

# Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis Syndrome: Current Literature Review with a Case Report

*Periyodik Ateş, Aftöz Stomatit, Farenjit ve Servikal Adenit Sendromu: Bir Olgu Nedeniyle Güncel Literatürün Gözden Geçirilmesi*

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Adnan Menderes University Faculty of Medicine, Department of Otorhinolaryngology, Aydın, Turkey



## Abstract

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis syndrome (PFAPA) is a frequently seen, important medical condition, which must be kept in mind in periodic fever etiology. Although its etiology is not clearly understood, autoimmune etiology is suspected due to response to steroids. There is no specific test for the diagnosis of disease. Diagnosis is based on symptoms and physical examination. Although medical treatment is the first choice for the management of the disease, tonsillectomy take over in treatment options for termination of attacks and permanent results. We have presented a patient that was performed tonsillectomy in our clinic for frequent attacks despite recurrent medical therapy with diagnosis of PFAPA with review of current literature.

## Keywords

Periodic fever, tonsillectomy, PFAPA

## Anahtar Kelimeler

Periyodik ateş, tonsillektomi, PFAPA

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## Address for Correspondence/Yazışma Adresi:

Mahmut Demirtaş MD,  
Adnan Menderes University Faculty of  
Medicine, Department of Otorhinolaryngology,  
Aydın, Turkey  
E-mail : drmdemirtas@gmail.com  
ORCID ID: orcid.org/0000-0002-9657-1064

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## Öz

Periyodik Ateş, Aftöz Stomatit, Farenjit ve Servikal Adenit sendromu (PFAPA), sık izlenen ve periyodik ateş etiyojisinde akılda bulundurulması gereken önemli bir sendromdur. Kesin olarak etiyojenini bilinmesi de steroid grubu ilaçlara cevap vermesi nedeni ile otoimmün bir hastalık olarak değerlendirilmektedir. Tanıda hastalığa özgü test mevcut değildir. Tanı, semptomlara ve fizik muayeneye dayanmaktadır. Medikal tedavi ilk seçenek olarak gözükse de atakların kesilmesi ve kalıcı yanıtların elde edilmesi nedeni ile tonsillektomi belirgin şekilde ön plana çıkmaktadır. Kliniğimizde PFAPA tanısı ile tekrarlayan medikal tedavi almasına rağmen atakların sık olarak tekrarlaması nedeni ile tonsillektomi uygulanan bir hasta eşliğinde güncel literatür gözden geçirilmiştir.

## Introduction

Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis syndrome (PFAPA) seen with periodic fever is first described by Marshall et al. (1) at 1987 and it's accepted as one of the most frequent etiologic reason of the pediatric periodic fever diseases

nowadays. PFAPA is an entity that contains one of the three main symptoms: Aphthous stomatitis, cervical adenitis, and pharyngitis, with periodic fever, which lasts 3-6 days and recurs every 3-8 weeks. Usually the initial age is 5 or less (1-4). It is partially more frequent in males and family history cannot be shown precisely. Diagnosis is based entirely on clinical evaluation and the exclusion of other periodic fever causes (1-4). Etiology and pathogenesis are still unclear (1-4). Treatment includes medical treatment and tonsillectomy and/or adenoidectomy. In this case, we discussed the efficacy of surgical treatment with the literature due to not recurring episodes and not seeing additional problems in clinical follow-up of a patient with PFAPA who underwent tonsillectomy.

### Case Report

A four-year-old boy admitted to our clinic with the complaint of frequent recurrent throat infection. It was learned that the illness was repeated every three weeks and that the febrile periods were very resistant despite the medical treatment. The patient, who was hospitalized in the pediatrics clinic from time to time, was found to have evidence of pharyngitis more frequently, although he had a cryptic tonsillitis episode once. Significant findings of lymphadenitis emerged during this period. From the history of the patient, it was learned that the findings improved dramatically, fever dropped, and clinical relief is achieved after the steroid treatment.

In the examination of the ear, nose and throat clinic, approximately 2x1 cm lymphadenopathy in the right anterior cervical area, marked pharyngeal hyperemia, tonsillar hyperemia, and minimal hypertrophy in pharyngeal tonsils were observed. In evaluating the patient's laboratory; complete blood counts were within normal limits and antistreptolysin O, erythrocyte sedimentation rate and C-reactive protein values were normal. The patient's family was informed about the operation and the surgical consent was approved and tonsillectomy was planned with the diagnosis of PFAPA syndrome. After general anesthesia preparations, tonsillectomy was performed at the fever free period. The patient did not have similar complaints in postoperative period, and no fever was observed in approximately one-year follow-up.

### Discussion

PFAPA, which is characterized by periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis, is an entity frequently seen in periodic fever etiology. It was first described by Marshall et al. (1) in 1987. It is a syndrome that involves at least one of the symptoms of aphthous stomatitis, cervical adenitis, and pharyngitis with periodic high fever, ending in 3-6 days without infection markers and recurring every 3-8 weeks (Table 1). Pharyngitis is seen in 65-100%, cervical adenitis in 61-100%, aphthous stomatitis in 38-71% (5). In addition, some patients may have headache, abdominal pain, diarrhea, joint aches, chills and redness in the body (5). Although antipyretics may provide benefit from time to time, antibiotics or anti-inflammatory drugs do not provide any benefit (2). The onset of the disease is usually under five years old and is observed in mild cases in males (55-62%). There are publications indicating some familial characteristics, but there is no genetically determined base (6). Diagnosis is made only clinically and excluding other causes. There is no laboratory-specific finding for the disease. Even though they are in etiology, there are no clear evidence for the presence of vitamin D deficiency or some viral infections in the patients (7). The disease heals spontaneously without significant sequelae until adolescence and without affecting growth and development (8). However, a few publications have shown this disease in the adult group (9). For this reason, it should be kept in mind and not missed in adults, the disease is not only limited to pediatric patients.

The pathogenesis is still unknown, but the dramatic response to steroids suggests that it is an immune disorder. In some studies, cytokines such as

**Table 1. Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis syndrome diagnostic criteria (4,7)**

Regular recurrent fever that starts at an early age (usually <5 years)
Without evidence of upper respiratory tract infection, there should be at least one finding: <ul style="list-style-type: none"> <li>• Aphthous stomatitis</li> <li>• Cervical lymphadenitis</li> <li>• Pharyngitis</li> </ul>
Exclusion of cyclic neutropenia
Completely asymptomatic between attacks
Normal growth and development

interferon-gamma and tumor necrosis factor-alpha have been shown to elevate during exacerbation. In the acute period, some complications were observed to increase. Stojanov et al. (10) suggest the concept of T-cell proliferation raised by activation of immune system established on a genetic basis after a microbial trigger in pathogenesis of PFAPA. Patients who underwent tonsillectomy had no histopathologically significant pathology other than chronic inflammation (2,5).

In differential diagnosis, although there are periodic febrile illnesses such as cyclic neutropenia, familial mediterranean fever, Hyperimmunoglobulin D syndrome, the genetic basis of these diseases has been demonstrated and their findings are unique (10). Differential diagnosis can be achieved by these unique findings.

The treatment method is still controversial. Medical and surgical options are available. Steroids have been successfully used. One or two doses of prednisone (1-2 mg/kg) or betamethasone (0.1-0.2 mg/kg) dramatically reduces fever within a few hours, other symptoms may take some time to recover. Steroids are only used during an attack. Except for irritability and transient sleep disturbances, no serious toxicity has been reported, but its use is limited due to its effects on child development and systemic effects. In addition, the use of drug can be restricted due to parents' anxiety (2-10,12). Colchicine (0.5-1 mg/day) has also been tried in treatment and has not proved an improvement in clinic, even if it prolongs time between attacks (2-10). Cimetidine is a histamine type 2 receptor blocker and has been used in therapy due to its immunomodulator effects. CD8+ T-cell suppression increases neutrophil chemotaxis and interferon-gamma production, increases lysosomal enzyme release and migratory inhibitor factor production. The effects were observed at a limited rate (26%) (2-10).

Treatment of tonsillectomy is controversial despite it meets definite treatment data at a certain rate. Renko et al. (13) showed that the success rate of tonsillectomy was 100% (14 patients), while Garavello et al. (14) rate was 63% (19 patients) (13-14). Garavello et al. (14) showed a significantly higher rate of recovery with surgery (63%) compared with medical treatment (5%), although the rate was lower. In a recent meta-analysis, the mean recovery rate was 83% (15). However, surgeons should be careful

about the surgery that it is an invasive procedure, it has complications such as possible postoperative bleeding, and the possible risks of anesthesia. Surgical treatment is also a source of anxiety for families. Despite the recovery with the medical treatment, due to recurrent status of PFAPA, families continue to seek permanent treatment. Families readily accept the surgical potential risks when considering risks such as recurrent fever, risks associated with treatments during recurrent episodes, and so on. Moreover, as mentioned above, the highest cure rate after surgery is evidence that tonsillectomy is an appropriate treatment approach with adequate information and with informed concept.

PFAPA syndrome, which is thought to be high in society, should be considered by both pediatricians and otorhinolaryngologists at the diagnosis stage and should be included in differential diagnosis. Although spontaneous regression can occur and respond to steroid therapy, an effective evaluation should be made. Tonsillectomy, which is an effective treatment method, can be applied by evaluating the patient's medical treatment response, the effect of illness on the quality of patient life (school-nursery continuity etc.) and the patient's anesthesia risk. After the tonsillectomy, complaints are nearly normal and the patient attacks do not repeat. Therefore, tonsillectomy remains an effective treatment, and surgery should be offered to the patients who are appropriate for surgery.

#### **Ethics**

**Informed Consent:** Informed consent form was obtained from the patient.

#### **Authorship Contributions**

Surgical and Medical Practices: M.D., Concept: A.O.O., M.D., Design: A.O.O., M.D., Data Collection or Processing: M.D., Analysis or Interpretation: M.D., Literature Search: M.D. Writing: A.O.O., M.D.

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