Long-term Surgical Outcomes of Adenotonsillectomy for PFAPA Syndrome

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Objective: To evaluate the long-term efficacy of adenotonsillectomy in the treatment of pediatric patients with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) syndrome.

Design: Prospective case series.

Setting: Tertiary care pediatric hospital.

Patients: Pediatric patients meeting the criteria for PFAPA syndrome.

Interventions: Tonsillectomy with adenoidectomy.

Main Outcome Measures: Resolution of PFAPA symptoms.

Results: A total of 124 patients (75 boys and 49 girls) underwent adenotonsillectomy from 2004 to 2011 for relief of cyclical fevers due to PFAPA syndrome. Of the 124 patients, 22 did not meet criteria for inclusion in this study because (1) they had less than 6 months of follow-up after surgery or (2) they were unavailable for follow-up; therefore, 102 patients were included in the study. The mean age at the time of surgery was 38 months (range, 18-179 months). The average duration of follow-up after adenotonsillectomy was 43 months (range, 6-98 months). Of 102 patients, 99 had complete resolution of their symptoms immediately after surgery.

Conclusions: Our findings showed complete resolution of symptoms in 99 of 102 patients with PFAPA syndrome who were treated surgically. Patients who meet the clinical criteria for PFAPA syndrome should be offered tonsillectomy and adenoidectomy as part of their treatment options.

ally, the tonsils or tonsillar pillars are described as erythematous, prompting throat cultures, which are almost always negative for group A β-hemolytic streptococcus. If routine laboratory studies are performed, the results may be normal, but an elevated white blood cell count or erythrocyte sedimentation rate is frequently found during acute episodes. Trials of antibiotics may be prescribed, with little if any effect on the fever course. Antipyretic agents may help reduce high temperatures; however, they are often not able to induce an afebrile state. Rarely are there any immediate or extended family members who are similarly affected.

Other common causes of fever such as viral infections must be considered. Even though cyclic neutropenia, with its regular periodicity that is similar to PFAPA syndrome, is rare, it should be kept in mind. Also, less common hereditary fever syndromes such as familial Mediterranean fever, Muckle-Weils syndrome, tumor necrosis factor receptor 1–associated syndrome, and hyperimmunoglobulinemia D syndrome can be evaluated with molecular-based tests. Furthermore, these conditions have other elements that help differentiate them from PFAPA syndrome.

The diagnosis of PFAPA syndrome should be considered a diagnosis of exclusion, after which medical or surgical treatments may be offered. In an attempt to solidify the diagnosis and to exclude other causes, each patient in our study was seen by a pediatric rheumatologist or infectious disease physician before any surgical intervention was undertaken. In 2008, we first reported our short-term success with adenotonsillectomy and postoperative symptom resolution in 26 of 27 pediatric patients who were diagnosed as having PFAPA syndrome. We present a follow-up study in a larger cohort of patients that demonstrates the long-term efficacy of adenotonsillectomy for the treatment of PFAPA syndrome along with a review of the current literature.

METHODS

PATIENTS

Patients aged 18 months to 18 years who presented with a constellation of symptoms associated with PFAPA syndrome were identified prospectively. Specifically, patients presented with regular intervals between fever episodes and often had cervical adenopathy, pharyngitis, and apthous ulcers, in decreasing incidence. All patients were evaluated by a rheumatologist and/or an infectious disease specialist and a pediatric otolaryngologist. If the clinical picture was consistent with PFAPA syndrome and there was no evidence of another cause for recurrent fevers, the patients were offered either medical treatment or adenotonsillectomy using a monopolar cautery technique.

FOLLOW-UP

Patients who underwent adenotonsillectomy were followed up for a minimum of 6 months. The primary outcome measure was time to cessation of fevers after surgery. A follow-up questionnaire was completed via telephone, and patients’ families were asked to report any unresolved or recurrent issues either before or after the follow-up telephone survey. The study was performed with approval from the institutional review board committee of Children’s Hospital, Boston, Massachusetts.

RESULTS

A total of 124 patients (75 boys and 49 girls) underwent adenotonsillectomy between 2004 and 2011 for relief of cyclical fevers due to PFAPA syndrome. Of the 124 patients, 22 did not meet the criteria for inclusion in this study because (1) they had less than 6 months of follow-up after surgery or (2) they were unavailable for follow-up. The presentation and demographics of this subgroup did not differ from the final cohort of 102 patients. The mean age at time of surgery was 58 months (range, 18-179 months). The average duration of follow-up after adenotonsillectomy was 43 months (range, 6-77 months). Of 102 patients, 99 had complete resolution of their symptoms immediately after surgery. No patient experienced complications as a result of their surgical intervention.

Of the remaining 3 patients who did not have immediate resolution of fevers after surgery, 1 continued to have cyclical fevers that were unchanged in duration or frequency compared with her preoperative state. The second child has had continued fever cycles that have been less intense and less frequent and was subsequently found to have hyperimmunoglobulinemia D syndrome. Our third patient had fevers of similar intensity and frequency immediately after surgery, but they had completely resolved at 6 months after surgery.

COMMENT

Based on our experience, we have made some general observations that can aid in determining whether a patient has PFAPA syndrome. The primary feature of this condition is recurrence of fevers higher than 39°C, with episodes lasting 3 to 7 days and occurring in a cyclical fashion between 21 and 42 days. The hallmark of this diagnosis is the distinct regularity of the fever cycles; eg, if a patient manifests the onset of a fever episode every 27 days, the fevers will typically recur every 27 days plus or minus 24 to 48 hours. Parents are encouraged to keep a calendar diary to provide this chronology and will often come into the office with these data, describing the fevers as occurring “like clockwork.” We have also observed that over a period of years, the fever cycles may shorten or lengthen somewhat and on occasion will stop for several months before restarting again with regularity. If patients present with a history that is consistent with PFAPA syndrome but are in a fever “hiatus,” treatment is not pursued, as it is possible that the fever episodes will not recur again in the future. Although the current wisdom is that most children will present by 5 years of age and will “outgrow” this syndrome by the age of 7 or 8 years, several of the children described herein first developed PFAPA syndrome as teenagers, and, indeed, there are sporadic reports in the literature of onset in adulthood.

In our study population, patients experienced 1 or more of the following symptoms in addition to fever: intraoral ulcers, sore throats, enlarged cervical lymph nodes, behavior changes, lethargy, and poor appetite in the absence of any other cause for their symptoms, such as an upper respiratory tract infection. In our group of pa-
tients, pharyngitis (79%) and cervical lymphadenopathy (84%) were commonly found, while aphthous ulcers (44%) were not as frequently reported by the parents, patients, or primary care providers who monitored these patients when they were acutely affected. Therefore, all of these features need not be present for a diagnosis to be made. Of note, most patients were evaluated during one of their episodes, which was helpful in solidifying the diagnosis. While antipyretic therapy with acetaminophen and/or ibuprofen often reduces patients’ temperatures to 38°C to 39°C, these medications do not provide complete cessation of the elevated temperature (87%). The administration of 1 to 2 mg/kg of prednisone at the onset of a fever episode uniformly aborts that individual fever episode and is thought to be diagnostic for this condition (96%). In most patients, a complete blood count was obtained during fever episodes, and the white blood cell count was usually normal (87%) or slightly elevated (5400-9700/µL) ([to convert to \( \times 10^9/L \), multiply by 0.001]) ([Figure]). Throat cultures, when obtained, were almost always negative for group A β-hemolytic streptococcus. Otherwise, the workup for each patient was negative for infectious processes, rheumatologic disorders, and genetic syndromes when performed as directed by the primary care physician or our rheumatology colleagues.

**OTHER PERIODIC FEVER SYNDROMES**

PFAPA syndrome may resemble other periodic fever syndromes, but it can be distinguished by careful attention to symptoms as well as the fever cycle history. Familial Mediterranean fever involves periodic fever, but its symptoms of peritonitis, erysypeloid rash, and amyloidosis are not found in patients with PFAPA syndrome. Patients with Behçet syndrome present with ulcers in the oral cavity, but these ulcers are large, painful, and numerous in contrast to the small, punctate ulcers that are frequently seen in PFAPA syndrome. Behçet syndrome also includes skin lesions, ocular involvement (uveitis, vasculitis), arthritis/arthralgia, central nervous system involvement, and cardiovascular complications. Hyper-IgD syndrome presents with lymphadenopathy and high fever, but it is not as regularly periodic in nature as PFAPA syndrome. Symptoms include diarrhea, arthralgia, and maculopapular lesions that are distinct from aphthous stomatitis. Hyper-IgD syndrome often starts in infancy, which is not usually the case for PFAPA syndrome. Like familial Mediterranean fever, this disease is also autosomal recessive in inheritance. Systemic onset juvenile rheumatoid arthritis (Still disease) presents with high fevers and adenopathy as well as arthritis, rash, hepatosplenomegaly, pleuritis, and pericarditis. The fevers are not typically periodic, and patients are sicker. Familial Hibernian fever, recently renamed tumor necrosis factor receptor 1–associated syndrome, has fever episodes lasting from 1 to 4 weeks, as well as abdominal pain, myalgia, and skin lesions occurring anywhere on the body. Although the fever, stomatitis, and pharyngitis of cyclic neutropenia are very similar to PFAPA syndrome, the former disease process is distinguished by a cyclic decrease in neutrophils, abdominal pain, and diarrhea.⁶

**INFECTIOUS VS IMMUNOLOGIC ETIOLOGY OF FEVERS**

PFAPA syndrome shares several features of both an infectious disease process and an immune system dysfunction. Long⁴ originally analyzed possible root causes of the PFAPA syndrome, characterizing each symptom as evidence of infection or immune dysregulation. These characteristics were further weighed according to how strongly they supported either theory. An infectious trigger is suggested by the diversity of patient ethnicity, although the incidence of PFAPA syndrome is underrepresented in African American and Hispanic children, even in more densely populated urban areas. Also, 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 stomatitis, persistence of the syndrome for several years, and lack of response to antibiotics.

To date, little is known regarding the cause and pathogenesis of PFAPA syndrome. One study and our own preliminary work (unpublished data, study in progress) suggest that tonsils have nonspecific chronic inflammation, consisting of lymphoid and follicular hyperplasia, fibrosis, and cryptitis.⁷ Both innate (interleukin [IL]-1, IL-6,
and tumor necrosis factor α) and adaptive (interferon gamma) immunity seem to play a role. Peripheral lymphoid tissue such as tonsils may play a role as a reservoir for a pathogen to which there is a dysregulated immune response. One hypothesis is that there is an abnormal adaptive immune response to a pathogen (virus or bacteria) in a local lymphoid tissue, causing an augmented innate immune response. The cure with tonsillectomy in most patients argues for the tonsils as being a microbial reservoir or a source for local immune dysregulation or both. The role of the innate immune system is further supported by resolution of the symptoms by the administration of the IL-1 receptor antagonist anakinra to patients with PFAPA syndrome. The involvement of IL-1 in PFAPA syndrome is a very similar feature to some of the other periodic fever and autoimmune inflammatory syndromes.

In our study, we had 2 sets of siblings diagnosed as having PFAPA syndrome, one set of which underwent adenotonsillectomy, with complete resolution of fevers, and one set that is still undergoing workup to exclude other causes of periodic fever with single-dose steroid therapy until it is thought that tonsillectomy is warranted. Other sibling sets and reports of positive family history in first- and second-generation members further support a possible genetic component to this entity.

**PHARMACOLOGIC TREATMENT**

Acetaminophen, ibuprofen, aspirin, other nonsteroidal anti-inflammatory drugs, acyclovir, and colchicine do not elicit a clinical response or, at best, temporarily reduce fever in some patients. Oral antibiotics are not effective. The use of cimetidine, an H2-blocker, was to be effective in resolving the fever cycles in 27% of patients who were treated daily for 6 to 12 months. Corticosteroids have a dramatic effect on abating the fever cycle: 1 dose of prednisone or prednisolone (1 to 2 mg/kg) causes cessation of a fever cycle usually within several hours. They are the most effective nonsurgical treatment, although the administration of corticosteroids does not prevent future fever cycles and often shortens the intervals between episodes, as was seen with our patient population and reported elsewhere.

**NATURAL HISTORY OF PFAPA SYNDROME**

Recently published long-term studies of patients with PFAPA syndrome give us insight as to the natural history of the disease. Wurster et al described 59 patients who were followed up for 12 to 21 years, with 50 patients reporting complete symptom resolution after a mean of 6.3 years. The remaining 9 patients had persistent symptoms for a mean of 18.1 years. As in our study, the authors noted that over the long term their patients with persistent symptoms had a shortening of their fever cycles and an increased interval to recurrence.

The histories of a larger sample of 105 patients with PFAPA syndrome were retrospectively reviewed over 10 years by Feder and Salazar in 2010. The syndrome resolved spontaneously in 20% of patients and continued to occur over the duration of the study (mean length, 23 months) for 63% of patients who were monitored conservatively. Eleven patients underwent tonsillectomy for improvement of their condition, and 100% experienced a curative effect.

**SURGICAL INTERVENTION**

Recent contributions to the literature have focused on the utility of surgical intervention as treatment. Garavello et al reviewed the available literature through 2010 to identify English-language studies evaluating the efficacy of tonsillectomy or adenotonsillectomy on PFAPA syndrome. In their analysis of 13 case studies and 2 randomized controlled trials, complete resolution of symptoms occurred in 83% of 149 children who underwent surgical intervention. In the cases in which surgery failed, there was insufficient information to determine what differentiated these patients from those who benefited from surgery. The 2 randomized studies referenced by Garavello and colleagues were the basis of a Cochrane review of the literature to assess the efficacy of tonsillectomy with or without adenoidectomy vs nonsurgical treatment in children with PFAPA syndrome and resulted in a pooled analysis of 67 patients. In the first study, 39 children were sorted into a surgical group (n = 19) or a nonsurgical group (n = 20) for 18 months after randomization, with follow-up every 3 months. The study included patients aged 3 to 13 years, with a mean age of 5.4 years for the surgical group and 4.9 years for the control group. Sixty-three percent of the patients who underwent adenotonsillectomy had complete and immediate resolution of fever cycles, while only 5% of patients experienced complete resolution with observation alone. In the 9 patients in whom surgery failed, no specific characteristics were noted to differentiate them from the children in whom surgery was immediately beneficial. However, it was noted that the number of PFAPA syndrome episodes was greatly reduced in these surgical patients as compared with the control group. Furthermore, the surgical “failures” had no further episodes by the 12th month of follow-up to the end of the study at 18 months of follow-up.

The second randomized controlled study evaluated 26 patients with a mean age of 4.1 years. All 14 patients in the tonsillectomy group and 6 of 12 patients in the control group were free of symptoms after 6 months of follow-up. Of the 6 control patients with persistent symptoms at 6 months, 5 chose to have surgery, with resolution in all. One retraction from this study is the somewhat less rigid adherence to the more common clinical descriptions of PFAPA syndrome when the patients were enrolled.

Several issues should be addressed when assessing the validity of our results. First, the controversy surrounding surgical intervention in PFAPA syndrome is based on the probability that the fever episodes will abate at some point in childhood. We agree that there is a time course, usually measured in years, over which the fever episodes will often cease. However, because nearly all patients seeking operative intervention had complete resolution immediately after surgery, we would argue against the likelihood of cure being secondary to natural resolution.

Also, surgery is not without its attendant risks and prolonged recovery, and all parents are counseled at length.
before adenotonsillectomy. What is striking is the impact that PFAPA syndrome often has on children’s quality of life as well as that of their parents or caretakers. Furthermore, the financial costs to the family caring for a child with a chronic illness has not been quantified. Surgical intervention can be considered based on the presumption of a chronic tonsillar infection triggering an autoinflammatory-type response. Whether adenoid removal in addition to tonsillectomy is necessary for positive outcomes is unclear.

Prior case studies have been criticized for not having a control group, for small cohort size, for lack of long-term follow-up, and for inconsistencies in reporting associated symptoms and physical findings. In this study, every patient who was considered for surgery was offered medical treatment and also was required to be evaluated independently by a pediatric rheumatologist to confirm PFAPA syndrome and to rule out other causes for fever. More than 100 children were followed up long term, and their initial evaluations were consistent with the current accepted clinical definition of PFAPA syndrome. Regarding the lack of a control group in this study, we believe that there is already ample evidence in the recent literature that shows the natural time course of this syndrome. Although ours is not a substitute for a randomized control study, existing data on medical management do provide a comparison for our patient population.

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, the response to steroids, and the associated symptoms of aphthous ulcers, pharyngitis, and cervical adenitis. To date, most articles on the effectiveness of surgery have been limited by the presentation of retrospective data and limited follow-up. To our knowledge, our study is the largest prospective series of surgically treated patients followed up long term showing that adenotonsillectomy provides sustained relief of PFAPA syndrome symptoms in the great majority of cases. All parents of children treated with adenotonsillectomy were immensely grateful for the cessation of symptoms and improvement in their children’s quality of life. We have an ongoing study at our institution evaluating the help and support of the children and their families.

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REFERENCES