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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(3):702-5

# PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome in children; surgical versus medical treatment?

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Received 20 January 2021; Accepted 28 March 2021
Available online 11.06.2021 with doi: 10.5455/medscience.2021.01.017

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**Abstract**

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy) syndrome usually presents in childhood and one of the most common periodic fever syndromes. The syndrome is self-limitted, characterized by periodic fevers at regular intervals and standard clinical features of pharyngitis, aphtous ulcers and cervical lympadenitis. The diagnosis is based upon clinical criteria with the exclusion of other recurrent fever causes. The treatment of PFAPA syndrome is divided two parts; to control of the acute attacks and to decrease the frequency of the attacks. In this retrospective study we aimed to compare the indications and efficiency of medical versus surgical treatment in children with PFAPA syndrome. Forty-five children with PFAPA syndrome whom treated with surgical or medical options were included and divided into two groups. The recovery rates before and after treatments were statistically analyzed. In both groups symptomatic improvement were seen. In surgical and medical treatment groups, complete clinical recovery was found 80% and 74%, respectively. Besides, statistically significant reduction in frequency ($p<0.05$) and duration ($p<0.05$) of recurrences in the incomplete clinical recovery cases were seen. Similar to literature our results support that both medical and surgical treatment are effective treatment methods. Surgery is a preferable treatment option especially in patients who do not response to medical treatment. The optimal strategy for management is depend on response to treatments.

**Keywords:** Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis, treatment

## Introduction

The syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA syndrome) is considered the most common cause of autoinflammatory syndrome in childhood and onset is especially before the age of 5. The syndrome was first described in 1987 by Marshall et al., characterized by fever episodes (>390C) that usually last 3-6 days with recurrence almost every 3-8 weeks, fever episodes accompanied by at least one of three main symptoms; aphthous stomatitis, cervical adenitis, and pharyngitis. The patients are asymptomatic between episodes and have normal growth and development. The disease resolves within few years in most children, usually before adolescence. But in adulthood, new existing of febril flares after initial recovery can be seen in 20% of the cases [1,2].

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The etiology and pathogenetic mechanisms of the disease remain substantially unknown. However, the resolution of the attacks by corticosteroid treatment and the elevated levels of cytokines during each process seems that autoimmunity play an important role. There is no evidence of microbial, ethnic or geographical factors in etiology and no specific genetic mutation has been described. Data suggest that PFAPA syndrome is caused by polygenic or complex inheritance of variants in many genes in association with environmental factors. Autosomal dominant genetic inheritence is considered due to the strong familial clustering [2-5].

The diagnosis of PFAPA is based on clinical and available diagnostic criterias of PFAPA syndrome in pediatric patients are reported in Table 1 [2]. Other diseases that cause periodic fever can be eliminated clinically and laboratory. During acute attack, laboratory analysis such as; culture of pharyngeal swab for group A hemolytic streptococcus (GABHS), serum immunoglobulin levels and MEFV gene mutations can be studied, if needed [1,6].

**Table 1.** Diagnostic criteria for PFAPA syndrome in children

| |
|---|
| I- Monthly periodic fevers with an early age of onset (<5 years of age) |
| II- Absence of upper respiratory infection with at least one of the following clinical signs<br>a-Aphthous stomatitis<br>b-Cervical lymphadenitis<br>c-Pharyngitis and negative throat culture |
| III- Exclusion of cyclic neutropenia |
| IV- Completely asymptomatic interval between episodes |
| V- Normal growth and development |

Although there is no consensus on the treatment of PFAPA syndrome, treatment based upon two goals; 1) control of the acute attacks and 2) decreasing the frequency of attacks. Childhood arthritis and rheumatology research alliance (CARRA) PFAPA work group defined four treatment strategies based on the literature review, survey, and the process; 1) Antipyretics during episodes; 2) Abortive treatment with corticosteroids; 3) Prophylaxis with colchicine or cimetidine; and 4) Surgical management with tonsillectomy. According to the consensus report tonsillectomy and steroid therapy is considered as the most effective treatments [7]. In this study, we aimed to compare the indication, efficacy, and success rates of medical and surgical treatment methods in PFAPA syndrome.

## Materials and Methods

Forty-five patients (24 male, 21 female) who were diagnosed as PFAPA syndrome, at the Pediatric and Otorhinolaryngology Head and Neck Surgery Departments, were analyzed retrospectively. Medical reports of all patients were reevaluated according to the demographic (age, gender), clinical (age at first attack, age at the time of diagnosis, duration of attacks before and after treatment, frequency of attacks before and after treatment, total time between first and last attack of completely recovered patients) and laboratory (leucocyte and erythrocyte counts, sedimentation rate (ESR), C-Reactive Protein (CRP) findings. The patients with comorbid diseases were excluded from the study.

Patients were divided into two groups, according to the treatment modality; Group 1 included 10 patients who were treated surgically (tonsillectomy with or without adenoidectomy) and Group 2 included 35 patients who were treated medically (single or double dose prednisolone 1 mg/kg).

Surgical treatment (tonsillectomy with or without adenoidectomy) was performed under general anesthesia to the patients with recurrent periodic attacks or patients who did not respond to prednisone treatment.

The follow-up period was at least 18 months for both groups, and the recurrence of the symtoms, intervals between attacks (if complete remission was not obtained) and the complications of the medical or surgical treatment was evaluated for each patient by means of a pre and post-operative occurrence were determined. Complete recovery or remission of the disease was accepted when no symptoms were seen for a minimum of 18 months. The results (before and after treatment) were statistically analyzed. In the case of pharyngeal swab culture positivity for GABS or the presence of clinical signs of concomitant infections the patients were excluded.

This study was approved by the Inonu University Institute's Committee on Human Research and the medical Ethics Committee under the reference number 2012/162. Consent forms were signed by parents of each patient before surgery.

The differences in pre and post-treatment scores (the rate of clinical improvement, the age at onset of the disease, the age of diagnoses, the frequency of attacks, the duration of the attacks and recovery rate) were tested by Wilcoxon signed-rank test and $p<0.05$ was considered as statistically significant. Because of the number difference between groups, power analysis was performed before statistical analysis.

## Results

The clinical features of patients and demographical characteristic in both groups were summarized in Table 2 and Table 3.

**Table 2.** Clinical features of patients

| Clinical Features | Number of Patients | Percent (%) |
|---|---|---|
| **Pharyngitis/exudative tonsillitis** | 41 | 91.1 |
| **Lenfadenitis** | 35 | 77.7 |
| **Aphthous stomatitis** | 21 | 46.6 |
| **Headache** | 12 | 26.6 |
| **Joint pain** | 3 | 6.6 |
| **Abdominal pain** | 3 | 6.6 |
| **Malaise** | 3 | 6.6 |

**Table 3.** Demographical findings in Group 1 and 2

| Demographical findings | Group 1 (tonsillectomy) | Group 2 (prednisolone) |
|---|---|---|
| **Patients** | 10 | 35 |
| **Female** | 4 | 17 |
| **Male** | 6 | 18 |
| **PFAPA onset of disease** | 2.4±0.75/year | 2.3±0.65/year |
| **Age of diagnoses** | 3.3±0.95/year | 3.5±0.85/year |
| **Frequency of attacks** | 29.8±4.5/day | 31.7±5.5/day |
| **Duration of attacks** | 4.6±0.85/day | 4.3±0.74/day |

Group 1 was consisted of 10 (six male and four female) patients who underwent tonsillectomy with or without adenoidectomy. All cases experienced clinical improvement after treatment; eight patients (80%) were completely recovered and two patients (20%) were continued to experience sporadic PFAPA symptoms, without regular intervals. In this group; the age at onset of the symptoms was 2.4±0.75 years, the age of diagnoses was 3.3±0.95 years, the frequency of attacks was 29.8±4.5 days, duration of the attacks was 4.6±0.85 days and recovery rate was 80%.

Group 2 was consisted 35 (18 male and 17 female) patients. All cases were treated by a single or double dose prednisolone (1 mg/kg). The age at onset of the disease was 2.3±0.65 years, the age of diagnoses was 3.5±0.85 years, the frequency of attacks was 31.7±5.5 days, duration of the attacks was 4.3±0.74 days and recovery rate was 74.2%. The age of patients whom completely recovered with prednisolone was 8.9±1.2 and the age of duration of the disease with prednisolone was 6.6±0.9.

Comparison of the pre and post-treatment parameters of each group revealed a significant difference on clinical improvement in the majority of patients ($p<0.05$). Moreover, findings from statistical analysis showed a significant reduction of PFAPA syndrome postoperatively.

In both groups, patients showed an important symptomatic improvement; but recurrence of the attacks was found 20% and 25.8% in group 1 and 2, respectively. The mean duration of attacks decreased from 4.6±0.85 to 1.2 day in group 1 and 4.3±0.74 to 1.1±0.85 day in group 2. The mean frequency of attacks increased to 8 weeks in group 1 and 7.3 weeks in group 2 after treatment. When compared with each other, there were not statistically significant ($p>0.05$) between post-treatment scores of two groups such as pre-treatment scores. Moreover, findings from statistical analysis showed that tonsillectomy (with or without adenoidectomy) was at least as effective as steroid therapy in the PFAPA syndrome.

In all patients, laboratory findings at the onset of attacks were as follows; hemoglobin level was normal, normal or mild leukocytosis, moderate increase of the ESR, normal platelet amounts. The patients whose pharyngeal swabs were negative for GABHS were included to the study. The mean follow-up period after tonsillectomy (with or without adenoidectomy) was 18 months (range, 12-40 months).

**Discussion**

PFAPA syndrome is a relatively benign and self-limited disease that generally resolves spontaneously before adolescence.. With time, the episodes become less frequent, less severe, and shorter in duration [8,9].

The optimal management strategy for patients with PFAPA syndrome depends upon to treatment responses. Generally, medical treatment (especially steroids) is the most preferred treatment choice in PFAPA syndrome. Surgery (tonsillectomy +/- adenoidectomy) is also a treatment method with satisfactory results, especially in patients with refractory to corticosteroid treatment. (CARRA) PFAPA work group suggested dose of 1 mg/kg, or 2 mg/kg prednisolone in cases of inadequate response or shortened interval (≤14 days) between episodes in abortive arm. And allowed intervals of ≥21 days for response to corticosteroids and recommended changing to another arm in the case of frequent flares (≤14days) (refractory to corticosteroid treatment [7]. Corticosteroids have an effect on reducing the duration of febrile attacks, but have no effects on the natural history of the disease. The dramatic resolution of attacks after a single dose of corticosteroids (1 or 2 mg/kg prednisone) can be used as diagnostic criteria for the disease. Complications due to administration of steroids are very rare in the literature [7,10,11]. Our results are similar to the literature and the recovery rate was found 74.2%, no complication was seen in steroid group. In the literature review, tonsillectomy considered as a practical treatment option by most authors, but the results based on retrospective studies [7,12-14]. In a small group of patients Wong et al., reported that resolution of the symptoms was seen in 89% of PFAPA syndrome and only in one patient complete recovery did not occured, however a decrease in the frequency of attacks was observed on early stage. This patient experienced complete resolution of symptoms two years after surgery (tonsillectomy) [15].

Several small studies have reported the effectiveness of surgery in PFAPA syndrome. Most authors concluded that tonsillectomy should be considered as an effective treatment option in PFAPA syndrome with complete recovery between 64% and 100% [4,7,14-18]. In our study, 80% of the patients experienced complete resolution of the symptoms, similarly with the literature. Other 20% of the patients experienced complete resolution two years after tonsillectomy.

In a metaanalysis, it has been showed that better resolution of symptoms in PFAPA syndrome in children after tonsillectomy (+/-adenoidectomy), than those treated with cimetidine and antibiotics. Also, the comparison of surgery versus steroid treatment showed that both treatment modality are effective for the resolution of symptoms. Further, the authors reported that the corticosteroid treatment does not prevent future fever cycles, but can shorten the interval between episodes. The cessation of PFAPA episodes has been observed after tonsillectomy. Therefore, tonsillectomy (+/-adenoidectomy) reported as the most effective intervention for long-term resolution of PFAPA syndrome symptoms [7,18].

The risks of each treatment strategy must be evaluated against the adverse effects and the effectiveness on the febrile episodes. Antipyretics; such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, found ineffective in controlling the symptoms of PFAPA other than fever by clinical experience [7,11,19].

Other medications (Cimetidine or Colchicine) for patients with an increase in episode frequency which require more than 2mg/kg steroid treatment per month can be used for prophylactic treatment. Cimetidine, may increase the interval of episodes, decrease the severity of episodes or lead to resolution of episodes. But the benefical effects of Cimetidine have been noted only in case reports or small case series [7,11,19]. Another option for prophlaxis is Colchicine and in a small amount of studies treatment with colchicine found to be associated with an increased interval between episodes, but complete responses have been rarely observed. The routine usage of Cimetidine is not recommended because of the necessity of a continuous daily administration [11,19-21].

In conclusion, PFAPA syndrome has favorable natural history and the diagnosis is based on clinical criterias and exclusion of other causes of recurrent fever. Because PFAPA is a self-limited disease without known long-term sequele, observation is acceptable if the patient or family wish not to treat. If treatment is considered, the primary treatment options are corticosteroids for episodic therapy and surgery for potentially curative therapy. Due to favorable natural history, type of treatment is optional. Corticosteroid treatment and tonsillectomy has demonstrated similar success rates in decreasing episodes or completely resolving of attacks. Especially, tonsillectomy considered to patients who refractory to medical treatment or children with long- lasting disease affecting the quality of life.

**Conflict of interests**
*The authors declare that they have no competing interests.*

**Financial Disclosure**
*All authors declare no financial support.*

**Ethical approval**

*This study was approved by the Inonu University Institute's Committee on Human Research and the medical Ethics Committee under the reference number 2012/162.*

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