Outcome of Tonsillectomy in Selected Patients With PFAPA Syndrome

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Objective: To assess the practicability of integrated medical and surgical management and the effectiveness of tonsillectomy in children with PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy).

Design: A prospective study.

Setting: Secondary pediatric and otolaryngological university center.

Patients: Of 30 patients evaluated for periodic fever, 18 children with PFAPA syndrome were included in the study.

Interventions: Patients underwent long-term pediatric and otolaryngological assessments, and their parents were asked to keep monthly diaries with reports of any subsequent episodes, symptom, and related sign. Patients received traditional medical therapies, and 9 patients underwent tonsillectomy for the lack of lasting recovery.

Main Outcomes Measures: The association between postoperative outcomes and age at tonsillectomy and the differences in the patients' condition before and after tonsillectomy were statistically tested. In addition, the removed tonsillar tissue was analyzed molecularly to evaluate concomitant infections.

Results: All of the surgical patients reported a symptomatic improvement, with complete clinical recovery in 5 cases (56%) and significant reduction in number ($P = .005$) and duration ($P = .03$) of recurrences in the remaining 4 (44%). Results of molecular analysis of tonsillar specimens were negative for bacteria in all but 1 patient.

Conclusion: Otolaryngologists should be trained to recognize PFAPA syndrome, for which management consists of a regular and prolonged second-level pediatric and otolaryngological follow-up, with surgery only after the failure of traditional medical therapy.

partial clinical overlap between PFAPA syndrome and other periodic fevers that are known to be hereditary (ie, hyper-IgM syndrome, familial Mediterranean fever, cyclic neutropenia), some authors have investigated the possible role of genetic abnormalities such as the Mediterranean fever gene mutations responsible for immunological deregulation, however, there is still no convincing evidence of their occurrence in children with PFAPA syndrome.

In terms of treatment, in addition to traditional medical therapy, surgery has been judged to be an effective therapeutic option in a few, mainly retrospective, studies because it is capable of removing the supposed antigen in lymphatic tissue that triggers the autoimmune reaction and switching off the phlogosis in tonsillar tissue.7–10

The management of PFAPA syndrome in children was initially entrusted to pediatricians alone but is now considered to need the cooperation of an adequately trained ear, nose, and throat (ENT) specialist. In this way, patients would be referred to specific second-level pediatric settings to confirm the diagnosis and establish the most appropriate treatment on the basis of an integrated medical and surgical therapeutic protocol.

The present study considered the multidisciplinary management of PFAPA syndrome in children, with particular reference to the clinical impact of tonsillectomy with the aim of encouraging ENT specialists to consider the syndrome among all the possible differential diagnoses of periodic fever, aphthous stomatitis, and pharyngitis.

METHODS

Of 30 children seen between January 2002 and December 2007 at the Pediatric and Otorhinolaryngological Departments of University of Milan, Milan, Italy, because of periodic fever, 18 fulfilled the traditional diagnostic criteria for PFAPA syndrome according to the diagnostic criteria of Marshall et al.1 After excluding other causes of periodic fever, PFAPA syndrome was diagnosed after at least 6 months of clinical observation and careful examinations of parent-completed monthly diaries providing detailed descriptions of each episode, symptom, and related sign, including periodic fever, aphthous stomatitis, pharyngitis, cervical lymphadenopathy, abdominal pain, arthralgia, headache, nausea or vomiting, diarrhea, and anorexia, as well as any treatments received. During acute exacerbations, on at least 1 occasion, all of the patients underwent assessments of erythrocyte sedimentation rate; hemochromogen, C-reactive protein; and anti-streptolysin O antibody levels; and pharyngeal swab positivity for group A β-hemolytic streptococcus (GABHS). Immunoglobulin titers, including IgD, and anti–herpes simplex virus 1, anticytomegalovirus, and anti–Epstein-Barr viruses were also measured.

The patients were divided into 5 groups on the basis of their clinical pattern of disease (CPD): group 1 included the patients with decreasingly frequent episodes over time; group 2, those with no change in episode frequency over time; group 3, those with alternating remissions and relapses; group 4, those with decreasingly frequent episodes over time; and group 5, those with clinical resolution (modified from Tascher et al.17).

Initially, prednisolone (1 mg/kg) was administered to all of the patients during acute attacks, and some also received prophylactic treatment with cimetidine (200 mg, 3 times a day) for at least 6 months. Patients in groups 1 and 2, because of the absence of spontaneous remission during the clinical observation period and the failure of traditional medical therapy in avoiding recurrences, underwent tonsillectomy between November 2003 and July 2007. Their tonsillar specimens were molecularly searched for atypical bacteria (Mycoplasma pneumoniae and Chlamydia pneumoniae) and some respiratory viruses, including respiratory syncytial virus A and B, influenza virus A and B, parainfluenza virus 1, 2, and 3, and adenoviruses.

Mycoplasma pneumoniae was detected using the nested polymerase chain reaction (PCR) developed by Abele-Horn et al.17 and C pneumoniae was detected by means of the nested PCR developed by Tong and Silvis.18 Mycoplasma pneumoniae-specific amplification was performed using the MP-1 and MP-2 primer set and nested PCR using the MUX-1 and MUX-2 primers.17,19 Touchdown-nested PCR for the detection of C pneumoniae DNA was performed using primers designed to detect the major outer-membrane protein.19,20 The respiratory viruses were detected by means of real-time PCR using a Rotor-Gene 3000 (Corbett Research, Cambridge, England). The primers were designed from the conserved regions of genes codifying the matrix protein, the nucleoprotein, the hexon antigen of influenza viruses A and B, respiratory syncytial virus, the parainfluenzae viruses, and adenoviruses.21,22

A threshold cycle value was calculated for each sample by determining the point at which the fluorescence exceeded a threshold limit of 0.01. The occurrence of episodes was evaluated for each patient by means of a preoperative and postoperative score index of occurrence (SIO): ie, the mean ratio between the number of episodes and the time from their onset (preoperatively) or from tonsillectomy (postoperatively). In the case of pharyngeal swab positivity or in the presence of clinical signs of concomitant infections, episodes were excluded from SIO computation. The patients underwent periodic pediatric and otorhinolaryngological assessments after tonsillectomy, and their parents were asked to continue completing monthly diaries with reports of any subsequent episodes. All the patients and their parents were informed about the aim of the study and gave their written consent to the procedure and follow-up.

The significance of the association between postoperative outcomes (postoperative CPD, SIO, and the duration of residual episodes) and age at tonsillectomy was tested using the Fisher exact test. The differences in CPD, SIO, and the mean duration of PFAPA episodes before and after tonsillectomy were tested using the Wilcoxon signed-rank test. P < .05 was considered statistically significant.

Table 1 summarizes the preoperative demographic characteristic, clinical features, and laboratory results relating to the patients in the nonsurgical (NSG) and surgical group (SG); and Table 2 summarizes the preoperative distribution of the patients by CPD.

In addition to periodic fever and pharyngitis, which occurred in all patients, cervical lymphadenopathy and aphthous stomatitis were reported in 16 patients each (89%). Twelve patients (67%) (7 in the NSG and 5 in the SG) showed the typical symptomatic cluster of PFAPA syndrome variably associated with atypical symptoms such as abdominal pain (8 patients [44%], including 3 in the SG), arthralgia (7 patients [39%], including 3 in the SG), headache (6 patients [33%], including 3 in the SG), nausea or vomiting (4 patients [22%], including 2 in the SG), diarrhea (4 patients [22%], including 1 in the SG), and anorexia (2 patients [11%], both in the SG). Isolated aph-
thousand stomatitis occurred preoperatively in 5 cases (28%), including 2 in the SG.

During recurrences, regular pharyngeal swabs for the assessment of GABHS positivity were useful to exclude acute infectious processes; the occurrence of GABHS positivity, observed in no more than 1 event, was not considered a PFAPA episode and thus was not included in SIO computation.

Prednisolone therapy did not lead to lasting remission in the SG, whereas prophylactic treatment with cimetidine administered to 10 patients (3 in the SG) was effective in 86% of the treated NSG patients and ineffective in all 3 SG patients (Table 1).

Nine patients underwent tonsillectomy (2 in CPD group 1 and 7 in CPD group 2) without any surgical complications. All experienced a subjective and clinical improvement: 5 patients (56%) completely recovered; 3 (33%) continued to experience sporadic PFAPA events but without clockwork periodicity, and 1 (11%) experienced further occasional relapses after a transient clinical remission. Furthermore, 4 patients (44%) occasionally presented isolated aphthous stomatitis after surgery.

Comparison of the preoperative and postoperative CPDs revealed a significant difference in median values, with a clear shift toward higher classes, as a result of significant clinical improvement in all patients (Figure 1). Postoperatively, complete cessation of episodes was observed in 5 cases (as attested by passage to CPD group 3), and a consistent reduction in frequency of episodes occurred in 3 cases (as attested by passage to CPD group 4). The remaining patient showed the alternation of remissions and relapses after surgery (as attested by passage to CPD group 3). Moreover, findings from statistical analysis showed a postoperative reduction of PFAPA episodes during the observational period, corresponding with a significant postsurgical SIO decrease (P = .005) (Figure 2); in patients with incomplete recovery after tonsillectomy, a statistically significant reduction in the duration of residual PFAPA episodes (P = .03) was also observed (Figure 3). Table 3 compares the preoperative and postoperative symptomatic clusters in the SG. There was no association between postoperative outcomes (postoperative CPD, SIO, and the duration of residual episodes) and age at tonsillectomy.

The mean follow-up period after tonsillectomy was 26 months (range, 12-53 months); the mean follow-up period from the time of first observation in the study population as a whole was 61 months (range, 6-74 months).

Molecular analysis of tonsillar tissue showed the absence of nucleic acids belonging to atypical bacteria, respiratory syncytial virus A and B, influenza viruses A and B, and parainfluenza viruses 1, 2, and 3 in all of the specimens and the presence of adenovirus in 1 case.

Of the 9 patients in the NSG, 8 had a stable CPD, 1 of whom (in CPD group 2) was scheduled for surgery. The ninth patient was lost to follow-up after a brief period.

**COMMENT**

Although medical therapy is currently used in patients with PFAPA syndrome both preventively (with cimetidine therapy) and during acute exacerbations (with corticosteroids), there is little evidence that it has any notable impact on the natural history of the disease, and it is not used in some countries such as Finland. Furthermore, the effectiveness of tonsillectomy in patients with PFAPA syndrome is still a matter of debate, and only

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**Table 1. Preoperative Demographic, Clinical, and Laboratory Characteristics of the Nonsurgical and Surgical Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonsurgical Group (n=9)</th>
<th>Surgical Group (n=9)</th>
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<tr>
<td>Male, %</td>
<td>67</td>
<td>88</td>
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<tr>
<td>Age at onset, median (range), mo</td>
<td>12 (6-36)</td>
<td>16 (3-60)</td>
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<tr>
<td>First observation, median (range), mo</td>
<td>36 (19-216)</td>
<td>53 (16-96)</td>
</tr>
<tr>
<td>Preoperative SIO, median (range)</td>
<td>1.0 (1.0-1.5)</td>
<td>1.5 (1.0-2.0)</td>
</tr>
<tr>
<td>Preoperative duration of episodes, mean (range), d</td>
<td>4.0 (3.0-7.0)</td>
<td>4.5 (3.0-7.0)</td>
</tr>
<tr>
<td>White blood cell count, median (range), cells/µL</td>
<td>13 200 (9420-17 500)</td>
<td>13 900 (9200-21 000)</td>
</tr>
<tr>
<td>ESR, median (range), mm/h</td>
<td>53 (35-102)</td>
<td>60 (30-91)</td>
</tr>
<tr>
<td>CRP, median (range), mg/L</td>
<td>61 (37-86)</td>
<td>75 (10-116)</td>
</tr>
<tr>
<td>GABHS positivitya at pharyngeal swab, %</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Increase in ASO antibodies, %</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>Increase in IgD, %</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Positive for IgG anti-HSV1, %</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Positive IgG anti-CMV, %</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Positive IgG anti-EBV, %</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Those receiving cimetidine, %</td>
<td>79</td>
<td>33</td>
</tr>
<tr>
<td>Those in whom cimetidine was effective, %</td>
<td>86b</td>
<td>0c</td>
</tr>
<tr>
<td>Time from onset to tonsillectomy, mo</td>
<td>NA</td>
<td>55 (27-243)</td>
</tr>
<tr>
<td>Age at tonsillectomy, median (range), mo</td>
<td>NA</td>
<td>82 (43-146)</td>
</tr>
</tbody>
</table>

Abbreviations: ASO, anti–streptolysin O; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; GABHS, group A β-hemolytic streptococcus; HSV1, herpes simplex virus 1; NA, not applicable; SIO, score index of occurrence.

*SI conversion factors: To convert white blood cell count to ×10^9/L, multiply by 0.001; CRP to nanomoles per liter, multiply by 9.524.

a Observed on no more than 1 occasion.

b Computed for 7 treated patients.

c Computed for 3 treated patients.
a few articles have been published, most of these support the efficacy of tonsillectomy, with complete recovery in 64% to 100% of cases, but the possibility of an incomplete recovery or a stationary clinical picture is well known. Leong et al have recently expressed some hesitancy about the effectiveness of tonsillectomy in children with PFAPA syndrome, based on the heterogeneity of the surgical success rate, the tendency for spontaneous resolution of the syndrome, the limited series of patients reported, and the scarcity of prospective studies.

In line with previously published findings, our results document complete clinical recovery or a significant clinical improvement in 100% of the treated cases: complete recovery in 5 (56%); sporadic postoperative PFAPA events without periodicity in 2; no change in episode frequency over time; and 5, clinical resolution. Preoperative median, 1 (range, 1-3); postoperative median, 5 (range, 3-5) \( (P = .005) \).

Table 2. Preoperative Clinical Pattern of Disease in the Nonsurgical and Surgical Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Pattern of Disease</th>
<th>Total</th>
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<tbody>
<tr>
<td>Nonsurgical</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgical</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Total</td>
<td>2</td>
<td>8</td>
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\(^{a}\) Modified from Tasher et al. \(^{12}\)

\(^{b}\) 1 indicates more frequent recurrence of episodes over time; 2, no change in frequency of episodes over time; 3, less frequent recurrence of episodes over time; 4, alternation of remission and relapses; and 5, clinical resolution.

\(^{c}\) One patient was lost to follow-up.

Figure 1. Clinical pattern of disease (CPD). Preoperative and postoperative CPD in the surgical group (1, increasingly frequent episodes over time; 2, no change in episode frequency over time; 3, alternating remissions and relapses; 4, decreasingly frequent episodes over time; and 5, clinical resolution). Preoperative median, 1 (range, 1-3); postoperative median, 5 (range, 3-5) \( (P = .005) \).

Figure 2. Score index of occurrence (SIO). Preoperative and postoperative SIO (the mean ratio between the number of episodes and the time from their onset and surgery [preoperatively] or from tonsillectomy to the end of follow-up period [postoperatively]) of PFAPA syndrome episodes (periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy) in the surgical group. Preoperative median, 1.5 (range, 1.0-2.0); postoperative median, 0.0 (range, 0.0-0.45) \( (P = .005) \).

Figure 3. Mean duration (days) of preoperative and postoperative PFAPA syndrome episodes (periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy) in the surgical group. Preoperative median, 4.5 (range, 3.0-7.0); postoperative median, 0.0 (range, 0.0-4.45) \( (P = .03) \).

In our case series, the objective clinical improvements were reflected in the finding of a statistically significant difference between the preoperative and postoperative CPDs, with a clear shift toward higher classes in all of the patients, a statistically significant reduction in the postoperative SIO \( (P = .005) \), and a significant postoperative reduction in the duration of residual PFAPA episodes \( (P = .03) \). Furthermore, the patients with postoperative recurrences had less severe symptomatic clusters compared with before surgery; periodic fever and pharyngitis were the only symptoms in 2 patients and were accompanied by pharyngitis and headache in one patient and by headache and arthralgia in the other.
Published data indicate the possible role of microorganisms in PFAPA syndrome, as the chronic viral infections and periodic episodes of high fever, pharyngitis, and cervical adenitis suggest their direct or indirect involvement.25,26 We examined the presence of atypical bacteria and respiratory viruses in the tonsillar tissue specimens of 9 patients in CPD groups 1 and 2, which, to our knowledge, is the first time that such specimens from patients with PFAPA syndrome have been molecularly analyzed for M pneumoniae, C pneumoniae, and viruses by means of nested and real-time PCR. Our preliminary data (given the small number of patients) show the involvement of adenovirus in 1 case and the absence of colonization by other respiratory viruses or atypical bacteria. However, further studies with larger numbers of patients are necessary to establish the real role of adenovirus or other viruses in PFAPA syndrome.

Our results documenting complete clinical recovery or a significant clinical improvement in 100% of the treated patients, with the complete cessation of episodes in 56% of cases and the persistence of sporadic residual episodes in 44% (33% without clockwork periodicity and 11% with relapses after remission), are in line with previously published findings,7,15,16 although our complete success rate may appear slightly lower. This may be because, unlike those in previous studies, all of our patients were stratified into different classes on the basis of their CPDs, which were established by means of long-term regular follow-up visits to our pediatric immunological and otolaryngological facilities. Only selected cases underwent tonsillectomy, ie, the children with more severe clinical features unresponsive to traditional medical therapy who experienced increasingly frequent recurrences of PFAPA episodes over time (CPD group 1) or in whom the frequency of the episodes did not change (CPD group 2).12

Most of the previous studies are retrospective, and their postoperative follow-up periods were not always predetermined. They sometimes included children who actually had recurrent infections as children with PFAPA syndrome.21,22 To our knowledge, only 1 randomized controlled trial on PFAPA syndrome has been published,16 although it presents some patients not fulfilling the accepted diagnostic criteria for PFAPA syndrome.24,27 On the contrary, our case series only included patients strictly fulfilling the diagnostic criteria for PFAPA syndrome, as our findings of sporadic positivity to serological tests for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus and occasionally slightly increased levels of IgD, probably reflecting the activation of phlogistic status in affected children, are consistent with the literature.5,7,28 Moreover, during recurrences, regular pharyngeal swabs for the assessment of GABHS positivity were useful to exclude acute infectious processes; the occurrence of GABHS positivity, observed in no more than 1 event, was not considered a PFAPA episode and thus was not included in SIO computation. In addition, we suspect that patients with occasional further episodes are sometimes considered completely recovered: for example Renko et al14 claimed that all 14 of their surgically treated patients showed a complete clinical recovery, although 4 experienced 1 episode compatible with periodic fever during the 6 months after tonsillectomy.

Finally, we believe that ENT specialists who evaluate recurrent upper airway infections in children should be trained to recognize this hardly debilitating syndrome to set up an appropriate therapeutic protocol with the cooperation of second-level pediatric facilities, deputed to the exclusion of other causes of periodic fever.7,29

In conclusion, ENT specialists should be trained to recognize PFAPA syndrome, for which the current management consists of regular and prolonged clinical observation within an integrated otolaryngological and pediatric diagnostic and therapeutic protocol. Our preliminary results support the importance of stratifying the patients, and we cautiously suggest that tonsillectomy is appropriate in children who do not improve spontaneously or do not respond to traditional medical therapy. However, randomized trials with more conspicuous case series could be useful to achieve clearer data, since the etiology is still unknown and currently adopted therapies are, at present, just alluring attempts.

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Table 3. Preoperative and Postoperative Symptomatic Cluster in the Surgical Group

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<tr>
<th>Patient</th>
<th>PF</th>
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<th>Ap</th>
<th>CL</th>
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Abbreviations: An, anorexia; AP, abdominal pain; Ap, aphthous stomatitis; Ar, arthralgia; CL, cervical lymphadenopathy; Di, diarrhea; He, headache; IAp, isolated aphthous stomatitis; NV, nausea or vomiting; PF, periodic fever; Ph, pharyngitis; Post, postoperative; Pre, preoperative.
Author Contributions: Dr Torretta 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. Drs Pignataro and Torretta contributed equally to this study. Study concept and design: Pignataro, Torretta, Pietrogrande, Dellepiane, Pavesi, and Capaccio. Acquisition of data: Pietrogrande, Dellepiane, and Pavesi. Analysis and interpretation of data: Pignataro, Torretta, Pietrogrande, Dellepiane, Pavesi, Bossi, Drago, and Capaccio. Drafting of the manuscript: Pignataro, Torretta, and Capaccio. Critical revision of the manuscript for important intellectual content: Pignataro, Torretta, Pietrogrande, Dellepiane, Pavesi, Bossi, and Drago. Statistical analysis: Bossi and Drago. Study supervision: Pignataro, Torretta, Pietrogrande, Dellepiane, Pavesi, and Capaccio.

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makrishnan. Analysis and interpretation of data: Ramakrishnan, Said, and Kingdom. Drafting of the manuscript: Ramakrishnan and Said. Critical revision of the manuscript for important intellectual content: Ramakrishnan, Said, and Kingdom. Administrative, technical, and material support: Ramakrishnan. Study supervision: Kingdom. Interpretation and evaluation of tissue: Said.
Financial Disclosure: None reported.

REFERENCES


Correction

Error in Author Affiliations: In the Original Article titled “Outcome of Tonsillectomy in Selected Patients With PFAPA Syndrome” by Pignataro et al, published in the June issue of the Archives (2009;133[6]:548-553), an error occurred in the Author Affiliations on page 548. The correct affiliation for Lorenzo Drago, MD, should have read: “Clinical-Chemistry and Microbiology Laboratory, IRCCS Galeazzi Institute, Department of Preclinical Science LITA (Dr Drago), University of Milan, Milan, Italy.”