Effect of Adenotonsillectomy in PFAPA Syndrome

Greg Licameli, MD, MHCM; Jessica Jeffrey, MA; Jennifer Luz, BS; Dwight Jones, MD; Margaret Kenna, MD, MPH

Objective: To assess the benefits of adenotonsillectomy in the treatment of pediatric patients with PFAPA (periodic fever, aphthous ulcers, pharyngitis, and adenitis) syndrome.

Design: Prospective case series.

Setting: Tertiary care pediatric hospital.

Patients: Pediatric patients meeting criteria for PFAPA syndrome.

Intervention: Tonsillectomy with or without adenoidectomy.

Main Outcome Measure: Resolution of PFAPA symptoms.

Results: Twenty-seven (14 female, 13 male) children with PFAPA syndrome underwent tonsillectomy with or without adenoidectomy from 2004 through 2006. The length of follow-up for all patients ranged from 8 to 41 months. A total of 26 patients experienced a complete resolution of their symptoms. The 1 child who continued to have febrile episodes had fever cycles that were not regular in duration or interval and in hindsight was not likely a patient with PFAPA syndrome.

Conclusions: Our findings showed complete resolution of symptoms in 26 of 27 patients with PFAPA syndrome treated surgically. Patients who meet clinical criteria for PFAPA syndrome should be considered for tonsillectomy and adenoidectomy if they do not respond to medical management.


First described by Marshall et al,1 PFAPA (periodic fever, aphthous ulcers, pharyngitis, and adenitis) syndrome is characterized by (1) onset in early childhood, predominantly in boys younger than 5 years; (2) periodic abrupt onset of febrile episodes that last 4 to 5 days and occur every 4 to 6 weeks on average; and (3) episodes that are often accompanied by intraoral ulcers, pharyngitis, and cervical lymph node enlargement. Largely owing to the fact that these physical findings are variably present in patients, the diagnosis is difficult to confirm until a pattern of cyclical fevers is established. Clinically, the patient seems to have a viral illness. Laboratory testing is not diagnostic and may show nondiagnostic elevation of acute inflammatory markers such as leukocytosis or elevated erythrocyte sedimentation rate. During the 4- to 5-day febrile cycle, temperatures can spike on average every 8 to 12 hours, often to 39.4°C to 40.5°C, with little or no response to common antipyretics. Patients are asymptomatic in the intervals between fever cycles, with normal growth parameters.

One must consider other common causes of periodic fever, such as juvenile rheumatoid arthritis and cyclic neutropenia. In addition, less common hereditary fever syndromes (eg, familial Mediterranean fever, Muckle-Wells syndrome, tumor necrosis factor receptor–associated periodic syndrome [TRAPS], and hyperimmunoglobulinemia D [hyper-IgD] syndrome) can be evaluated with molecular-based tests.2

Methods

Patients referred for evaluation from 2004 to 2006 who met the criteria for PFAPA syndrome were included in the study. Patients were referred from the rheumatology department at Children’s Hospital or by their primary care physician for recurrent fever. After the first patient (see “Report of a Case” section), all patients were enrolled in the study in a prospective fashion.

PFAPA SYNDROME INCLUSION CRITERIA

Patients were selected based on meeting several inclusion criteria, including an age of 2 to 18 years and a medical history consistent with PFAPA syn-
drome. The criteria included cyclical febrile episodes that lasted 4 to 5 days and occurred every 4 to 6 weeks on average. Intraoral ulcers, pharyngitis, and cervical lymph node enlargement may have accompanied these fevers. Other causes for cyclical fevers were entertained and eliminated from the differential diagnosis. Patients were excluded if they did not meet the criteria or if they did not want to be followed in the study.

LABORATORY STUDIES

In most patients, a complete blood cell count was obtained during febrile episodes and the white blood cell count was usually normal or slightly elevated (reference range for white blood cell count, 5400-9700/µL). (To convert the white blood cell count to ×10⁹/L, multiply by 0.001.) Findings from throat cultures, when performed, were negative for group A β-hemolytic streptococcus.

Resolution of recurrent fever was the main outcome measure. This study was conducted after receiving institutional review board approval from Children’s Hospital.

REPORT OF A CASE

A healthy 14-month-old girl presented with a 6-month history of recurrent fever. Her birth history and medical history were unremarkable. These fevers occurred every 22 days and lasted 4 to 5 days. Fevers occurred 2 to 3 times per day, usually to temperatures of 39.4°C to 40.5°C, and would rise rapidly within 1 hour from an afebrile state. Acetaminophen and ibuprofen did not reduce the fever, and antibiotic therapy did not alter the clinical course. During the fever cycle, the child would refuse oral intake and occasionally drooled. Cervical adenitis and fine ulcers on the buccal mucosa were often seen with each episode. Between episodes, the child was thought to be very healthy, but she would display lassitude just prior to a fever cycle. On 3 occasions the fevers were associated with febrile seizures.

The patient underwent consultations with the infectious disease, rheumatology, and neurology departments at Children’s Hospital, Boston, Massachusetts. Findings from white blood cell count with differential, liver function studies (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and amylase) were largely unremarkable except for an elevated alanine aminotransferase. Laboratory studies (aspartate aminotransferase, alkaline phosphatase, bilirubin, and amylase) were largely unremarkable except for an elevated alanine aminotransferase.

RESULTS

Twenty-seven children (14 female, 13 male) with a diagnosis of PFAPA syndrome underwent tonsillectomy with or without adenoidectomy. The length of follow-up ranged from 8 to 41 months. Table 1 lists the details for all 27 patients as well as their responses to surgery. The mean age at the time of surgical intervention was 56 months (range, 19-152 months), and the mean duration of symptoms before surgery was 23 months (range, 6-72 months). Twenty-six patients had complete cessation of their symptoms after surgery. Their postoperative recovery was typical of other children who undergo this surgery for chronic tonsillitis or obstructive sleep disturbance. One child developed a fever (temperature, 38.3°C) on postoperative day 7 that was not thought to be of an infectious etiology. The child was treated with 1 dose of prednisone and subsequently had no further issues. The 1 child who continued to have febrile episodes had fever cycles that were not regular in duration or interval and in hindsight was not likely a patient with PFAPA syndrome. However, this patient did have an overall mean lengthening between febrile episodes after surgery from 12 to 20 days.

COMMENT

The PFAPA syndrome may resemble other periodic fevers, but it can be distinguished by careful attention to symp-
toms. It is characterized by (1) onset in early childhood, predominantly in boys younger than 5 years; (2) periodic abrupt onset of febrile episodes that last 4 to 5 days and occur every 4 to 6 weeks on average; and (3) intraoral ulcers, pharyngitis, and cervical lymph node enlargement, which may accompany these fevers to varying degrees. All 3 physical findings may not be present in all patients. Pharyngitis in a young child who is unable to express pain may present as excessive drooling and decreased oral intake. Oral ulcers are often small in size and can be overlooked. The use of antipyretics, such as acetaminophen and ibuprofen, has little effect on reducing the temperature of the child during these episodes.

The diagnosis is difficult to confirm until a pattern of cyclical fevers is established. Familial Mediterranean fever has periodic fever (low to high grade), but its symptoms of peritonitis, arthritis or arthralgia, erythema, and amyloidosis are not found in patients with PFAPA syndrome. Patients with Behçet disease present with ulcers in the oral cavity, but these ulcers are large, painful, and numerous compared with the small, punctate ulcers occasionally seen in PFAPA syndrome. Behçet disease also includes skin lesions, ocular vasculitis, arthritis or arthralgia, central nervous system involvement, and cardiovascular complications. Hyper-IgD syndrome presents with lymphadenopathy and high fever, but it is not periodic. Symptoms include diarrhea, arthritis, arthralgia, and macular or papular lesions distinct from aphthous ulcers. This disease clusters in families and affects males and females equally. Systemic-onset juvenile rheumatoid arthritis (Still disease) presents with high fevers and adenopathy as well as arthritis, rash, hepatosplenomegaly, pleuritis, and pericarditis. Familial Hibernian fever has febrile episodes lasting from 1 to 4 weeks, as well as abdominal pain, myalgia, and skin lesions occurring anywhere on the body. Although the fever, ulcers, and pharyngitis of cyclic neutropenia are very similar to PFAPA syndrome, it is distinguished by a cyclic drop in neutrophils and (although not always) by abdominal pain and diarrhea. For patients with a specific ethnic background and symptoms, molecular genetic testing is available. It is characterized by (1) onset in early childhood, predominantly in boys younger than 5 years; (2) periodic fever (low to high grade), but its symptoms related to PFAPA syndrome. Tonsillectomy and adenoidectomy were subsequently performed for large obstructing tonsils and adenoids. The specimens were not pathologically examined, but the surgeons reported that this patient had PFAPA syndrome instead of infection by *M chelonae*.

**INFECTION VS IMMUNE DYSREGULATION**

The PFAPA syndrome shares several features of both an infectious disease process and an immune system dysregulation. Long provided an excellent analysis of the possible root cause of the PFAPA syndrome, characterizing each symptom as evidence of infection or immune dysregulation. These characteristics were further weighed according to how strongly Long supported either theory. An infectious etiology is suggested by the diversity of patient ethnicity, although the incidence of PFAPA syndrome is underrepresented in black and Hispanic children, even in more densely populated urban areas. The predominance of male subjects, the waning of symptoms and spontaneous resolution in some cases, the decreased intervals between episodes after corticosteroid therapy, and cure after tonsillectomy point to an infectious cause. Immune dysregulation is suggested by the periodicity of fever, aphthous ulcers, persistence of the syndrome for several years, and lack of response to antibiotics. Elevated levels of cytokines measured during and between febrile episodes and the ability of steroids to resolve febrile episodes further support the hypothesis that this syndrome represents a dysregulation of the immune response.

**PHARMACOLOGIC TREATMENT**

Acetaminophen, ibuprofen, aspirin, other nonsteroidal anti-inflammatory drugs, acyclovir, and colchicine do not elicit a clinical response or only temporarily reduce fever in some patients. Oral antibiotics are not effective. One study has reported the successful use of cimetidine hydrochloride, a histamine-receptor 2 blocker, but these results have not been replicated. Corticosteroids can have a dramatic effect on symptoms: 1 dose of prednisone or prednisolone sodium phosphate (1-2 mg/kg) causes cessation of a fever cycle within 12 to 24 hours. This is the most effective nonsurgical treatment, although the administration of corticosteroids does not prevent future fever cycles and often shortens the intervals between episodes.

**SURGICAL INTERVENTION**

Surgical intervention can be considered based on the presumption of a chronic tonsillar infection triggering symptoms. Usually there is no history of findings from throat cultures that are positive for streptococcal infection. Several small studies have previously reported cures after adenotonsillectomy. In 1989, Abramson et al reported the cases of 4 male pediatric and adolescent patients with PFAPA syndrome who had no response to antibiotics. They highlighted a particular case in which a 13-month-old boy was seen 3 times in 4 months for symptoms related to PFAPA syndrome. Tonsillectomy and adenoidectomy were subsequently performed for large obstructing tonsils and adenoids. The specimens were not pathologically examined, but the surgeons reported that
the tonsils were in direct proximity to enlarged cervical nodes.13 At 27 days after surgery, 1 patient had no further febrile episodes and only 1 episode of pharyngitis. In the remaining 3 patients, the episodes had ceased or were markedly decreased (duration of follow-up, 5-27 months). Thomas et al11 mentioned cessation of PFAPA syndrome episodes in 7 of 11 children who underwent tonsillectomy (without adenoidectomy) and decreased fever symptoms in 2 others.

In 2002, Galanakis et al14 described 15 patients (11 males, 4 females) referred for tonsillectomy who also presented with classic PFAPA symptoms. All had received antibiotics with no resolution of symptoms; neither steroids nor cimetidine were prescribed. Every patient presented with periodic fever and pharyngitis, all 3 with adenitis, and 5 (all male) with aphthous ulcers. Every patient had striking postoperative improvement after surgery, and parents reported that no more episodes had occurred. Dahn et al15 conducted a retrospective medical chart review of 5 patients with PFAPA syndrome (4 males, 1 female) who made multiple trips to their primary care physician for treatment of PFAPA symptoms (a mean number of 11.6 PFAPA complaints over a 3-month period). All underwent adenotonsillectomy for either recurrent pharyngitis or adenotonsillar hypertrophy. Surgery was uneventful and successful for every patient, resulting in complete cessation of PFAPA symptoms. Parents described the outcomes as a significant improvement. One patient was lost to follow-up. Subsequent sick or well-child visits were not related to PFAPA syndrome (at 3-month follow-up). Berlucchi et al16 described the cases of 5 patients with PFAPA syndrome (4 male, 1 female) who were unsuccessfully treated with antibiotics and nonsteroidal anti-inflammatory drugs. Corticosteroids resolved symptoms in 24 to 36 hours but did not delay the next episode. Patients underwent uneventful tonsillectomies 2 to 3 years after onset of the syndrome. No patient experienced any febrile episodes after the surgery (duration of follow-up, 7-14 months).

In contrast to these reports, Parikh et al17 found no improvement in symptoms in 2 patients diagnosed retrospectively after adenotonsillectomy. In a review of the literature, Leong et al18 came to the conclusion that tonsillectomy should not be performed for the treatment of PFAPA syndrome. This was based on the authors’ feeling that some patients may have actually had tonsillitis and that observational biases or placebo effect could also explain the results found. Furthermore, they felt that since PFAPA syndrome does resolve over time, resolution of symptoms could not be solely attributed to the surgical intervention. Although much is unclear about the etiology of this condition, and the diagnosis should be made after carefully looking for other causes of cyclical fever, our study reached a different conclusion. Surgery immediately caused cessation of symptoms in most of our patients, and although the natural history is for the fevers to abate spontaneously, this may not occur for several years.12

In conclusion, the diagnosis of PFAPA syndrome is made based on the strict periodicity of high fevers, the inability to control the fevers with antipyretics, and associated findings of aphthous ulcers, pharyngitis, and cervical adenitis. Steroid treatment does tend to resolve the acute fever cycle within 12 to 14 hours but also may make the fever cycles occur more frequently. We found that the male to female ratio of our patients was nearly equal, a slight departure from the ratios reported in the literature. Although patients were enrolled in this study in a prospective fashion, it was limited by not having a control group for comparison. We feel that our study shows that surgery is potentially a very effective treatment for patients with PFAPA syndrome. An update of this ongoing study is under way. Physicians should consider patients’ and families’ quality of life when contemplating surgical intervention. All parents of children treated by tonsillectomy were immensely grateful for the cessation of symptoms. Better recognition and treatment of this interesting syndrome through increased physician awareness will allow for more timely intervention.

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Female to Male Ratio</th>
<th>Fever (Duration, d)</th>
<th>AU, %</th>
<th>Pharyngitis, %</th>
<th>CA, %</th>
<th>TA Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall et al1</td>
<td>12</td>
<td>5:7</td>
<td>40°C (5)</td>
<td>75</td>
<td>75</td>
<td>67</td>
<td>Not performed</td>
</tr>
<tr>
<td>Thomas et al12</td>
<td>94</td>
<td>42:52</td>
<td>40°C (3.8)</td>
<td>71</td>
<td>69</td>
<td>82</td>
<td>7 of 11 had complete cessation</td>
</tr>
<tr>
<td>Padeh et al</td>
<td>28</td>
<td>8:20</td>
<td>(Mean, 4.3)</td>
<td>68</td>
<td>NR</td>
<td>100</td>
<td>100% Cessation (3 surgeries)</td>
</tr>
<tr>
<td>Abramson et al13</td>
<td>4</td>
<td>4 M</td>
<td>41°C (5)</td>
<td>25</td>
<td>100</td>
<td>75</td>
<td>100% Cessation TA</td>
</tr>
<tr>
<td>Galanakis et al14</td>
<td>15</td>
<td>11:4</td>
<td>40°C (4-6)</td>
<td>30</td>
<td>100</td>
<td>80</td>
<td>100% Cessation TA</td>
</tr>
<tr>
<td>Dahn et al15</td>
<td>5</td>
<td>1:4</td>
<td>&gt;39°C</td>
<td>40</td>
<td>60</td>
<td>60</td>
<td>All “significantly improved”</td>
</tr>
<tr>
<td>Berlucchi et al16</td>
<td>5</td>
<td>1:4</td>
<td>39°C-40°C (4-5)</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>100% Cessation TA</td>
</tr>
<tr>
<td>Parikh et al17</td>
<td>2</td>
<td>1:1</td>
<td>(&gt;38.5°C)</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>None improved TA</td>
</tr>
<tr>
<td>Current study</td>
<td>27</td>
<td>14:13</td>
<td>39°C-40°C (5)</td>
<td>37</td>
<td>55</td>
<td>52</td>
<td>96% Cessation TA</td>
</tr>
</tbody>
</table>

Abbreviations: AU, aphthous ulcers; CA, cervical adenitis; NR, not reported; PFAPA, periodic fever, aphthous ulcers, pharyngitis, and adenitis; TA, tonsillectomy with adenoidectomy.
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Correspondence: Greg Licameli, MD, MHCM, Department of Otolaryngology and Communication Disorders, Children’s Hospital, 300 Longwood Ave, LO 367, Boston, MA 02115 (greg.lacameli@childrens.harvard.edu).

Author Contributions: Drs Licameli, Jones, and Kenna and Ms Jeffrey and Luz had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Licameli, Jeffrey, Jones, and Kenna. Acquisition of data: Licameli, Jeffrey, Jones, and Kenna. Analysis and interpretation of data: Licameli, Jeffrey, Luz, Jones, and Kenna. Drafting of the manuscript: Licameli, Jeffrey, Luz, Jones, and Kenna. Critical revision of the manuscript for important intellectual content: Licameli, Jeffrey, Jones, and Kenna. Administrative, technical, and material support: Licameli, Jeffrey, Luz, Jones, and Kenna. Study supervision: Licameli, Jones, and Kenna.

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REFERENCES


