Role of Tonsillectomy in PFAPA Syndrome

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Objective: To examine the efficacy of tonsillectomy in ameliorating symptoms and preventing recurrence of episodes in children with PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis).

Design: Retrospective case series.

Setting: Tertiary care children’s hospital.

Patients: Patients who presented to a major tertiary teaching hospital in Vancouver, British Columbia, Canada, between 2000 and 2004 with the diagnosis of PFAPA syndrome or for whom the diagnosis was made on their initial consultation.

Intervention: Tonsillectomy.

Main Outcome Measures: Resolution of symptoms at 3, 12, and 24 months after tonsillectomy.

Results: Eight of the 9 patients achieved complete remission within 3 months. In the remaining patient, the frequency of episodes decreased from every 2 weeks to once every 3 to 4 months. This patient eventually had resolution of symptoms at 2 years after tonsillectomy. No complications resulted from the tonsillectomy.

Conclusion: Tonsillectomy is a viable treatment option for patients with PFAPA syndrome.


M ARSHALL SYNDROME, OR PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis), was first described in 1987 by Marshall et al.1 This clinical syndrome usually manifests in children younger than 5 years. Periodic fevers (temperature >39°C) last from 3 to 6 days and occur at fixed intervals approximately every 3 to 6 weeks. Along with aphthous stomatitis, pharyngitis, and cervical adenitis, other less common symptoms have been observed including malaise, headaches, abdominal pain, vomiting, hepatosplenomegaly, and arthralgias.2,3 Children are usually well between episodes. The condition lasts a mean of 4.5 years.

While many theories exist, the exact cause of PFAPA syndrome is unknown. Infectious causes (bacterial and viral) have for the most part been ruled out as potential causes through cultures and serologic and skin tests. Theories involving autoimmune and rheumatologic disorders have also been disproved. As well, no geographic or ethnic predilection has been found among patients. Diagnosis is made on a clinical basis because no definitive laboratory tests can positively identify PFAPA syndrome. During acute episodes, white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) are consistently elevated in these patients.1

Treatments for PFAPA syndrome are based primarily on case series or retrospective medical chart reviews. To our knowledge, no controlled studies exist in this area. Treatment has predominantly consisted of oral steroids. In one study, prednisone was prescribed for patients with PFAPA resulting in a 76% improvement in symptoms.4 However, prednisone did not prevent further episodes and on occasion resulted in shorter intervals between episodes in some patients.4 Cimetidine has also been used to prevent recurrences and reduce severity of the condition, but its success is limited.5 Several small series of case reports have been published within the past decade describing the use of tonsillectomy in patients with PFAPA. Tonsillectomy has improved symptoms, based on limited data.6 Herein, we describe 9 patients with PFAPA syndrome who underwent tonsillectomy.

METHODS

We undertook a retrospective case series analysis of all patients who presented to the British Columbia Children’s Hospital between Janu-
A total of 9 patients were identified with PFAPA syndrome, 5 boys and 4 girls. The mean age at presentation was 4.1 years (age range, 3–5 years). The fevers exhibited by these patients lasted for a mean of 4.1 weeks and occurred within 2 to 6 weeks of the onset of illness. None of the patients had any prior medical treatment. All 9 patients were observed for a minimum of 24 months after surgery, and recurrence of disease, intervals between episodes (if complete remission of symptoms was not obtained), and any complications arising from the surgical procedure were noted. Ethics approval was obtained for this study from the clinical ethics review board at the University of British Columbia.

## RESULTS

The symptoms that make up PFAPA syndrome, especially fever and pharyngitis, are commonly observed in an otolaryngology setting. Marshall et al note that periodic fevers were first described as early as the 1940s, but PFAPA syndrome has only been recognized for the past 2 decades. Consequently, prior to its recognition, cases of PFAPA syndrome may have been incorrectly diagnosed as other syndromes or diseases that share its symptoms and signs. When considering the diagnosis of PFAPA syndrome, the physician must have a clear knowledge and understanding of the differential diagnosis that includes syndromes such as cyclic neutropenia, hereditary fevers, and Behcet disease. These diseases must be ruled out before PFAPA syndrome can be correctly diagnosed: PFAPA syndrome is a diagnosis of exclusion.

Cyclic neutropenia is rarer than PFAPA syndrome, but the 2 conditions are almost clinically indistinguishable. In cyclic neutropenia, episodes recur about every 21 days (range, 14–35 days) and are often associated with aphthous ulcers, gingivitis, cervical lymphadenopathy, and fever. The neutropenia occurs as a result of oscillatory production of neutrophils by the bone marrow. During the neutropenic period, the polymorphonuclear leukocyte (PMN) count is generally reduced to lower than 200 cells/µL for 3 to 5 days, with rapid recovery to normal levels. (To convert PMNs to number of cells x 10⁹ per liter, multiply by 0.001.) During the symptomatic period, the PMN count may have already recovered. Therefore, diagnosis requires twice-weekly complete blood cell counts, ideally for 6 weeks, or at least starting 2 weeks prior to the expected febrile episode. Histologically, bone marrow shows maturation arrest at the myelocyte stage. Treatment usually involves granulocyte colony–stimulating factor.

Hereditary periodic fevers are a generalized group of diseases that include familial Mediterranean fever (FMF), hyper-IgD syndrome, and Hibernian fever. Familial Mediterranean fever is an autoinflammatory disease characterized by periodic attacks of fever and serositis. It is an autosomal recessive disease occurring mainly in patients of Turkish, Armenian, Arab, and Sephardic Jewish descent. The recurrent attacks of fever are accompanied by severe abdominal pain, arthritis, and/or pleuritic chest pain along with a marked increase in level of acute-phase reactants. The diagnosis of FMF should be considered in individuals of an appropriate ethnic background who present with febrile disease of an episodic nature. Colchicine is recognized as the primary treatment because it controls the attacks and prevents the development of amyloidosis.

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### Table 1. Study Patient Clinical Characteristics and Episode Outcomes After Tonsillectomy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Onset (Initial Consult), y</th>
<th>Symptoms</th>
<th>Symptom Period, wk</th>
<th>Postsurgical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (6)</td>
<td>F, A, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
<tr>
<td>2</td>
<td>5 (7)</td>
<td>F, A, P</td>
<td>2</td>
<td>Frequency decreased</td>
</tr>
<tr>
<td>3</td>
<td>3 (6)</td>
<td>F, A, Aph, P</td>
<td>6</td>
<td>Resolved</td>
</tr>
<tr>
<td>4</td>
<td>4 (6)</td>
<td>F, A, Aph, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
<tr>
<td>5</td>
<td>5 (5)</td>
<td>F, A, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
<tr>
<td>6</td>
<td>4 (6)</td>
<td>F, A, Aph, P</td>
<td>5</td>
<td>Resolved</td>
</tr>
<tr>
<td>7</td>
<td>4 (5)</td>
<td>F, A, Aph, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
<tr>
<td>8</td>
<td>4 (5)</td>
<td>F, A, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
<tr>
<td>9</td>
<td>5 (6)</td>
<td>F, A, P</td>
<td>4</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

**Abbreviations:** A, cervical adenopathy; Aph, aphthous ulcers; F, periodic fevers; P, pharyngitis; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

*a* This patient continued to have PFAPA episodes, but frequency was less than once every 3 to 4 months; by 1 year after surgery, the patient had experienced 3 episodes.
Similar to PFAPA syndrome, hyper-IgD syndrome usually first presents at a very early age (median age at onset, 6 months) and involves a periodic fever. Fevers characteristically last for 3 to 7 days, and the attacks typically occur every 4 to 8 weeks. As the patient ages, the frequency and severity of attacks decreases. However, fever episodes differ from those of PFAPA syndrome episodes in that they usually continue to occur throughout the patient's life. Other symptoms include chills, lymphadenopathy, abdominal pain, vomiting, diarrhea, and headaches. During attacks, an acute-phase response is demonstrated by leukocytosis, neutrophilia, and an increased erythrocyte sedimentation rate. Elevated serum IgD and IgA levels (>100 U/mL) are characteristic but not always present; repeated testing may be required during these episodes. The cause of this disease is believed to be a mutation of the MVK gene that encodes for mevalonate kinase. Treatment consists mainly of supportive therapy.10,11 Recent studies examining treatment with the drug etanercept, a tumor necrosis factor receptor Fc fusion protein, have yielded mixed results regarding its effectiveness.12,13

Behçet disease is a multiple-organ disease characterized by oral aphthae and by at least 2 of the following: (1) genital aphthae, (2) synovitis, (3) posterior uveitis, (4) cutaneous pustular vasculitis, (5) meningoencephalitis, (6) recurrent genital ulcers, and (7) uveitis in the absence of inflammatory bowel disease or collagen vascular disease.14 Similar to PFAPA, no pathognomonic laboratory test exists, but clinical criteria can assist in establishing the diagnosis.15 Behçet disease does not usually involve febrile episodes, and oral ulcers are more severe than in PFAPA syndrome. These characteristic symptoms of Behçet disease help to distinguish it from PFAPA syndrome.

A review of the literature examining the utility of tonsillectomy in the treatment of patients with PFAPA syndrome reveals 6 articles describing a total of 41 documented cases (Table 2). A substantial decrease in the frequency of PFAPA episodes occurred in greater than 84% of patients (37 of 44). Most authors who have studied tonsillectomy in PFAPA syndrome conclude that tonsillectomy can be considered a viable treatment option. The inherent problem with the current literature is that it is based solely on retrospective case series (level 5 evidence). Leong et al19 argue that some patients diagnosed as having PFAPA syndrome may have merely experienced a recurrent infection and that complete resolution of symptoms would be expected after the procedure. In our case series, 89% of patients experienced resolution of their symptoms (8 of 9), which is similar to the data found in the literature. For the 1 patient in our series who did not experience complete resolution of symptoms, the frequency of episodes decreased. By 2 years after the tonsillectomy, he had experienced complete resolution of symptoms. Whether this was a direct result of the tonsillectomy or due to the self-resolving nature of the disease is not known.

Although PFAPA syndrome has an eventual self-limiting course, most authors recommend that treatment be initiated relatively promptly once the diagnosis is made. Medical management (ie, steroids and cimetidine) is the most common treatment used. Tonsillectomy is not yet considered a mainstay of treatment, but both medical and surgical management have demonstrated success in the resolution of symptoms. Current medical management supports the use of steroid treatment. Various dosages of oral prednisone have been proposed, with the dose of 1 to 2 mg/kg given as a single dose being the most commonly used. Other approaches include an escalating 7-day dose regimen or alternate-potency steroid preparations (eg, every-other-day administration of prednison at 2 mg/kg/d and betamethasone at 0.3 mg/kg/d given on alternating days). Twice daily doses of cimetidine at 150 mg by mouth for 6 months has also been used with some success. Cimetidine is an H2 antagonist that inhibits chemotaxis and T-cell activation. Thomas and Edwards4 found that 8 of 28 patients treated with cimetidine had complete remission of their symptoms.

The use of nonsteroidal anti-inflammatory agents has shown poor results in controlling symptoms of PFAPA syndrome. Acetaminophen and ibuprofen reduced fever in 6% and 33% of patients, respectively, but once the drugs' effects had worn off, the fevers returned.2 Other medications, including antibiotics, acyclovir, and colchicines, have provided minimal if any relief of symptoms.9 Complications related to a single dose of steroids are extremely rare in children;20 however, the potential risks should be explained to parents.

Tonsillectomy is the only surgical option found to improve symptoms in patients with PFAPA syndrome. To our knowledge, no studies have examined the use of neoadjuvant or adjuvant medical treatment with tonsillecto-

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**Table 2. Reported Outcomes for PFAPA Syndrome Treated With Tonsillectomy**

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Complete Resolution</th>
<th>Prior Treatment (Patients, No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tasher et al</td>
<td>2006</td>
<td>6</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>Parikh et al</td>
<td>2003</td>
<td>2</td>
<td>0</td>
<td>Cimetidine (1)</td>
</tr>
<tr>
<td>Bertucchi et al</td>
<td>2003</td>
<td>5</td>
<td>5</td>
<td>Steroids (5)</td>
</tr>
<tr>
<td>Galanakis et al</td>
<td>2002</td>
<td>15</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>Dahn et al</td>
<td>2000</td>
<td>4</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>1999</td>
<td>11</td>
<td>7a</td>
<td>Steroids (NR)</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

* a In addition, 2 patients experienced partial resolution, retaining some residual postsurgical symptoms.
tonsillectomy. However, adenoidectomy by itself did not appear to be no difference in patient outcome whether or not an adenoidectomy was performed alongside of the tonsillectomy. However, adenoidectomy by itself did not result in resolution of symptoms. No complications were experienced by any patients in our study. We found in the literature no documented complications of tonsillectomy performed in patients with PFAPA syndrome. There is no reason to expect potential higher tonsillectomy complication rates in patients with PFAPA than in other patients.

In conclusion, PFAPA syndrome is an uncommon condition, and its diagnosis is one of exclusion. With the exception of tonsillectomy, treatment is primarily medical consisting of steroid therapy. Treatment options such as prednisone, cimetidine, or tonsillectomy have demonstrated success in decreasing or completely resolving symptoms. Treatment is based on the theory that PFAPA syndrome is caused by dysregulation of the immune response. According to this theory, if the aberrant immune response is curtailed, the symptoms will resolve. We have observed excellent results with tonsillectomy in 8 of 9 patients in our study who exhibited complete remission of their symptoms after tonsillectomy. The remaining patient initially experienced a dramatic decrease in the frequency of attacks and had resolution of symptoms by 24 months.

Because PFAPA syndrome is a relatively newly recognized clinical entity, more research needs to be conducted to determine the optimum treatment. From our experience, we found that in a child who is a good surgical candidate, tonsillectomy is a viable treatment option for PFAPA syndrome.

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Author Contributions: Dr Moxham had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Moxham. Acquisition of data: Finlay and Moxham. Analysis and interpretation of data: Wong and Moxham. Drafting of the manuscript: Wong and Moxham. Critical revision of the manuscript for important intellectual content: Finlay and Moxham. Statistical analysis: Wong. Administrative, technical, and material support: Finlay and Moxham. Study supervision: Moxham.

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REFERENCES