Role of tonsillectomy in PFAPA syndrome: A literature review and retrospective study

Original Article

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Abstract

Objective: Literature review and compare the pharmacological therapeutics effectiveness with the tonsillectomy in the disease remission.
Material and methods: Retrospective analysis of clinical data (age, gender, clinic, family history), types of treatment (pharmacological and/or surgical), time of remission (after medical and surgical treatment) and remission in the 1st, 3rd and 6th month after tonsillectomy in children with PFAPA syndrome evaluated at Hospital Pedro Hispano between January 2016 and December 2021.
Results: Nine children were evaluated (56% female, 44% male) aged between 1 and 4 years old (mean age 1.9 ± 1.3 years). At diagnosis, the mean number of weeks of remission was 4.0 ± 1.8. After corticotherapy it was 3.88 ± 1.0 and after tonsillectomy it was 50.6 ± 33.8 weeks.
Conclusion: Tonsillectomy has demonstrated to be a very useful therapeutic option in the disease's remission in children with PFAPA syndrome.

Keywords: PFAPA Syndrome, Tonsillectomy, Corticotherapy, Colchicine

Introduction

PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis/tonsillitis, and cervical adenitis) is a syndrome of unknown origin that usually starts before the age of five years. In most patients, the syndrome resolves before adolescence; however, it can persist into adulthood. The mean duration of the syndrome is 4.5 years[1].

It is the most frequent cause of recurrent fever in children from countries with a low prevalence of familiar Mediterranean fever[2]. Decreased quality of life of patients and their families and school absenteeism are the main problem associated with this syndrome[3].

Fever is a diagnostic marker, unlike aphthous stomatitis, cryptic tonsillitis, or pharyngitis

and adenitis. Other less common symptoms include nausea, vomiting, diarrhea, arthritis, conjunctivitis, and abdominal pain[4].

Marshall first described this syndrome in 1989[5]. Ten years later, Thomas[1] established the diagnostic criteria:

1. Recurrent fever starting before the age of five years
2. At least one of the following signs: aphthous stomatitis, cervical lymphadenopathy, or pharyngitis
3. Exclusion of cyclic neutropenia
4. Absence of symptoms between episodes
5. Normal growth and development

Typically, the fever does not respond to paracetamol, ibuprofen, acetylsalicylic acid, metamizole, or antibiotics. It responds well to corticosteroid therapy: a single dose of prednisolone (1–2 mg/kg/day) or betamethasone (0.3 mg/kg/day)[6]. It usually resolves spontaneously within five days, even without treatment.

The role of tonsillectomy in the treatment of PFAPA syndrome was suggested in 1989 by Abramson, who described a beneficial effect on disease remission[7]. In adults with PFAPA syndrome, the response to tonsillectomy appears to be weaker than in children[8]. Tonsillectomy can be combined with adenoidectomy, especially in cases with obstructive sleep disorder, but the latter is not useful if performed alone[7].

This study aimed to conduct a review of the literature and compare the effectiveness of pharmacological treatment with that of tonsillectomy in the remission of febrile episodes in children with PFAPA syndrome.

Materials and Methods

This study involved a retrospective analysis of cases diagnosed with PFAFA syndrome between January 2016 and December 2021 at the Pedro Hispano Hospital. The study was based on the data obtained from the patients' clinical records.

The collected data were entered into an Excel (MAC version) database and included the following study variables: age, sex, signs/symptoms, family history of recurrent febrile syndrome, types of treatments used (medical and/or surgical), duration of remission (after the start of medical treatment and after surgical treatment), and remission in the 1st, 3rd, and 6th months after tonsillectomy. All operated patients had a minimum follow-up of six months. The data were processed and analyzed using SPSS (version 28.0, IBM Corporation, Chicago, USA) and Excel (MAC version, Microsoft, Washington, USA) software.

The inclusion criteria were as follows: age < 18 years, recurrent febrile syndrome that met the Thomas criteria for the PFAPA syndrome.

The exclusion criteria were as follows: age ≥ 18 years, other recurrent febrile syndromes that did not meet the Thomas criteria for the PFAPA syndrome, and lack of data in the clinical records.

Results

A total of nine children were evaluated (56% girls, 44% boys) aged between one and four years (mean age: 1.9 ± 1.3 years).

All patients had fever and tonsillitis at diagnosis (Table 1), with five having adenitis (55.6%) and three having aphthous stomatitis (33.0%). Only two children (22.2%) had a family history of recurrent fever during childhood (father and/or mother).

Figure 1
Distribution by sex, n=9

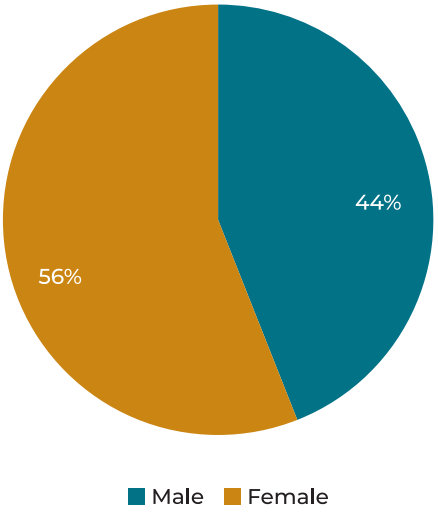

Table 1
Clinical characteristics, treatment, and remission

Patient N°	Age at diagnosis, years	Clinical presentation	Remission at diagnosis, weeks	Medical treatment	Surgical treatment	Remission after surgery		
						1st month	3rd month	6th month
1	2	F, Ton, S	8	Ant, Cor	Tons, Aden	✓	✓	✓
2	1	F, Ton, Ad	4	Ant, Cor	Tons, Aden	✓	✓	✓
3	4	F, Ton, Ad	3	Ant, Cor, Col	-	-	-	-
4	4	F, Ton	4	Ant, Cor	-	-	-	-
5	1	F, Ton, Ad	4	Ant, Cor	-	-	-	-
6	1	F, Ton, Ad, S	2	Ant, Cor	Tons, Aden	✓	✓	✓
7	1	F, Ton, Ad, S	5	Ant, Cor	-	-	-	-
8	1	F, Ton	4	Ant, Cor	Tons, Aden	✓	✓	✓
9	2	F, Ton	5	Ant, Cor	Tons, Aden	✓	✓	✓

Abbreviations: F, fever; Ton, tonsillitis; Ad, adenitis; S, stomatitis; Ant, antibiotic; Cor, corticosteroid; Col, colchicine; Tons, tonsillectomy; Aden, adenoidectomy

During the febrile crises, the temperature varied between 39.0 °C and 41.0 °C, and the mean temperature was 39.9 ± 0.6 °C (Table 2). The mean duration of the crises at diagnosis was 4.1 ± 0.8 days, with a minimum of three days and a maximum of five days.

During the crises, the mean values of the acute phase reactants were 15,895.6 ± 5,759.5 leukocytes/μL and C-reactive protein (CRP) of 94.1 ± 94.7 mg/L. The minimum and maximum values obtained for leukocytes were 9,300/μL and 26,790/μL, respectively. Regarding CRP, the minimum and maximum values were 2.8 mg/L and 248.7 mg/L, respectively.

Table 2
Clinical and laboratory characteristics during crises

Fever (°C)	39,9 ± 0,6
Leucocytes (/μL)	15895,6 ± 5759,5
C-Reactive Protein (mg/L)	94,1 ± 94,7

Table 3
Pharmacological treatment

Antibiotic	100 %
Corticosteroid	100 %
Colchicine	11,1 %

Note - antibiotic: amoxicillin and/or amoxicillin + clavulanic acid and/or penicillin; corticosteroid: single dose of prednisolone

Table 4
Remission (weeks) at diagnosis and after medical/surgical treatment

At diagnosis	4,00
After the start of corticosteroid therapy	3,88
After tonsillectomy	50,6

All children received pharmacological treatment after being diagnosed (Table 3). At some stage of the disease, all children (100%) were treated with antibiotics for suspected bacterial infection. During the crises, all children (100%) received corticosteroids. One child (11.1%) was treated with colchicine to prevent further crises.

At the time of diagnosis of PFAPA syndrome, the mean number of weeks in remission was 4.0 ± 1.8 and was 3.88 ± 1.0 weeks after the start of corticosteroid therapy (Table 4) (minimum of three weeks and maximum of eight weeks). The only child who was given colchicine (outside a crisis) had the remission period increased by one week (from three to four weeks).

Five of the nine children (55%) underwent tonsillectomy through classic dissection with adenoidectomy (Table 1). Two (40%) of these five children were boys, and three (60%) were girls. Four children (80%) were operated at two years of age, and one child (20%) had surgery at three years of age.

The mean number of weeks in remission with tonsillectomy was 50.6 ± 33.8 (minimum of 24 weeks and maximum of 88 weeks) (Table 4). All children achieved remission of the disease in the 1st, 3rd, and 6th months after tonsillectomy (Table 1).

Discussion

The differential diagnoses of PFAPA syndrome are infectious and autoimmune diseases characterized by recurrent febrile episodes (cyclic neutropenia, familiar Mediterranean fever, hyperimmunoglobulin D syndrome, Behçet's disease, juvenile rheumatoid arthritis, and autosomal dominant hereditary periodic fever syndrome). One inclusion criterion for this study was meeting the Thomas diagnostic criteria[1].

In the PFAPA syndrome, the body temperature typically increases suddenly and reaches values between 39 °C and 41 °C. The fever usually lasts between three and five days and may recur after three to six weeks if there is no preventive treatment[2].

In this study, all children were diagnosed before the age of five years, and there was a predominance of the female sex. During crises, laboratory tests showed an increase in the acute phase reactants (namely CRP) and the absolute serum concentration of leucocytes, as reported in the literature. The serum levels of IgD and IgE can also increase[2]. There is no specific laboratory marker for this syndrome, and cultures and direct antigen rapid tests for Streptococcus pyogenes are usually negative[2].

Although PFAPA syndrome has a self-limited course, most authors recommend that treatment should be offered after the diagnosis[9,10]. As the pathogenesis is unknown, there is a degree of uncertainty regarding its treatment. Pharmacological treatment (corticosteroids and colchicine) is the most frequently used option. Moreover, in everyday clinical practice, tonsillectomy is not commonly considered initially to treat this syndrome.

Corticosteroid therapy is one of the few pharmacological therapies that can shorten or resolve febrile episodes[9]. The occurrence of complications associated with a single dose of corticosteroids in children is extremely rare[10]; however, the potential risks should be explained to parents. In this study, a slightly shorter remission period was observed after the start of corticosteroid therapy. According to the international literature[9], patients requiring recurrent corticosteroid therapy exhibit a shorter period of remission[9]. Other therapeutic options described in the literature include IL-1 inhibitors, which are usually reserved for crises refractory to corticosteroid therapy[11]. According to the literature[1], nonsteroidal anti-inflammatory drugs (NSAIDs) are of limited use. Acetaminophen and ibuprofen lower the body temperature in only 6% and 33% of cases, respectively, and this effect is transient.

Regarding pharmacological prevention of febrile episodes, colchicine (1 mg/kg) was shown to reduce the number of events significantly[12]. In this study, it was only used in one child and increased the disease remission period by one week. Conversely, it was concluded in a recent meta-analysis that cimetidine is ineffective in the prevention of new events[8,13-15].

Tonsillectomy has not been considered a therapeutic tool for initial treatment. In this study, the absence of a response and/or reduction in the remission period after pharmacological treatment led to five children being referred for an otorhinolaryngology (ORL) consultation and to be enrolled for tonsillectomy. According to the latest recommendations of the American Academy of Otolaryngology and Head and Neck Surgery, the diagnosis of PFAPA syndrome is one of the indications for tonsillectomy in children[16]. Several randomized clinical trials[17,18] and case series have been published that describe the positive effect of tonsillectomy. Recent studies have demonstrated that remission with medical treatment is significantly lower than that with surgery[19]. Some authors reported the complete resolution of febrile episodes after tonsillectomy[17-18,20]. The pathophysiological basis of this beneficial effect of tonsillectomy

remains unknown. Some studies[21] have suggested that it is the result of the control of the excessive and recurrent inflammatory response of the palatine lymphoid tissue to internal or external stimuli—at the level of the tonsillar cells.

Although the study had a small sample size, the surgical results are in line with those of previous reports in the literature , with a much longer period of remission after tonsillectomy than after pharmacological treatment. None of the children who underwent surgical treatment exhibited new exacerbation of the disease during the evaluation period, a fact that strengthens the role of tonsillectomy in the therapeutic approach to PFAPA syndrome in children.

Conclusion

In this study, tonsillectomy was shown to be an effective treatment option for achieving disease remission. A prospective assessment of the efficacy of this surgical procedure may further confirm its importance in the treatment of PFAPA syndrome.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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