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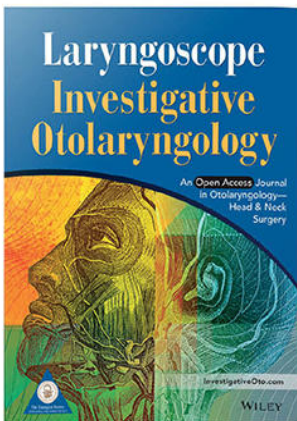


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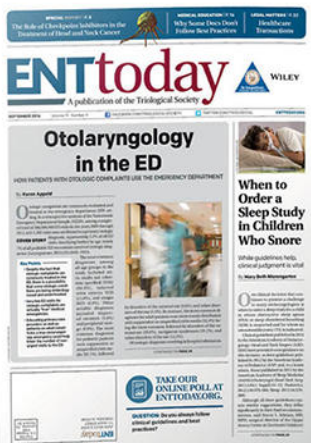
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Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome: Relapse and Tonsillar Regrowth After Childhood Tonsillectomy

Ulla Lantto, MD, PhD ; Petri Koivunen, MD, PhD; Terhi Tapiainen, MD, PhD; Marjo Renko, MD, PhD

Objectives/Hypothesis: Tonsillectomy is an effective treatment for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, but the role of adenoidectomy, as well as later tonsillar regrowth, is unclear. To find out if the volume of lymphoid tissue is pivotal to the efficacy, we analyzed the association between the relapse of the symptoms of PFAPA syndrome and regrowth of tonsillar tissue after tonsillectomy or adenotonsillectomy.

Study Design: Prospective cohort study of operated PFAPA patients.

Methods: We invited all patients that had undergone tonsillectomy or adenotonsillectomy due to PFAPA syndrome at the Oulu University Hospital, Oulu, Finland, between the years 1990 and 2007, at the age of ≤ 12 years, to a follow-up visit, after an average period of 9.8 years after their diagnoses. Out of the 132 invited, 94 (71%) participated in the follow-up study.

Results: At the follow-up study visit, 5 (5%) of the 94 PFAPA syndrome cases experienced recurrent fevers. The regrowth of palatine tonsillar tissue was seen in four of them (80%) as compared to 19/89 (21%) of symptom-free patients ($P = .006$). Two of the patients with clear PFAPA relapse at the time of the study visit were reoperated with clear effect on the symptoms. At the time of the study visit, 59/63 (94%) of the patients who had undergone adenotonsillectomy and 30/31 of the patients (97%) who had undergone tonsillectomy earlier were free of fever flares ($P = .99$).

Conclusion: Palatine tonsil regrowth was associated with PFAPA syndrome relapse after tonsillectomy. Reoperation might be a treatment option in these patients.

Key Words: Adenoidectomy, adenotonsillectomy, lymphoid tissue, reoperation.

Level of Evidence: 4

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INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most common pediatric periodic fever syndrome,¹ first described by Marshall in 1987.² Patients with PFAPA experience high recurrent fever at regular intervals, and fever flares are often associated with pharyngeal symptoms. However, patients are completely healthy between episodes, and their growth and development are normal. The etiology of PFAPA syndrome is

unknown.^{3–5} PFAPA syndrome is considered to be an autoinflammatory disease as the activation of interleukin-1 (IL-1 β) and inflammatory-related pathways during fever flares is evident in affected patients.^{6–8} However, unlike other autoinflammatory periodic fever syndromes, PFAPA syndrome can be treated effectively using tonsillectomy (TE).^{5,9–11}

The mechanism of how TE prevents further fever flares in PFAPA syndrome has not yet been fully elucidated. It has been suggested that, as part of the pathogenesis of PFAPA syndrome, naïve, polyclonal T lymphocytes accumulate in tonsils from the peripheral blood.^{12,13} The microbiome of the tonsils has also been explored as an inflammatory stimulus or disease modulator.^{13–15} These hypotheses offer some explanations for the effectiveness of TE, but the exact mechanisms responsible for the symptoms and their resolution remain unknown. It has been postulated that the volume of removed lymphoid tissue is pivotal to the efficacy of operative treatment but the role of adenoidectomy (A) and later tonsillar regrowth is unclear.¹¹

To clarify the significance of nasopharyngeal lymphoid tissue reservoirs in PFAPA syndrome, we analyzed the association between tonsil operations, the presence of tonsillar tissue, and outcomes in a cohort of PFAPA syndrome patients earlier treated with TE or adenotonsillectomy (TEA) and followed up for 10 years on average (Fig. 1).

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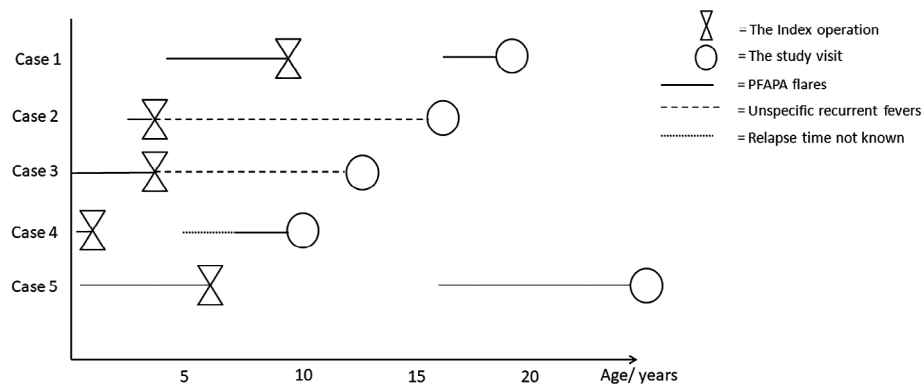


Fig. 1. Fever profile of the periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis patients who were febrile between the index operation (TE) and study visit.

MATERIALS AND METHODS

The recruitment and follow-up of this cohort of PFAPA syndrome patients have previously been described.¹⁶ Children aged ≤ 12 years and undergoing TE or TEA due to PFAPA syndrome at the Oulu University Hospital, Oulu, Finland, between the period from 1990 to 2007, were included in the study. TE/TEA performed due to PFAPA syndrome was considered to be the index operation. The Oulu University Hospital serves a population of 405,635 people (Statistics Finland 31.12.2014). The majority of children with periodic fever syndromes in the area are diagnosed and treated at this hospital. The protocol of the study was approved by the Regional Ethics Committee, Northern Ostrobothnia Hospital District, Oulu, Finland.

A total of 132 children fulfilled the criteria for PFAPA syndrome (Table I).

Out of this, 94 (72%) patients agreed to participate in a follow-up study (mean age of 10.4 years after their diagnoses).¹⁶ The visit included an examination of the ears, nose, larynx, and pharynx; special attention was given on the postoperative status of the palatine and pharyngeal tonsil areas. Each patient completed a detailed questionnaire about the symptoms before and after TE or TEA and provided information on the long-term postoperative condition and health. Data on the surgical operations performed on the nasopharyngeal tonsillar tissue (A, TE, and TEA) prior to or after the index operation

(i.e., TE, to treat PFAPA syndrome) were collected from interviews with the patients and their medical records.

We have earlier reported the outcome and background characteristics of the follow-up cohort. In brief, 55 of the cases were male (59%). The ethnic background of all patients was North European. The mean follow-up period from the onset of PFAPA syndrome symptoms to clinical control or the interview was 9.8 years (standard deviation [SD] of 4.5, $n = 92$). The mean age of the patients at the time of the study visit was 12.4 years (SD of 4.8, $n = 94$).

In the present study, the regrowth of tonsillar and adenoid tissue at the follow-up clinical examination was compared between symptomless patients and those with PFAPA syndrome relapse. The clinical course of patients with ongoing recurrent fever at the time of the study visit was carefully reviewed, and four or five of them were reached once more for an interview by telephone in 2019, on average, 9 years after the study visit. The impact of A on PFAPA syndrome symptoms was analyzed in patients who had undergone A after being diagnosed with PFAPA syndrome.

Statistical methods

Statistical analyzes were performed using IBM SPSS® Statistics version 21.0 (IBM Corp., Armonk, NY) and StatsDirect version 3.2.8 (StatsDirect Ltd., Altrincham, UK). The proportions of dichotomic variables were calculated and compared between symptom-free patients and those with enduring fever during the visit. A standard normal deviate (SND) test was used to analyze the statistical significance of the differences. For continuous variables, the mean \pm SD or median (range) was calculated. The statistical significance of any differences was tested using Student's *t*-test or the Mann-Whitney *U* test, depending on the distribution.

RESULTS

At the study visit, 5 (5%) of the 94 PFAPA syndrome cases experienced recurrent fevers. The regrowth of palatine tonsillar tissue was seen during the clinical examination in 4 (80%) of the five patients with ongoing fevers

TABLE I.
The Diagnostic Criteria Used for PFAPA Syndrome.²⁵

No.	Diagnostic criteria
1.	Regular, periodic episodes of fever (history of ≥ 5 regular periods)
2.	No other explanation (e.g., respiratory or urinary tract infection) for the episodes of fever
3.	An evaluation of the risk of cyclic neutropenia, as well as genetic periodic fevers, depending on their background rate
4.	Asymptomatic intervals between fever episodes
5.	Normal growth and development

PFAPA = periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis.

TABLE II.
Details of the PFAPA Syndrome Patients Treated With Tonsillectomy Who Reported Recurrent Fever at the Time of the Study.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Male	Male	Female	Male	Female
Age at PFAPA syndrome fever onset (years)	0.5	0.7	4.1	2.7	0.1
Index operation	TEA	TEA	TEA	TE [†]	TEA
Age at the time of the index operation (years)	1.6	6.8	8.8	3.3	3.0
Age at the time of the study visit (years)	9.7	26.4	18.1	15.8	12.3
Fevers after the index operation TE(A)	Relapse of PFAPA flares	Relapse of PFAPA flares	Relapse of PFAPA flares	Recurrent unspecific fever	Recurrent unspecific fever
Tonsillar regrowth	Yes	Yes	Yes	No	Yes
Re-TE	No	Yes	Yes	No	No
Fevers at the follow up contact	No	No	No	No	No
PFAPA cases in family	No	Yes	No	Yes	Yes

[†]Adenoidectomy prior to undergoing tonsillectomy.

PFAPA = periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis.

and in 19/89 (21%) symptom-free patients ($P = .006$). The regrowth of palatine tonsils was relatively small in size, approximately 10 mm in diameter. The regrowth of adenoid tissue was noted in 3/25 patients (12%), of whom 2/22 were symptom-free and 1/3 experienced recurrent fever flares ($P = .225$). The clinical examination was otherwise normal in all the patients.

The mean duration of PFAPA syndrome symptoms before the index operation was 37 months for those with ongoing fevers at the time of the study visit and 18 months for symptom-free cases ($P = .170$).

Three of the five patients having recurrent fevers at the time of the study visit had clear PFAPA relapse (Cases 1–3). All of them had achieved remission right after the index operation but had started experiencing PFAPA symptoms after years of remission. They all had regrowth of palatine tonsils at the study visit, and revision tonsillectomy (Re-TE) was scheduled for them. One patient (Case 1) achieved remission prior to re-TE and did not undergo surgery. Two others (Cases 2 and 3) underwent re-TE and both achieved remission. Case 3 experienced a PFAPA syndrome relapse after a few months. The lingual tonsils of Case 3 were treated with intratonsillar bipolar radio frequency-induced thermotherapy (RFA) owing to strong hypertrophy and exudates of the lingual tonsils at the time of the fever. High fever episodes started again after 1 year postoperatively. The fever was accompanied by genital ulcers. Bechet's disease was suspected but not verified. Genetic test panel for autoinflammatory syndromes was negative. After a symptomatic period of 5 to 6 years, the symptoms gradually stopped.

Two of the five symptomatic patients reported a change in their symptom profile after the index operation (Cases 4 and 5, Table II). Their ongoing recurrent fever was not strictly periodic, and the symptoms were milder and no longer fulfilled the PFAPA syndrome diagnostic criteria. One of them experienced the regrowth of palatine tonsils, and the other patient had the regrowth of adenoid tissue, but further surgery was not performed. In 2019, Cases 4 and 5 reported that they had not

experienced recurrent fever since the study visit. Other chronic diseases were not diagnosed in these five patients.

Of the 94 patients, TEA was the index operation in 63 (67%) and TE in 31 (33%). All the patients had undergone total TE, and no tonsillectomies were performed. The operative technique used had been cold dissection, and suction-monopolar diathermy had been used to control bleeding. Thirteen patients (14%) underwent A before the index operation. PFAPA syndrome symptoms were experienced by five patients prior to undergoing A. The adenoid tissue was not removed in 20 (21%) of the 94 patients. At the time of the study visit 59 (94%) of the 63 patients who underwent TEA and 30 (97%) of the 31 patients who had TE, were free of fever flares ($P = .99$).

DISCUSSION

In this cohort study of 94 children with PFAPA and earlier TE/TEA, we found an association between palatine tonsil regrowth and ongoing fevers. At the follow-up visit, on average about 10 years after the initial operation, 80% (4 out of 5) of the patients who were febrile at the follow-up study visit had tonsillar regrowth compared to 21% (19 out of 89) in those who had remained asymptomatic. It is not known whether regrowth of the tonsils causes fever or whether the activation of PFAPA syndrome leads to regrowth.

Although PFAPA syndrome can heal spontaneously, fever may persist for on average of 4 to 5 years and even up to 20 years without operative treatment.^{1,17,18} Removing the palatine tonsillar tissue strongly impacts PFAPA syndrome symptoms. The effectiveness of TE has been confirmed in randomized trials.^{9,11,19} In some cases, the symptoms can be reduced using TE, even though they do not completely disappear.²⁰ Postoperative relapse, after years of being symptom free, has been reported,^{21–24} but they were rare in the nine-year follow-up in the current study.¹⁶

Adenoidectomy appeared to play no role in the treatment of PFAPA in the present study. In the current study, 13 patients had undergone A before the index operation,

but as an initial treatment, A did not prevent PFAPA syndrome symptoms or cure PFAPA syndrome. It was interesting that relapsed PFAPA disease responded well to re-TE in two cases and RFA of lingual tonsils in one case. Reoperation and RFA treatment of lingual tonsils need to be further studied as a treatment for relapsed PFAPA.

At the time of the study visit, the palatine tonsil regrowth was seen more often in patients with recurrent fevers than in asymptomatic patients; yet, several asymptomatic patients had regrowth as well, even though all patients had undergone total TE. Previous data on regrowth of palatine tonsils after TE in general is very limited and the activity of lymphatic tissue of pharynx in PFAPA after remission is not known.

In this study, the mean duration of preoperative symptoms was 37 months for patients who experienced a relapse or recurrent fever and 18 months for those with an immediate and long-lasting remission response to index TE. The difference was not statistically significant; but the result raises an interesting question for further studies about the timing of TE.

The strengths of this study lie in the long follow-up period and thorough clinical examination at the study visit. Effectiveness of TE was good and it was long-lasting as only five patients reported recurrent fevers at the time of the study visit. The small number of relapses should be taken account when drawing conclusions from the results. Another weakness of this study is that we had no control group to compare the postoperative status after TEs with the PFAPA patients and the patients operated for other reasons.

CONCLUSION

In this cohort study, palatine tonsil regrowth after TE was more common in PFAPA patients with relapse than in asymptomatic PFAPA patients. Re-TE might be considered in patients with PFAPA relapse and palatine tonsil regrowth.

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