

Effectiveness of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome: a case series

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Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is characterized by periodic high fever (febrile attacks) lasting for 3-6 days and recurring regularly. In this syndrome, fever is associated with aphthous stomatitis, pharyngitis, and cervical adenitis.¹⁻⁴ Almost all patients with PFAPA syndrome spontaneously resolve approximately 8 years after the onset of symptoms. However, the cause and etiology of PFAPA syndrome remain unclear.⁴ Oral prednisolone reduces fever during febrile attacks.⁵⁻⁷ Tonsillectomy has also been reported to induce remission of PFAPA syndrome.⁸⁻¹² However, tonsillectomy is not a popular treatment for PFAPA syndrome because its effectiveness is still unclear. Furthermore, tonsillectomy is generally recommended for patients aged 3 years and older to avoid post-operative complications.¹³

We report here on four patients aged 3 years and older with PFAPA syndrome. Tonsillectomy completely eliminated febrile attacks and was safely performed without post-operative complications in all of our patients. [Paediatr Indones. 2021;61:171-4 ; DOI: 10.14238/pi61.3.2021.171-4].

Keywords: tonsillectomy; PFAPA syndrome; febrile attack; remission; therapeutic strategy

The Cases

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Tara Town Hospital, Japan) and with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent for inclusion was obtained from the four subjects' parents. Patient 1 was a boy and patients 2, 3, and 4 were girls (**Table 1**). These patients were diagnosed with PFAPA syndrome in accordance with the diagnostic criteria advocated by Thomas *et al.*³ (**Table 2**), and they underwent tonsillectomies. We prospectively analyzed the patient characteristics, including the age at onset, age at diagnosis, oral medications, age at tonsillectomy, and recurrence of PFAPA syndrome after tonsillectomy.

Patient 1 was diagnosed with PFAPA syndrome at the age of 3 years, although the onset of this disease was at the age of 1 year (**Table 1**). He experienced periodic febrile attacks accompanied by aphthous stomatitis, pharyngitis, and cough every 2-8 weeks. During his

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Table 1. Patients' characteristics

Patient no.	Sex	Age at onset, years	Age at diagnosis, years	Oral medication	Age at tonsillectomy, years
1	Male	1	3	PSL	6
2	Female	1	1	PSL	3
3	Female	1	2	PSL	5
4	Female	1	2	PSL, cimetidine	5

PSL=prednisolone

Table 2. Diagnostic criteria advocated by Thomas *et al.*³

- I Regularly recurring fever with an early age of onset (< 5 years)
- II Constitutional symptoms in the absence of upper respiratory infection and 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

febrile attacks, oral prednisolone treatment (single dose of 0.5 mg/kg, repeated in 12 hours if necessary, depending on response to treatment) effectively reduced the fever. He underwent tonsillectomy at the age of 6 years. He experienced no febrile attacks for more than 50 months post-tonsillectomy.

Patient 2 was diagnosed with PFAPA syndrome at the age of 1 year, soon after the disease onset. She experienced periodic febrile attacks accompanied by aphthous stomatitis and pharyngitis every 2-7 weeks. During her febrile attacks, oral prednisolone treatment (single dose of 0.5 mg/kg, repeated in 12 hours if necessary, depending on response to treatment) effectively reduced the fever. She underwent tonsillectomy at the age of 3 years. She experienced no febrile attacks for more than 36 months post-tonsillectomy.

Patient 3 was diagnosed with PFAPA syndrome at the age of 2 years, although the disease onset was at the age of 1 year. She experienced periodic febrile attacks accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis every 3-10 weeks. During the febrile attacks, oral prednisolone treatment (single dose of 0.5 mg/kg) effectively reduced the fever. She underwent tonsillectomy at the age of 5 years. She experienced no febrile attacks for more than 15 months post-tonsillectomy.

Patient 4 was diagnosed with PFAPA syndrome at the age of 2 years, although the disease onset

was at the age of 1 year. She experienced periodic febrile attacks accompanied by aphthous stomatitis and pharyngitis every 4-8 weeks. During her febrile attacks, oral prednisolone treatment (single dose of 0.5 mg/kg) effectively reduced the fever. She received oral cimetidine (20 mg/kg, twice daily) as prophylactic treatment for febrile attacks. She did not suffer from a febrile attack for 12 months during cimetidine treatment. Febrile attacks of PFAPA syndrome recurred 9 months after she had finished cimetidine treatment. She underwent tonsillectomy at the age of 5 years. She experienced no febrile attacks for more than 5 months post-tonsillectomy.

No post-operative complications occurred in any of these patients. Pathological examinations of these patients showed chronic tonsillitis, including enlarged and hyperplastic lymphoid follicles (data not shown).

Discussion

The courses of our patients suggested two important clinical issues. First, tonsillectomy completely induced remission of PFAPA syndrome in all of our patients. This finding suggests that tonsillectomy is a highly effective treatment for PFAPA syndrome. Previous studies have reported that tonsillectomy was effective in 63-100% of patients with PFAPA syndrome.⁸⁻¹² Our findings support these previous data.

Second, tonsillectomy was safely performed in our patients at the age of 3 years and older. Tonsillectomy is generally recommended for patients aged 3 years and older to avoid post-operative complications, in accordance with clinical guidelines advocated by the *American Academy of Otolaryngology-Head and Neck Surgery Foundation*.¹³ Findings in patient 2 indicated that tonsillectomy can be safely performed in 3-year-old patients without post-operative complications.

However, PFAPA syndrome can also be treated

with oral medications. Prednisolone is highly effective against febrile attacks of PFAPA syndrome, although it shortens the interval between febrile attacks.^{7,14} A study showed more than 80% effectiveness of orally administered prednisolone or betamethasone as treatment for febrile attacks.¹⁵ Although they suggested colchicine, cimetidine, and anakinra as prophylactic treatments, the effectiveness of these drugs is still controversial.¹⁵ Other study groups have suggested cimetidine as prophylactic treatment for febrile attacks of PFAPA syndrome.^{3,4,7} Previous studies reported that cimetidine was effective in 43%, 27%, and 24% of patients with PFAPA syndrome, respectively.^{3,4,7} Cimetidine is a common H₂ antagonist that inhibits suppressor CD8+ T-lymphocyte activation and chemotaxis.^{6,7} Patient 4 received oral cimetidine as prophylactic treatment and it successfully prevented febrile attacks. Febrile attacks of PFAPA syndrome can begin as early as 1 month of age.^{1,3,11,16} Since younger patients with PFAPA syndrome should wait until 3 years of age for tonsillectomy, cimetidine as prophylactic treatment is a viable therapeutic strategy for children under 3 years.

Patients with PFAPA syndrome have to sacrifice many pleasurable activities, such as field days, festivals, and travel, because of sudden febrile attacks. These social events are indispensable for the development of children. We would have liked to perform tonsillectomies earlier in patients 1, 3, and 4. However, we could not because of the circumstances described as follows. Patient 1 was already 6-years-old when clinicians became aware that tonsillectomy was effective for PFAPA syndrome. Patients 3 and 4 were 3-years-old at the time of evaluation, but hospitalization for tonsillectomy was difficult, as parents had other children to care for at home. These patients could have improved their lives if they could have undergone tonsillectomy at an earlier age.

In conclusion, tonsillectomy is an effective treatment for PFAPA syndrome, and can be safely performed in patients aged 3 years and older. We recommend that tonsillectomy be considered as soon as possible for patients with PFAPA syndrome aged 3 years and older. Further research should be done to determine whether tonsillectomy would be useful as the main therapeutic strategy for PFAPA syndrome.

Conflict of Interest

None declared.

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