

Tonsillectomy efficacy in children with PFAPA syndrome is comparable to the standard medical treatment: a long-term observational study

G. Vigo¹, G. Martini¹, S. Zoppi², F. Vittadello¹, F. Zulian¹

¹Department of Paediatrics, Rheumatology Unit, University of Padova, Padova, Italy;

²Division of General Paediatrics, St. Bortolo Hospital, Vicenza, Italy.

Giulia Vigo, MD

Giorgia Martini, MD, PhD

Silvia Zoppi, MD

Fabio Vittadello, MSc, DrPH

Francesco Zulian, MD

Please address correspondence and reprint requests to:

Francesco Zulian, MD,
Dipartimento di Pediatria,
Università di Padova,
Via Giustiniani 3,
35128 Padova, Italy.

E-mail: zulian@pediatria.unipd.it

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ABSTRACT

Objective. Tonsillectomy has recently been suggested as an effective treatment for periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome but little is known about its long-term efficacy. We compared the clinical features and the long-term outcome of a large cohort of patients with PFAPA syndrome treated with tonsillectomy or with standard medical treatment.

Methods. We conducted a retrospective study on patients with PFAPA syndrome followed at a tertiary care centre from January 1993 to August 2010. Clinical characteristics and laboratory parameters were evaluated at onset and during the follow-up. Disease outcomes of patients who underwent tonsillectomy and of those treated with medical therapy (NSAIDs, prednisone) were compared. Clinical remission on medication (CRM) was considered the persistence of fever attacks which were well controlled by medical therapy, clinical remission (CR) was defined as the absence of fever attacks, without any treatment, for more than 12 months.

Results. 275 patients with PFAPA syndrome, 59.6% males, aged 27.9 months at onset and followed for mean 54.5 months, entered the study. CR was reported in 59.6% of the patients and was significantly less frequent in those with positive family history for PFAPA (46.4% vs. 66.1%, $p=0.003$). 27/41 patients (65.9%), responded to tonsillectomy and this result was comparable with that observed in those treated with medical therapy (59.1%, $p=0.51$). Disease duration, age at remission or presence of associated symptoms were not significantly different in both groups. No predictors of tonsillectomy failure were found.

Conclusion. In a large cohort of patients with PFAPA syndrome, tonsillectomy efficacy was comparable to the standard medical treatment.

Introduction

Periodic fever associated with aphthous stomatitis, pharyngitis and cervical lymphadenopathy (PFAPA) syndrome represents the most frequent form of non-infectious periodic syndrome of childhood (1).

The treatment of PFAPA syndrome is still a matter of debate. Recently, a few studies reported that tonsillectomy has been effective to control the recurrence of the fever episodes and even to induce the complete remission of the disease (2-8).

The present study aimed to evaluate the role of tonsillectomy in comparison to standard medical treatment in a large cohort of patients followed in a unique tertiary care centre.

Methods

We performed a retrospective study through the analysis of medical records of all patients with PFAPA syndrome followed at the Paediatric Rheumatology Unit, University of Padua.

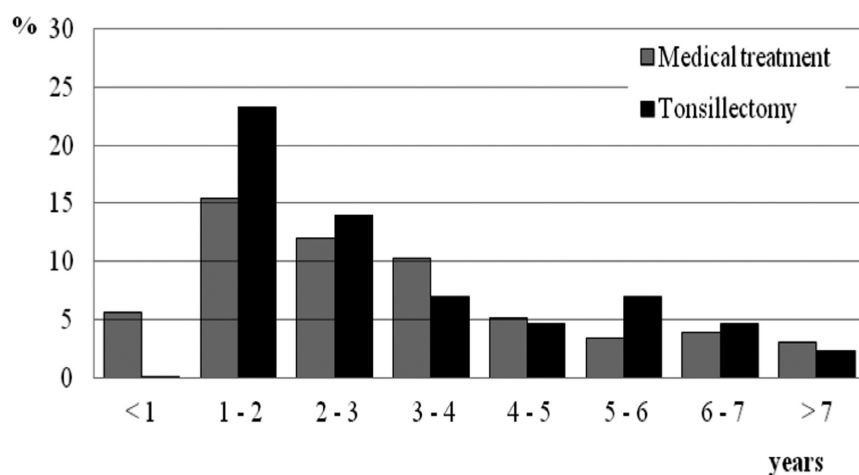
The diagnosis of PFAPA was established on the basis of clinical criteria that require the presence of regularly (often clockwise) recurrent episodes of high grade fever lasting for 3–6 days, associated with at least one of the three accompanying symptoms, aphthosis, cervical adenitis, pharyngitis, in the absence of upper respiratory tract infections or cyclic neutropenia (1). Periodicity was defined as the presence of fever-free interval time similar in length between two flares for at least three consecutive cycles.

Competing interests: none declared.

Table I. Demographics, clinical aspects and outcome of children with PFAPA syndrome.

		Tonsillectomy (n=41)	Medical treatment (n=234)	Overall (n=275)
Gender (male)		23 (56.1)	139 (59.4)	162 (58.9)
Positive family history for PFAPA		14 (34.1)	70 (29.9)	84 (30.5)
Age at onset (months)	mean	27.1	28.0	27.9
	range	6–113	6–148	6–148
Disease duration at diagnosis	mean	22.3	18.7	20.4
	range	6–72	6–57	6–72
Follow-up duration (months)	mean	68.9	52.0	54.5
	range	20–149	12–201	12–201
Associated symptoms		20 (48.8)	123 (52.5)	143 (52.0)
Disease duration (months)	mean	39.7*	40.0†	39.9§
	range	15–100	7–170	7–170
Age at clinical remission (months)	mean	66.3*	66.1†	66.1§
	range	29.8–142.5	17.5–216.2	17.5–216.2
Clinical remission rate		27 (65.9)	147 (62.8)	174 (63.3)

§n=174; *n=27; †n=147. Data are number (%) or mean (SD) unless otherwise indicated.

**Fig. 1.** Disease duration in accordance with the type of treatment.

In case of doubtful diagnosis, patients underwent genetic testing to rule out monogenic autoinflammatory syndromes. The criteria for performing molecular analysis of genes associated with periodic fever were the presence of recurrent fever attacks of unknown origin with symptom free intervals characterised by abnormal levels of acute phase reactants and/or presence of unusual PFAPA symptoms such as splenomegaly, chest pain, gastrointestinal, musculoskeletal or unusual muco-cutaneous manifestations such as glossitis, keilitis or polymorphous skin rash. Indeed, all patients refractory to tonsillectomy underwent genetic analysis, if available at that time.

For each patient we analysed sex, positive familial history for PFAPA or other autoinflammatory diseases in 1st degree relatives, age at disease onset, age at diagnosis, disease duration at the time of diagnosis, duration of follow-up since the first periodic fever episode and disease duration for those patients who went into remission.

We also recorded the type of medical treatment adopted and, for those who underwent tonsillectomy, the age and disease duration at the time of the surgical procedure.

Patients were regularly followed every 3–6 months by clinical evaluation and those who did not come to the regular

checks for more than 6 months were contacted by telephone.

Disease outcome was arbitrarily defined as clinical remission on medication (CRM) the persistence of fever attacks which were, however, well controlled by the medical treatment and complete clinical remission (CR), the absence of fever attacks and associated symptoms, without any treatment, for more than 12 months.

Statistical analysis

The statistical significance of differences between groups was assessed with the Pearson's Chi-square test (or Fisher's exact test) for categorical variables. Continuous variables were compared with the Student's *t*-test for independent samples or the Mann-Whitney rank-sum test, as appropriate. Backward stepwise logistic regression analysis (Wald statistic) was performed in order to identify prognostic factors for complete clinical remission. For each analysis, the statistical significance was defined with a *p*-value <0.05 (2-tailed test). All data were processed using the statistical software SPSS 14.0 (SPSS Inc., Chicago IL).

Results

From January 1993 to August 2010, 329 patients with periodic and recurrent fever syndromes have been followed at the Paediatric Rheumatology Unit, University of Padua and 27 were lost to follow-up. Among the 302 remaining, 27 were diagnosed as having monogenic hereditary autoinflammatory syndromes and 275 patients, 162 males (58.9%) and 113 females (41.1%) fulfilled the criteria for PFAPA syndrome and entered the study (Table I).

The mean age at disease onset was 27.9 months and the overall clinical follow-up lasted 54.5 months (range 12–201). For 174 patients (63.3%) who went into complete clinical remission (CR), the mean disease duration was 39.9 months (6.5–170). A positive familial history for PFAPA in first degree relatives was reported in 84 patients (30.5%).

The mean duration of the febrile episodes was 4.0 days (range 3–7) with a disease-free interval of 3.5 weeks (range 2–8). In the tonsillectomy group

the mean interval time between the fever attacks was 3.2 weeks (range 2.4–7.8) while in the medical treatment group it was 3.7 weeks (range 2–8). The mean disease duration, at the time of diagnosis, was 20.4 months which was not significantly different in the tonsillectomy group (22.3 months) than in the medical treatment group (18.7 months) (Table I).

Symptoms accompanying the febrile episodes were pharyngitis in 192 (69.8%), aphthous stomatitis in 83 (30.2%) and cervical adenitis in 131 (47.6%). Other symptoms reported during febrile attacks, at the disease onset, were: abdominal pain (16.4%), arthralgias (14.5%), vomiting (12.4%), headache (7.2%) and skin rash (5.1%).

Fifty-three (19.3%) patients underwent genetic analysis: 12 patients because were refractory to tonsillectomy and 41 because had unusual PFAPA symptoms. None of these cases resulted positive for monogenic periodic fever (namely FMF or MVK deficiency). 219 patients (79.6%) received prednisone (PDN) (1 mg/kg in single dose) at the beginning of each fever attack: 165 (75.3%) reported a dramatic resolution of fever within 2–4 hours, 49 patients (22.4%) had a partial response and needed 2 or more doses of PDN to control their symptoms, 5 (2.3%) were non responders. 56 patients (20.4%) have been treated with either non-steroidal anti-inflammatory drugs (NSAIDs), namely ibuprofen (10.9%), or paracetamol (9.5%).

Among 275 PFAPA patients in which we are able to obtain information on the long-term outcome, 174 (63.3%) achieved complete clinical remission, the remaining 101 (36.7%) had still disease manifestations at time of the last follow-up (Table I). In the group of patients on standard medical treatment, 62.8% achieved durable CR after mean 40 months disease duration.

During the course of the disease, 41 patients (14.9%) underwent tonsillectomy which led to a complete and persistent remission in 27 (65.9%) and was ineffective in 9 (21.9%). Five patients (12.2%), after an initial response, relapsed months later with new fever attacks. Figure 1 summarises the disease duration in patients with complete

Table II. Clinical characteristics of the PFAPA patients responding or refractory to tonsillectomy.

		Tonsillectomy		<i>p</i> -value
		Clinical remission on medication (n=14)	Complete clinical remission (n=27)	
Sex (M)		9 (64.3)	14 (51.9)	0.447
Positive family history for PFAPA		3 (21.4)	11 (40.7)	0.194
Age at onset (months)		29.7 (22.6)	25.8 (26.5)	0.638
	range	4.0–84.0	1.0–113.0	
Disease duration (months)		28.2 (17.6)	37.4 (23.2)	0.201
	range	2.8–55.3	11.3–98.5	
Age at tonsillectomy (months)		64.5 (36.5)	63.7 (32.9)	0.946
	range	19.4–157.0	28.9–140.7	
Inadequate response to prednisone (months)		2 (14.3)	7 (25.9)	0.393
Associated symptoms		7 (50.0)	13 (48.1)	0.873
Abdominal pain		3 (21.4)	4 (14.8)	0.923
Arthralgias		2 (7.1)	2 (7.4)	0.881
Vomiting		0 (0.0)	4 (14.8)	0.336
Headache		2 (14.3)	1 (3.7)	0.547
Skin rash		0 (0.0)	2 (7.4)	0.779

Data are number (%) or mean (SD) unless otherwise indicated.

remission according with the type of treatment. As shown, the proportion of patients with complete recovery was not significantly different in each time class. The decision of performing tonsillectomy was based on previous positive results of tonsillectomy in first degree relatives with PFAPA in 13 patients (31.7%), inadequate response to PDN in 9 (21.9%), following the ear nose throat (ENT) specialist indication in 11 (26.8%), the parental concern for PDN-related side effects in 4 (9.8%) and other reasons in 4 (9.8%). All patients who underwent tonsillectomy used PDN previously at least once and in all it was effective in controlling fever attacks. The comparison between the group of patients who reached CR and those who needed standard medical treatment after tonsillectomy (CRM) failed to show significant predictors of surgery efficacy (Table II).

As shown in Table I, the response rate of patients who underwent tonsillectomy (65.9%) was similar of those treated with standard medical treatment (62.8%) and the mean disease duration was also comparable (39.7 vs. 40 months). The clinical characteristics of the two groups of patients are also comparable for the other demographic and clinical characteristics, included the frequency of associated symptoms.

Around one third of patients (30.5%) had at least one family member with a personal history of recurrent fever episodes similar to that observed in the child. In many of them the fever episodes resolved after tonsillectomy. The search for specific epidemiological or clinical features in this particular group of “familial PFAPA” did not reveal significant associations except for a higher percentage of patients with unremitting disease. In fact, complete clinical remission was achieved in 46.4% of patients with PFAPA positive familial history and in 66.1% of non-familial cases ($p=0.003$). This was confirmed by the multivariate analysis (Backward method-Wald statistic) showing that, in presence of positive familial history, the remission probability significantly reduced ($p=0.001$).

Discussion

PFAPA syndrome is not a rare disease in childhood since a mean of 16 patients/year were referred to our tertiary care centre in 17 years.

The treatment of PFAPA is still controversial and, at present, there are no validated guidelines addressing this issue (12). During the last decade, tonsillectomy has been proposed as an effective treatment to control the recurrence of the fever episodes and even to induce

the complete remission of the disease (2-8).

However, as clearly shown in a recent review article (9), while these studies reported a complete recovery after tonsillectomy in 56–100% of the patients, they were generally small sample sized and the duration of follow-up was quite short, varying between 12 and 26 months (2-8).

Our study, including 234 patients on medical treatment and 41 who underwent tonsillectomy, is one of the largest ever done and the follow-up duration (4.5 years) one of the longest. In general, the probability to reach a complete clinical remission is higher in patients without a positive family history for PFAPA as two thirds of the patients in this group went into CR. Only 46% of those with positive family history went into CR and this finding is concordant with a recent study showing a significant association between familial history of PFAPA and long lasting disease (10). Conversely from ours, however, in this study, only 11.7% of the patients had a positive family history for periodic fevers and in 6.7% other diagnoses, such as Behçet's disease and FMF were made.

Interestingly, our data show that the percentage of patients responding to tonsillectomy was not significantly different from that observed in those on standard medical treatment. Furthermore, neither the age at disease onset, nor the disease duration or the frequency of associated symptoms was significantly different in the two groups.

The search for possible predictors of tonsillectomy efficacy failed to show significant variables. In particular, neither the positive family history for PFAPA nor the disease duration or the age at the time of the surgical procedure were significantly correlated with the outcome (Table II). As far as indication to tonsillectomy, psychosocial factors played a major role. In fact, the majority of patients in the tonsillectomy group had previous positive experience in the family and this induced the parents to prefer the surgical option to the standard medical treatment. Another parental

concern was related with the worry for possible corticosteroid-related side effects although single CS doses, given at prolonged intervals, do not seem to have major consequences (9, 10).

On the other hand, tonsillectomy is not always a safe procedure, as possible risks may be associated with both surgical and anesthetic interventions. Major surgical complications range between 9 and 14% and include bleeding and infections (11, 12). Anesthesia-related complications occur rarely but can be life threatening. They include nausea, vomiting, cardiac arrhythmia, airway-related problems such as oxygen desaturation and difficult laryngoscopy (13, 14). After hospital discharge, secondary haemorrhage are reported in 12–16% of the patients, with the need for additional surgery in 3% of them (15, 16).

A few limitations of this study should be underlined. Its retrospective nature may have partially influenced the results. However, the small proportion of patients lost to follow-up (8.2%) and the fact that the majority of patients have been regularly checked according to an internal clinical protocol, render this limitation less important. Another limit consists in a possible referral bias related to the tonsillectomy group. In fact, patients who relapsed were more motivated to come back to our observation than those who completely recovered after tonsillectomy. This occurrence, however, might have involved also patients on standard medical treatment, partially balancing the hypothetical selection bias.

In conclusion, our study shows that tonsillectomy in PFAPA syndrome is not superior to the standard medical treatment. Since PFAPA, in the majority of patients, is a benign self-limiting disease, the benefit-risk cost of tonsillectomy should be carefully considered.

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