Surgical outcomes and histology findings after tonsillectomy in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome

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Abstract

Purpose: This study aimed to evaluate (a) specific histologic findings in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome who had tonsillectomy and (b) to assess any improvement of symptoms after tonsillectomy with or without adenoidectomy.

Materials and Methods: This project is a retrospective study performed at “Aghia Sophia” Children’s Hospital (Athens, Greece), between May 2007 and July 2008. Nine children were recruited into this study. Patients with defined diagnostic criteria for PFAPA syndrome till 14 years of age undergoing tonsillectomy with or without adenoidectomy were included in the study.

Results: Nine children met our inclusion criteria in the PFAPA group, of which 5 were male (55.56%) and 4 were female (44.44%), with ages ranging between 2.5 and 5 years at the age of surgery (mean, 3.4 years). The length of follow-up ranged from 6 to 19 months. Eight (88.89%) of 9 patients had complete remission of symptoms immediately after surgery. The histologic and immunohistochemical examination showed features of chronic tonsillar inflammation.

Conclusions: (a) No specific findings were observed in the tonsils of PFAPA patients; (b) we could not find any difference in tonsillar histology between PFAPA and chronic tonsillar inflammation; and (c) tonsillectomy is an effective treatment for PFAPA syndrome, improving patients and parental quality of life.

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1. Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome was first described by Marshall et al [1] and is characterized by periodic episodes of fever (>39°C) lasting 3 to 6 days and recurring every 3 to 8 weeks, accompanied by aphthous stomatitis, pharyngitis, cervical adenitis, and normal growth and development [2]. Because specific laboratory abnormalities have not been shown, PFAPA syndrome is defined clinically and the diagnosis is one of the exclusion [3]. The purposes of the present study are (a) to evaluate specific histologic findings in children with PFAPA syndrome who had tonsillectomy and (b) to assess any improvement of symptoms after tonsillectomy.

2. Materials and Methods

This is a retrospective study of children with PFAPA syndrome who underwent tonsillectomy with or without adenoidectomy at the Department of Otorhinolaryngology Head and Neck Surgery of “Aghia Sophia” Children’s Hospital, a tertiary care pediatric hospital in Athens (Greece), between May 2007 and July 2008. Nine children
with PFAPA syndrome were recruited into this study. Patients with defined diagnostic criteria for PFAPA syndrome till 14 years of age undergoing tonsillectomy with or without adenoidectomy were included in the study. These criteria included the following signs and symptoms: regularly recurring fevers of unknown origin with a typical, regular, and completely asymptomatic intervals of 2 to 5 weeks between episodes, and at least one of the following clinical signs: aphthous stomatitis, cervical lymphadenitis, and pharyngitis. Patients with cyclic neutropenia and significant medical disorders were excluded. A full blood count and erythrocyte sedimentation rate was performed to all of the children included.

The method of tonsillectomy used was the classical cold knife with emphasis on blunt dissection. Hemostasis especially in upper and lower tonsillar poles was obtained by clipping the site of hemorrhage and using silk sutures. Adenoidectomy was performed with the use of mirrors and curettes and suction cautery used for hemostasis. Tonsils were sent to the pathology department for histologic examination. Hematoxylin-eosin stains were used for histology examination. The immunohistochemical Bond Refine detection, a biotin-free polymeric horseradish peroxidase–linker antibody conjugate system (Bond Polymer Refine kit: Vision Biosystems Ltd, Newcastle Upon Tyne, UK), was used on paraffin sections for the detection of B (CD20/L-26: Novocastra Ltd, Newcastle Upon Tyne, UK) and T (CD3/PS1; Novocastra Ltd, Newcastle Upon Tyne, UK) lymphocytes on the Bond-automated system [4].

The research protocol was conducted after its approval by the departmental scientific and ethical review board. Informed parental consent was obtained from each eligible child before enrollment of the study.

3. Results

Nine children met our inclusion criteria in the PFAPA group, of which 5 were male (55.56%) and 4 were female (44.44%), with ages ranging between 2.5 and 5 years at the age of surgery (mean, 3.4 years). The mean duration of symptoms before surgery was 18.78 months (range, 12–30 months). Fever during the attack had a mean duration of 4.3 days (range, 3–6 days). Aphthous stomatitis was observed in 66.7% of children, cervical adenitis in 100%, pharyngitis in 66.7%, abdominal pain in 44.4%, and arthritis in 33.3% of children included in this study. Eight (88.89%) of 9 patients had complete remission of symptoms immediately after surgery. One child (followed up only by telephone) had 2 episodes of fever after surgery with signs and symptoms compatible with PFAPA syndrome; the first episode was 2 months and the second one was 7 months after surgery. The patient was treated with cimetidine. Since then, the child’s symptoms resolved completely. For the rest of PFAPA patients, the postoperative recovery was typical of other children who undergo this surgery for chronic tonsillitis or

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<th>Study characteristics of children with PFAPA syndrome</th>
<th>Patient</th>
<th>Age at surgery (y)</th>
<th>Duration of fever (d)</th>
<th>Cervical adenopathy</th>
<th>Aphthous stomatitis</th>
<th>Pharyngitis</th>
<th>Arthritis</th>
<th>Follow-up (mo)</th>
<th>Recurrence of PFAPA after surgery</th>
<th>Therapy</th>
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<tr>
<td>Sexual Distribution (male/female)</td>
<td>5/4</td>
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<td>Age at onset of PFAPA (months)</td>
<td>3–6</td>
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| TE indicates tonsillectomy; AE, adenoidectomy; A, antibiotic; Co, cortisone; Ci, cimetidine.
obstructive sleep disturbance. Table 1 lists details for all PFAPA patients.

Blood analysis showed during the episodes leukocytosis (mean, 16 000/μL) with an elevated count of polymorpho-
nuclear leukocytes (mean, 65%) and erythrocyte sedimenta-
tion rate (mean, 40 mm/h).

The histology result of all PFAPA tonsils showed features characteristic of chronic tonsillar inflammation, such as lymphoid and follicular and interfollicular immunoblastic hyperplasia, some cases of focal histiocytic clusters, foci of hyalinizing fibrosis, some crypt abscesses, and keratinizing debris (Fig. 1). Immunohistochemistry revealed preservation of tonsillar architecture with expression of B- and T-cell markers in the B and T tonsillar regions, respectively, without any particular abnormality. The clear center of the lymphoid follicles was essentially occupied by B lymphocytes, whereas T lymphocytes appeared mostly disposed at the lymphoid follicles periphery (Figs. 2 and 3).

The length of follow-up ranged from 6 to 19 months (mean, 12.11 months). Telephone follow-up was performed to the parents of 4 children because they live in islands. The remaining 5 children were examined in our department a week after surgery and 1, 3, 6, and 12 months after surgery. A final telephone follow-up was performed to all the parents at maximal follow-up.
4. Discussion

The PFAPA syndrome may resemble other periodic fevers, such as cyclic neutropenia, familial Mediterranean fever, hyperglobulinemia D syndrome, Behçet disease, juvenile rheumatoid arthritis, and the autosomal dominant familial fevers [2,3,6,7]. Because PFAPA syndrome is a diagnosis of exclusion, cardinal signs and symptoms must be carefully observed for a differential diagnosis, such as onset in early childhood, before the age of 5 years (male predominance has been described) [5]; periodic abrupt onset of febrile episodes that last 4 to 5 days and occur every 4 to 6 weeks on average; and episodes that are often accompanied by intraoral ulcers, pharyngitis, and cervical lymph node enlargement [6]. 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 (not always) by abdominal pain and diarrhea [6].

Treatment suggested consists of conservative (pharmacologic) and surgical intervention. The most effective nonsurgical treatment is corticosteroids: 1 dose of prednisone or prednisolone sodium phosphate (1–2 mg/kg) causes cessation a fever cycle within 12 to 24 hours. Administration of corticosteroids does not prevent future fever cycles and often shortens the intervals between episodes [6,7]. The dramatic resolution of febrile attacks by single oral administrations of corticosteroids is distinguished by a cyclic drop in neutrophils and (not always) by abdominal pain and diarrhea [6].

Cimetidine, a common H2 antagonist, has been used with disappointing results. Adenoidectomy by itself does not result in resolution of symptoms, and it seems of no difference in patient outcome whether or not an adenoidectomy is performed alongside of the tonsillectomy [7]. Immuno histochemistry revealed preservation of tonsillar architecture with expression of B- and T-cell markers in the B and T tonsillar regions, respectively, without any particular abnormality.

In conclusion, (a) no specific findings were observed for tonsillar histology in PFAPA patients; (b) we could not find any difference in tonsillar histology between PFAPA and chronic tonsillar inflammation; and (c) tonsillectomy is an effective treatment for PFAPA syndrome, improving patients and parental quality of life.

References