Tonsillectomy in Children with Periodic Fever with Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome

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Objective To seek evidence supporting a role for tonsillectomy or adenotonsillectomy in the management of affected children with periodic fever with aphthous stomatitis, pharnygitis, and adenitis (PFAPA) syndrome.

Study design A comprehensive literature search was conducted to identify all published English-language observational and randomized studies evaluating the efficacy of tonsillectomy or adenotonsillectomy on PFAPA syndrome. A combination of keywords was used to identify relevant articles.

Results A total of 15 studies including 149 treated children were found, including 13 observational noncomparative studies and 2 randomized controlled trials. The pooled rate of complete resolution emerging from the combined analysis of all treated children was 83% (95% CI, 77%-89%). A meta-analysis of the two randomized controlled trials showed homogeneity of the results ($P = .37$, Breslow-Day test) and a common odds ratio for complete resolution of 13 (95% CI, 4-43; $P < .001$).

Conclusions Surgery appears to be a possible option for management of PFAPA syndrome. Available evidence is limited, however, and the precise role of surgery remains to be clarified. We suggest considering this option when symptoms markedly interfere with the child's quality of life and medical treatment has failed. *(J Pediatr 2011;159:138-42)*.

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is a clinical entity occurring in young children.[1,2] It arises before age 5 years and is characterized by short phases of illness (3-4 days) that recur regularly every 3-8 weeks for several years. These episodes follow a strict periodicity with intervals of complete health.[3] Even though it does not affect child growth and development, symptoms can impact the physical, psychological, and social well being of affected children and can have a profound effect on their parents. Moreover, the PFAPA-associated costs to the family might be considerable, although they have not yet been quantified.

The pathogenesis of PFAPA syndrome remains enigmatic.[3-5] Cases in family members with similar periodic episodes of fever are beginning to suggest a possible roles of both genetics and the environment.[6]

The elusiveness of PFAPA syndrome's origin has inevitably led to treatment uncertainties. Antibiotics are not effective, but nonsteroidal anti-inflammatory drugs may have modest therapeutic benefits.[3,5,7] The most effective treatment is corticosteroid therapy, which is associated with cessation of the fever cycle within 12-24 hours.[3,5,7] The role of tonsillectomy has remained uncertain. In 2006, Leong et al[8] published a review of the literature on PFAPA syndrome and, finding only weak evidence on the effectiveness of tonsillectomy in this syndrome, concluded that tonsillectomy should not be performed. The potential benefits of surgery have attracted the interest of researchers, however, and some important clinical studies have been published over the last 3 years. Here we review the literature and assess the benefits, if any, of tonsillectomy in treating PFAPA syndrome.

Methods

An electronic database search (MEDLINE and PubMed) was performed with the objective of identifying all studies published in the English language between January 1987 and May 2010 on the effect of tonsillectomy or adenotonsillectomy in the management of PFAPA syndrome. Combinations of keywords including "PFAPA," "periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis," "therapy," "treatment," "surgery," "randomized controlled trial (RCT)," "randomized," "tonsillectomy," and "adenotonsillectomy" were used. All pertinent articles were retrieved, and the relative reference lists were reviewed systematically to identify other reports that could be included. Studies presented at meetings or congresses with only abstracts available were not included. No attempt was made to identify unpublished studies. The Clinicaltrial.gov Web site was also consulted to identify ongoing studies.

PFAPA	Periodic fever with aphthous stomatitis, pharyngitis, and adenitis
RCT	Randomized controlled trial

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Two authors (W.G. and L.P.) performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant by both observers. Studies were also excluded if data from the same series were reported repeatedly. Review articles were included only if original data were reported. The two reviewers independently evaluated all articles and abstracted data unto standardized forms. Correction or resolution of any discrepancies between the two reviewers was done by consensus after discussion or arbitration by a third author (R.G.).

The main outcome considered was complete resolution of the PFAPA episodes after tonsillectomy. We conducted two separate analyses to evaluate the magnitude of the effect of tonsillectomy. First, we evaluated the benefits emerging from clinical series. The main aim was to determine the absolute rate of resolution combining all series on this topic. A binomial distribution model was used to calculate the 95% CI of this rate. Second, we focused on controlled studies to assess the relative rate of resolution compared with medical management. To do so, we calculated a combined estimate of the OR across studies using the Mantel-Haenszel method. We assessed congruence among comparative studies using the Breslow-Day test.[9] All data analyses were performed with SPSS version 16.0 (SPSS Inc, Chicago, Illinois).

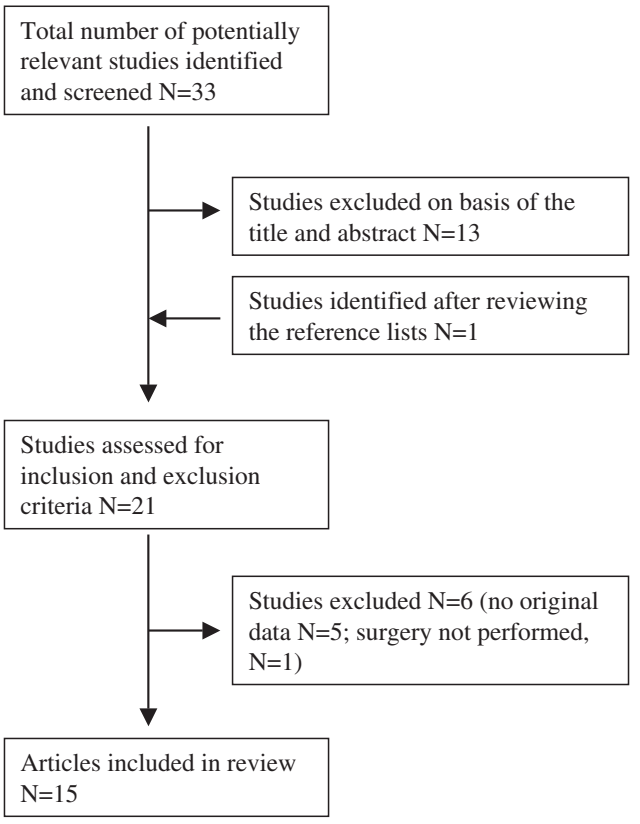

Figure 1. Study selection flow chart. Overall, 15 studies[5,7,10-22] were included in the present review.

Results

Figure 1 shows a flow diagram of the literature search results. A total of 15 studies were included. The main characteristics of these selected studies are summarized in the Table. Two of these studies were published by our groups. With the exception of the initial study of Abramson et al,[10] all studies were published between 1999 and 2010. Thirteen studies were noncomparative case series,[5,7,10-18] of which 2 were prospective.[19,20] The remaining 2 studies were RCTs.[21,22] The criteria used for the diagnosis of PFAPA were unclear in 2 studies.[10,21] The duration of follow-up varied widely. The intervention involved tonsillectomy alone in 8 studies, adenotonsillectomy alone in 3 studies, and a combined approach in 4 studies. The quality of the evidence provided was unanimously considered to be limited for the 13 observational noncomparative studies and adequate for the 2 RCTs.

Complete resolution varied from 0% to 100% in treated patients (Figure 2). Overall, 124 of 149 children experienced complete resolution after surgery, for a pooled rate of complete resolution of 83% (95% CI, 77%-89%). Surgery failed in 25 cases; information regarding these children was too incomplete to identify some specific clinical characteristics that may predict incomplete recover after surgery (data not shown).

The results of the two RCTs are illustrated in Figure 3. The Breslow-Day test for heterogeneity between studies was not statistically significant ($P = .37$). Compared with medical management, tonsillectomy had a combined OR for complete resolution of 13 (95% CI, 4-43; $P < .001$). Of note, however, the 2 RCTs differed in several important aspects. First, the diagnostic criteria for PFAPA were stricter in the study of Garavello et al[22] compared with the study of Renko et al.[21] Second, the control group was treated with corticosteroids in the former study, whereas no treatment was given in the latter. Finally, the nature of the surgical intervention differed; all of the children in the study of Renko et al[21] underwent tonsillectomy, whereas those in the study of Garavello et al[22] underwent adenotonsillectomy.

Discussion

Our review documents that there remains insufficient evidence on the effectiveness of tonsillectomy for PFAPA syndrome. The available studies generally had small sample sizes. The duration of follow-up varied widely among the studies and was relatively short in some studies. This may be of concern, because the duration of the postsurgical episode-free period needed to conclude that the patient is definitely cured has yet to be defined. Moreover, the criteria for diagnosing PFAPA were not always clear. The possibility that children with other autoinflammatory syndromes were included in some series cannot be excluded. Of note, there are concerns

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