odds of a favorable colchicine response. This knowledge might help both clinicians and caregivers in selecting the most suitable treatment option.

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Ethics Committee Approval: Study complies with the Declaration of Helsinki and was performed according to ethics committee approval of Karadeniz Technical University Ethical Comittee (30/06/2021-2021/150).

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