

Surgery vs medical treatment in the management of PFAPA syndrome: a comparative trial

Firat Erdogan¹, Kudret Kulak², Ozmen Öztürk³, Ilke Özahı İpek¹, Ömer Ceran¹, Hüseyin Seven³

¹Department of Pediatrics, Medipol University, ²Department of Pediatrics, Bilim University, ³Department of Otorhinolaryngology, Medipol University, Istanbul, Turkey

Background: Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a common disorder in children but there is little or no consensus on its optimal diagnosis and management.

Objectives: To compare the outcome of different management approaches – medical therapy or tonsillectomy.

Methods: The medical records of children diagnosed with PFAPA between 2008 and 2013 were retrospectively reviewed according to the modified Thomas test criteria. Patients were divided into two groups: group 1 for medical treatment – corticosteroids, a single intramuscular injection of methylprednisolone, and group 2 for surgery – tonsillectomy alone or tonsillectomy plus adenoidectomy. The course of the disease including the number and duration of episodes and the presence of remission, was documented.

Results: 105 patients (30 in group 1, 75 in group 2) met the study's inclusion criteria. Groups 1 and 2 were followed up for a mean (SD) of 23.6 (11.0) and 24 (10.3) months, respectively. At the end of the follow-up period, the number of episodes was 5.8 (6.3) vs 1.8 (1.9) ($P<0.01$) and their duration was 2.2 (1.3) vs 1.1 (0.8) days ($P=0.03$), both of which were significantly lower in group 2. The need for hospitalization during this period was significantly lower for group 2 at 1.1 (2.0) vs 0.1 (0.3) ($P<0.01$) and the remission rate in group 2 was significantly higher than in group 1 (98.6% vs 56.6%, $P<0.01$).

Conclusion: This study demonstrated that surgery is superior to medical treatment for PFAPA in terms of increased remission rates and a decrease in the number and duration of episodes.

Keywords: Medical treatment, Periodic fever, PFAPA syndrome, Surgery

Introduction

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome was first described in 1987 by Marshall and co-workers.¹ It is characterised by recurrent episodes of fever ($>39.8^{\circ}\text{C}$) occurring every 3–8 weeks and lasting 3–6 days, with an age of onset of <5 years), an absence of upper respiratory tract infection and at least one of the following: aphthous stomatitis, pharyngitis and/or cervical adenitis; completely asymptomatic intervals between episodes; and normal growth and development.^{1–4} The exact aetiology of the disease remains uncertain but it is thought to result from interaction between environmental factors and the immune system.^{5,6} In parents of children with PFAPA syndrome, the incidence of auto-immune disease and atopic diseases is 7% and 30%, respectively.⁷

A typical PFAPA episode occurs about once every 3–6 weeks and lasts for 4–5 days, with fever being the predominant symptom.^{2–4} In some patients, abdominal pain,

nausea and vomiting may accompany other symptoms. The diagnosis is made using a modification of Marshall's criteria in addition to laboratory findings, as described by Thomas and co-workers.⁸ Although there are no specific laboratory findings, during episodes there is commonly mild leucocytosis with neutrophilia, moderate elevation of the erythrocyte sedimentation rate and C-reactive protein⁹ and a decrease in vitamin D levels.^{10,11} Even without treatment, characteristically, the number of episodes and duration of symptoms gradually decrease during the course of the disease,⁷ and remissions may last up to 3 years. Clinical manifestations can resolve spontaneously, and, between episodes, patients appear healthy and go on to develop normally without long-term consequences.⁹ However, early diagnosis and appropriate treatment are important as they may protect against unnecessary medical treatment and hospitalisation which can increase costs and lead absences from school and parental employment losses.

PFAPA should be excluded by reference to the clinical history, physical findings and/or laboratory investigations.

Correspondence to: F Erdogan, MD, İstanbul Medipol University, Department of Pediatrics, Koşuyolu Mah. Lambacı Sok No: 1–2, Kadıköy, İstanbul. Email: firaterdogan34@gmail.com

The differential diagnoses include cyclic neutropenia and auto-immune or inflammatory diseases such as systemic juvenile-onset idiopathic (rheumatoid) arthritis, Behçet's disease, familial Mediterranean fever (FMF), hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndromes.¹²

Medical treatment options for resolution of the symptoms are limited. They are essentially symptomatic and consist of single doses of corticosteroids: prednisone (1–2 mg/kg) or betamethasone (0.1–0.2 mg/kg) can halt the fever within a few hours.¹³ Other treatment options include cimetidine (an H₂ receptor antagonist), non-steroidal anti-inflammatory drugs and antibiotics.^{7,8,10,14–22} Corticosteroids, although effective during PFAPA episodes, do not prevent recurrence. A Cochrane review²³ found tonsillectomy to be superior to other options in preventing the symptoms and recurrence of the syndrome. However, the optimal treatment remains debatable. In this study, the outcome of two different approaches – medical therapy and tonsillectomy – to resolve the symptoms of PFAPA syndrome were compared.

Methods

Children diagnosed with PFAPA syndrome in the otorhinolaryngology (ENT) and paediatric outpatient departments during the 5-year period from January 2008 to 2013 were retrospectively reviewed. Patients' medical records were examined and subjects fulfilling the criteria by Thomas *et al.*⁸ for the diagnosis of PFAPA (Table 1) were enrolled.

Procedure

All children with signs of PFAPA syndrome were referred to a multi-disciplinary grand round meeting attended by paediatricians and ENT, paediatric rheumatology and paediatric infection specialists for thorough assessment. Patients whose fever resulted from forms of periodic fever syndromes, e.g. FMF, HIDS, etc., or cyclic neutropenia were excluded, and, when indicated, were referred to the institution's paediatric rheumatology or paediatric infectious diseases departments, as appropriate.

In 2014, the study patients and/or their families were interviewed, either during their hospital visit or by telephone. Patients were classified into two groups: group 1,

medical treatment – corticosteroids; or group 2, surgery – tonsillectomy alone or tonsillectomy plus adenoidectomy (group 2). The course of the disease – including the number and duration of episodes and the presence of remission (defined as the absence of the symptoms within, at least, a 1-year time-frame) – was documented. Data concerning the patients' demographics and the type of treatment they received were extracted from the chart reviews. Table 2 presents the patients' baseline characteristics.

The medical treatment of PFAPA syndrome was subject to a standardised protocol. A single dose of methylprednisolone (1 mg/kg/day) was administered by intramuscular injection only during episodes of PFAPA because young children have difficulties with oral administration, e.g. swallowing tablets and vomiting. No prophylactic treatment was given. All patients were treated with corticosteroids during each episode for about 3–6 months within the follow-up period between the initial diagnosis of PFAPA syndrome by the multi-disciplinary grand round meetings and the latest interview with the family. All patients with persistent episodes were then asked to decide whether to accept surgery or continue with medical treatment. The advantages and disadvantages of surgery and medical treatment were explained to parents and the child. After obtaining informed consent, the type of treatment was then decided. The surgical options for PFAPA syndrome included tonsillectomy alone or tonsillectomy plus adenoidectomy, based on the size of the hypertrophic adenoids or tonsils. The type of surgery was decided following examination with a flexible endoscope.

Statistical analysis

All variables were statistically compared between the two groups. SPSS Statistics (version 17.0) software was used. The Mann–Whitney *U* and independent *t*-tests were applied for purposes of comparison. A χ^2 test was used to compare remission rates. Parameters were given as mean (SD) and *P*<0.05 indicated statistical significance.

Ethics approval

Ethical approval was granted by the Ethics Committee of the Faculty of Medicine of Medipol University. Patients were not coerced to participate in the study, and written informed consent was sought from participants before any data were collected. The confidentiality of the data and the participants' privacy were respected at all times.

Results

A total of 105 children (30 in group 1, 75 in group 2) with PFAPA syndrome were eligible for and participated in the study. Patients' baseline characteristics are shown in Table 2. Mean (SD) age at diagnosis was 59.3 months (23.5) for group 1 and 52.3 (19.5) months for group 2. Other parameters, including the male-to-female ratio, the number and duration of episodes and the number of hospital admissions were comparable.

Table 1 Diagnostic criteria for PFAPA*

I	Regularly recurring fevers with an early age of onset (<5 years of age)
II	Constitutional symptoms in the absence of upper respiratory infection with at least one of the following clinical signs: (a) aphthous stomatitis (b) cervical lymphadenitis (c) pharyngitis
III	Exclusion of cyclic neutropenia
IV	Completely asymptomatic interval between episodes
V	Normal growth and development

*Thomas *et al.*⁸

Mean (SD) follow-up was 23.6 (11) months and 24 (10.3) months for groups 1 and 2, respectively (Table 3). At the end of the follow-up period, the mean (SD) number of episodes [respectively 5.8 (6.3) vs 1.8 (1.9)] and their duration [respectively 2.2 (1.3) vs 1.1 (0.8)] were significantly lower in the surgery group ($P = 0.03$). Furthermore, the need for hospitalisation during the follow-up period was also significantly lower in the surgery group: 1.1 (2) vs 0.1 (0.3) for groups 1 and 2, respectively ($P < 0.01$).

Remission rates were significantly higher in group 2 than in group 1 (98.6% vs 56.6%, $P < 0.01$, Table 3). Only one of 75 patients in the surgery group did not achieve complete remission, but, nonetheless, this patient's number and duration of episodes gradually decreased. In contrast, nearly half of the patients (13 of 30) in the medical treatment group had not achieved complete remission at a mean follow-up of around 2 years. In the medical group, however, all patients responded well to each corticosteroid treatment, and the frequency of fever decreased during follow-up.

Discussion

Within a follow-up period of 2 years, 74 of 75 children who underwent surgery for PFAPA seemed to be completely cured, whereas nearly half of the patients who received corticosteroid treatment continued to experience episodes, with a shorter interval between each episode. Thus, as reported in the literature,^{8,12,14,18,23–25} these findings demonstrate that surgery is superior to medical treatment for managing PFAPA syndrome.

Although PFAPA syndrome requires serious attention, there is little or no consensus on its optimal diagnosis and management. Although criteria for diagnosis are well established, they are generally based on exclusion. The effectiveness of many drugs for managing the disease has been investigated; for example trials featuring cimetidine, antibiotics, and corticosteroid treatments. The strongest evidence to date suggests that the only effective medical treatment regimen is one incorporating a single-dose corticosteroid for each episode.²⁵ This achieves dramatic relief

during febrile episodes, but has no effect on preventing their recurrence.

Several trials have investigated the effectiveness of medical and surgical treatment in the management of PFAPA syndrome,²⁵ with the primary objective of comparing the efficacy of each treatment approach. In one, cimetidine and antibiotics were both shown to be significantly ineffective compared with surgery, but corticosteroid treatment was found to be comparable.²⁵ In a cohort study in which 125 patients with PFAPA syndrome were prospectively evaluated, 18 underwent tonsillectomy and all of them had full symptom resolution.²⁶ In the same study, a single dose of prednisone for each episode was administered during the episodes to the children who did not undergo surgery, which resulted in reduction of symptoms in 94% of cases. However, only 46 had remission at the end of the follow-up period. Another case series investigated a total of 102 patients who underwent surgery for PFAPA syndrome.¹⁸ After a follow-up period of 43 months, 99 children had complete resolution of symptoms following tonsillectomy and adenoidectomy.¹⁸ A Cochrane systematic review²³ on tonsillectomy for PFAPA analysed two randomised controlled trials involving 67 children with PFAPA who were followed up for 18 and 6 months, respectively.^{17,20} PFAPA patients treated with surgery had less fever and fewer episodes, and the episodes were less severe than in those who did not undergo surgery.²³ The results of such meta-analyses suggest that antibiotics were ineffective but that surgery (i.e. tonsillectomy with or without adenoidectomy) was more effective than antibiotics and cimetidine prophylaxis.^{23,25} However, Esposito *et al.*¹² criticised this study because there are methodological problems in evaluating the difference between treatment with corticosteroids and surgery.

Two important randomised clinical trials for PFAPA syndrome support the effectiveness of surgery in children.^{17,20} They reported significant positive effects of adeno-tonsillectomy on symptom resolution compared with medical treatment. Both studies also confirmed substantial reduction in the frequency and duration of febrile episodes

Table 2 Study patients' baseline characteristics

	Medical treatment (SD) <i>n</i> = 30	Surgical treatment (SD) <i>n</i> = 75	<i>P</i> -value
Age at onset, mths	59.3 (23.5)	52.3 (19.5)	0.53
Male, %	58	65	0.47
No. of episodes/year	9.3 (4.9)	10.8 (6.3)	0.24
Duration of episodes, days	3.4 (2.1)	3.7 (1.9)	0.52
No. of hospital admissions	0.5 (1.0)	1.1 (2.0)	0.08

Table 3 Comparison of surgery vs medical treatment

	Medical treatment (SD) <i>n</i> = 30	Surgical treatment (SD) <i>n</i> = 75	<i>P</i> -value
Follow-up, mths	23.6 (11.0)	24.0 (10.35)	0.88
Complete remission, <i>n</i> (%)	17.0 (56.6)	74.0 (98.6)	<0.01
No. of episodes/year	5.8 (6.3)	1.8 (1.9)	<0.01
Duration of episodes, days	2.2 (1.3)	1.1 (0.8)	0.03
No. of hospital admissions	1.1 (2.0)	0.1 (0.3)	<0.01

in children. In a study by Garavello *et al.*,¹⁷ 39 patients with PFAPA syndrome were randomised into two groups – surgery vs expectant management – and the proportion of patients experiencing immediate and complete resolution of symptoms within 18 months was assessed. Immediate symptom resolution was achieved in 63% vs 5% in the surgery and control groups, respectively. Further-more, no episodes were experienced in the surgery group after 12 months. In the second of these randomised trials conducted by Renko *et al.*,²⁰ 26 children with a mean age of 4.1 years were randomly allocated to surgery and follow-up groups. Six months after randomisation, all of the 14 patients in the tonsillectomy group were free of symptoms, whereas only 50% of the follow-up group were cured. Moreover, in the control group comprising those who were not responsive to medical treatment, tonsillectomy was required in five of six children. Tonsillectomy was therefore found to be effective in the management of PFAPA syndrome in both of the studies.²⁰ However, as stated in the Cochrane review,²³ the evidence in both of these trials is of moderate quality owing to the relatively small sample sizes of the studies and some methodological concerns about the applicability of the outcomes, and further research is therefore warranted to confirm the benefit of surgery in managing the disease.

Alongside its high success rates, the major drawbacks of tonsillectomy, with or without adenoidectomy, include its invasiveness and the potential surgical and anaesthesia risks. In this study, none of the children undergoing surgery had intra- or post-operative complications (e.g. bleeding, pain, feeding difficulties). However, major complications have been reported in the literature, especially in inexperienced hands, and therefore a final decision to undertake surgery should be made only after consulting with the parents and their child.

There are several limitations to this study. First, the design was retrospective and the findings should therefore be cautiously interpreted. Also, the diagnostic criteria for PFAPA proposed by Marshall¹ and modified by Thomas *et al.*⁸ might not be valid, although no alternative assessments for PFAPA were available. Also, the definition of remission in PFAPA syndrome could prove limiting, and we therefore defined it as a 12-month asymptomatic period. Third, there might be bias in the evaluation of treatment responses such as the satisfaction of patients and their families, the number of admissions and their effect on patients and families, and irregularities of follow-up. A further possible limitation was the corticosteroid therapy administered to children in the control group. Despite these limitations, however, in view of the lack of evidence on this particular subject, this comparative trial with a sufficient duration of follow-up period contributes to the current literature.

Surgery offers significant advantages over medical treatment of PFAPA. The disease's remission rates and number and duration of episodes, as well as related hospital

admissions, can all be considerably reduced by surgical treatment. Taking account of the number of hospital visits, periods of absence from school and unnecessary medical treatments, surgery should be advocated as the first-line therapy for PFAPA syndrome.

Disclaimer statements

Contributors Firat Erdogan and Hüseyin Seven contributed to the conception and design of the study, Kudret Kulak, Özmen Öztürk, Mustafa Eliacik and Firat Erdogan completed acquisition of the data. Firat Erdogan, Omer Ceran and Ilke Ozahi Ipek wrote the first draft of the manuscript.

Funding None

Conflict of interest None.

References

- Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr.* 1987;110:43–6.
- Rigante D. The fresco of autoinflammatory diseases from the pediatric perspective. *Autoimmun Rev.* 2012;11:348–56.
- Stojanov S, Lapidus S, Chitkara P, Feder H, Salazar, Fleisher TA, *et al.* Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. *Proc Natl Acad Sci USA.* 2011;108:7148–53.
- Kolly L, Busso N, von Scheven-Gete A, Bagnoud N, Moix I, Holzinger D, *et al.* Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome is linked to dysregulated monocyte IL-1b production. *J Allergy Clin Immunol.* 2013;131:1635–43.
- Stojanov S, Hoffmann F, Kery A, Renner ED, Hartl D, Lohse P, *et al.* Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. *Eur Cytokine Netw.* 2006;17:90–7.
- Long SS. Syndrome of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) - what it isn't. What is it? *J Pediatr.* 1999;135:1–5.
- Tasher D, Somekh E, Dalal I. PFAPA syndrome: new clinical aspects disclosed. *Arch Dis Child.* 2006;91:981–4.
- Thomas KT, Feder HM, Lawton AR, Edwards KM. Periodic fever syndrome in children. *J Pediatr.* 1999;135:15–21.
- Valenzuela PM, Araya A, Perez CI, Maul X, Serrano C, Beltran C, *et al.* Profile of inflammatory mediators in tonsils of patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. *Clin Rheumatol.* 2013;32:1743–9.
- Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). *Acta Paediatr.* 2010;99:178–84.
- Mahamid M, Agbaria K, Mahamid A, Nseir W. Vitamin D linked to PFAPA syndrome. *Int J Pediatr Otorhinolaryngol.* 2013;77:362–6.
- Esposito S, Bianchini S, Fattizzo M, Baggi E, Marchisio P, Rigante D. The enigma of periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome. *Pediatr Infect Dis J.* 2014;33:650–2.
- Kyvsgaard N, Mikkelsen T, Korsholm J, Veirum JE, Herlin T. Periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis. *Dan Med J.* 2012;59:A4452.
- Galanakis E, Papadakis CE, Giannoussi E, Karatzanis AD, Bitsori M, Helidonis ES. PFAPA syndrome in children evaluated for tonsillectomy. *Arch Dis Child.* 2002;86:434–5.
- Pignataro L, Torretta S, Pietrogrande MC, Dellepiane RM, Pavesi P, Bossi A, *et al.* Outcome of tonsillectomy in selected patients with PFAPA syndrome. *Arch Otolaryngol Head Neck Surg.* 2009;135:548–53.
- Berlucchi M, Meini A, Plebani A, Bonvini MG, Lombardi D, Nicolai P. Update on treatment of Marshall's syndrome (PFAPA syndrome): report of five cases with review of the literature. *Ann Otol Rhinol Laryngol.* 2003;112:365–9.
- Garavello W, Romagnoli M, Gaini RM. Effectiveness of adenotonsillectomy in PFAPA syndrome: a randomized study. *J Pediatr.* 2009;155:250–3.
- Licameli G, Jeffrey J, Luz J, Jones D, Kenna M. Effect of adenotonsillectomy in PFAPA syndrome. *Arch Otolaryngol Head Neck Surg.* 2008;134:136–40.
- Peridis S, Koudounakis E, Theodoridis A, Stefanaki K, Helmis G, Houlakis M. Surgical outcomes and histology findings after

- tonsillectomy in children with periodic fever aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *Am J Otolaryngol.* 2010;31:472–5.
- 20 Renko M, Salo E, Putto-Laurila A, Saxen H, Mattila PS, Luotonen J, *et al.* A randomized, controlled trial of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. *J Pediatr.* 2007;151:289–92.
- 21 Leong SC, Karkos PD, Apostolidou MT. Is there a role for the otolaryngologist in PFAPA syndrome? A systematic review. *Int J Pediatr Otorhinolaryngol.* 2006;70:1841–5.
- 22 Parikh SR, Reiter ER, Kenna MA, Roberson D. Utility of tonsillectomy in 2 patients with the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. *Arch Otolaryngol Head Neck Surg.* 2003;129:670–3.
- 23 Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP. Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst. Rev.* 2014;9:CD008669. doi:<http://dx.doi.org/10.1002/14651858.CD008669.pub2>.
- 24 Wong KK, Finlay JC, Moxham JP. Role of tonsillectomy in PFAPA syndrome. *Arch Otolaryngol Head Neck Surg.* 2008;134:16–9.
- 25 Peridis S, Pilgrim G, Koudounakis E, Athanasopoulos I, Houlakis M, Parpounas K. PFAPA syndrome in children: a meta-analysis on surgical versus medical treatment. *Int J Pediatr Otorhinolaryngol.* 2010;74:1203–8.
- 26 Król P, Böhm M, Sula V, Dytrych P, Katra R, Nemcová D, *et al.* PFAPA syndrome: clinical characteristics and treatment outcomes in a large single-centre cohort. *Clin Exp Rheumatol.* 2013;31:980–7.