SHORT REPORT

PFAPA syndrome in children evaluated for tonsillectomy

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Among 40 children undergoing tonsillectomy for recurrent pharyngitis, 15 (37.5%) had presented preoperatively with complaints compatible with PFAPA syndrome. All 15 had had periodic fever every three to four weeks and pharyngitis; 12 (80%) had cervical adenitis and five (33%) aphthous stomatitis. All children had been well between episodes and showed a dramatic postoperative improvement. PFAPA syndrome is not uncommon among children having tonsillectomy. Tonsillectomy is curative in most of these patients.

PFAPA syndrome is a clinical entity consisting of periodic fever associated with aphthous stomatitis, pharyngitis, and cervical adenitis in young children. Additional manifestations have occasionally been reported including malaise, headache, arthralgia, abdominal pain, vomiting, and hepatosplenomegaly.[1 2] The syndrome was first described in 1987[3] and the acronym PFAPA was coined in 1989.[1 4] However, other authors have considered the syndrome insufficiently defined and have chosen not to assign this diagnosis.[5] The cause remains unknown and no evidence linking geographic or ethnic factors or infections to this clinical entity has been found.[1 2 6] As specific laboratory abnormalities have not been shown, PFAPA syndrome is defined clinically and the diagnosis is one of exclusion.[6 7] The prognosis is excellent.[1 2 6–9]

The syndrome has been considered to be quite rare; however, larger series of patients have recently begun to appear.[1 2 7] As recurrent pharyngitis is an indication for tonsillectomy, a proportion of the children who are evaluated for tonsillectomy may have manifestations of PFAPA syndrome. We present our experience with such children.

METHODS

The study included all 101 children aged less than 7 years who had undergone tonsillectomy with or without adenoidectomy in the Otorhinolaryngology Department at the University Hospital in Heraklion, Crete during the three year period 1998–2000. Medical records were reviewed and parents were retrospectively contacted by phone; they attended a structured interview during the spring of 2001.

Parameters investigated included demography, individual and family history, age at tonsillectomy, unusual infections, overall health, and the preoperative characteristics of febrile pattern, pharyngitis, oral ulcers, and cervical lymph node enlargement. Laboratory investigation and throat cultures, management, and postoperative outcome were also recorded. Parents were asked about the efficacy of antipyretics, antibiotics, other regimens, and tonsillectomy. Criteria evaluated were both subjective (such as the child's wellbeing during the episode free interval) and objective (such as the number of visits to the primary care physician for pharyngitis). Recently defined diagnostic criteria for PFAPA were used.[1] These include: regularly recurring fevers; at least one of the following clinical signs of aphthous stomatitis, cervical lymphadenitis, and pharyngitis; exclusion of cyclic neutropenia; completely asymptomatic intervals between episodes; and normal growth and development.

RESULTS

Telephone follow up was attempted for each of the 101 cases and was successful for 79 (78%). Twenty one families were not found and one refused to answer the questionnaire. Thirty nine of these 79 children had undergone tonsillectomy for obstructive symptoms such as snoring, obstructive sleep apnoea, and mouth breathing, and were excluded from the study. Among the remaining 40 children with tonsillectomy for recurrent episodes of febrile pharyngitis, 15 (37.5%) were found to have presented preoperatively with periodic febrile episodes and signs compatible with PFAPA syndrome (table 1). Fevers of up to 40°C were commonly reported. Pharyngitis was mostly described as exudative tonsillitis. Enlarged lymph nodes were usually bilateral. At the time of tonsillectomy children had a mean age of 5.2 (range 3–7) years. Children had a history of complaints for one to four years before tonsillectomy and all had received multiple antibiotic regimens. Leucocyte counts and acute phase reactions were not investigated during all the fever episodes. Mean leucocyte count was 8.9×10^9 cells/l (range 5.9–13.7×10^9 cells/l) and mean neutrophil count was 3.9×10^9 cells/l (range 1.7–8.8×10^9 cells/l). Neutropenic episodes were not documented; however, cyclic neutropenia was not rigorously investigated by appropriate serial blood counts. Positive blood cultures were not documented. Serum immunoglobulin D concentrations were not measured. Children were completely asymptomatic during the intervals between episodes and had normal growth and development. None of the children were specifically referred because of PFAPA syndrome. None had affected siblings and no family history of similar episodes or other chronic diseases was recalled. All children experienced a striking postoperative improvement. In all cases, parents declared that no more recurrent fevers, pharyngitis, or episodes of lymphadenitis occurred. Children were well at their programmed postoperative follow up and since then had only presented with the usual minor viral infections.

DISCUSSION

The term periodic fever syndrome has been used either in a general sense to encompass a group of disorders characterised by recurrent fevers without a strictly periodic pattern, including juvenile rheumatoid arthritis, familial Mediterranean fever, Behçet's syndrome, the hyperimmunoglobulin D syndrome, and the autosomal dominant familial fevers, or in a more restricted sense to denote two diseases in which fevers occur with a periodicity: cyclic neutropenia and PFAPA syndrome.[1 2 6 9]

For the diagnosis of PFAPA syndrome two features are considered to be cardinal.[6] The first is the clockwork periodicity of the episodes with a usual interval of three to four weeks, although intervals of two to nine weeks have been reported.[1 2 6] Fever is high (up to 40.0°C) and lasts for about four to six days.[2 7 8] Fevers in the present study showed this pattern, presenting with a periodicity of three to four weeks,

Table 1 Clinical features suggestive of PFAPA syndrome in 15 children who underwent tonsillectomy for recurrent pharyngitis

Patient	Gender	Duration of symptoms (y)	Age at surgery (y)	Periodicity of fever (wk)	Pharyngitis	Cervical adenopathy	Aphthous stomatitis	ESR (mm/h)
1	Male	1.5	6.0	4	+	+	+	100
2	Male	2.0	4.0	4	+	+	+	20
3	Male	0.5	4.5	4	+	+	–	Not done
4	Male	3.0	6.0	4	+	+	–	12
5	Male	3.0	7.0	4	+	+	+	14
6	Male	2.0	5.0	6	+	+	–	72
7	Male	1.0	4.0	4	+	–	–	9
8	Male	2.0	5.0	4	+	+	–	16
9	Male	2.0	3.0	3	+	–	+	Not done
10	Male	2.0	6.0	3	+	+	+	3
11	Male	3.0	5.0	4	+	+	–	23
12	Female	2.0	5.5	3	+	+	–	18
13	Female	1.0	4.0	4	+	+	–	16
14	Female	2.0	7.0	3	+	+	–	15
15	Female	4.0	6.0	3	+	–	–	11

with the exception of patient 6 who had six week intervals. The second cardinal feature of PFAPA syndrome is the child's complete good health between episodes.[6] Although the episodes may last for years, the children exhibit normal growth.[8] Pharyngitis has been described in 65–89% of the patients.[1 8] All children in the present study had recurrent pharyngitis prior to tonsillectomy. Cervical lymphadenopathy has been described in 72–88% of patients,[1 2 8] a rate compatible with our 80%. Aphthous stomatitis rates have been reported up to 67–71%[1 8] compared to our 33%. Aphthous stomatitis is frequently overlooked.[6] Notably, none of the girls in the present study presented with stomatitis. Symptoms occur between the age of 3 months and 12 years, with a mean age less than 5 years.[2 7 9] Children in the present study had a mean age of 5 years at tonsillectomy, and a period of one to three years of complaints had elapsed before surgery. Predominance of male subjects has already been reported.[1 2 6]

Administration of antibiotics has no effect.[1 5] Most of the patients given one or two doses of corticosteroids present with a dramatic resolution of fever.[1 2 6 8] This dramatic response is unique to PFAPA syndrome and may be used as a diagnostic criterion.[2] Immunomodulation with cimetidine has been discussed as a potential treatment, although the value of cimetidine treatment has not been borne out since the initial publication.[1 6] In the present study no child had received steroids or cimetidine. Tonsillectomy has been retrospectively shown to be an effective treatment,[1 6 7] as it was in the present study. Although a possible role of tonsillectomy in children with recurrent fever and tonsillopharyngitis has already been suggested,[10] it should be emphasised that none of the children were specifically referred for tonsillectomy because of suspected PFAPA syndrome. On the other hand, children who do not have tonsillectomy commonly cease presenting with new episodes after several years.[1 2 6]

In conclusion, our experience suggests that PFAPA syndrome is not uncommon among children who are evaluated for tonsillectomy and must be included in the differential diagnosis of such cases. A striking clinical response following surgical intervention was noted in this small series of patients.

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REFERENCES

1 **Thomas KT**, Feder HM Jr, Lawton AR, *et al*. Periodic fever syndrome in children. *J Pediatr* 1999;**135**:15–21.
2 **Padeh S**, Brezniak N, Zemer D, *et al*. Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. *J Pediatr* 1999;**135**:98–101.
3 **Marshall GS**, Edwards KM, Butler J, *et al*. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr* 1987;**110**:43–6.
4 **Marshall GS**, Edwards KM, Lawton AR. PFAPA syndrome. *Pediatr Infect Dis J* 1989;**8**:186–7.
5 **Miller LC**, Sisson BA, Tucker LB, *et al*. Prolonged fevers of unknown origin in children: patterns of presentation and outcome. *J Pediatr* 1996;**129**:419–23.
6 **Long SS**. Syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)—what it isn't. What is it? *J Pediatr* 1999;**135**:1–5.
7 **Dahn KA**, Glode MP, Chan KH. Periodic fever and pharyngitis in young children: a new disease for the otolaryngologist? *Arch Otolaryngol Head Neck Surg* 2000;**126**:1146–9.
8 **Feder HM Jr**. Periodic fever, aphthous stomatitis, pharyngitis, adenitis: a clinical review of a new syndrome. *Curr Opin Pediatr* 2000;**12**:253–6.
9 **Scholl PR**. Periodic fever syndromes. *Curr Opin Pediatr* 2000;**12**:563–6.
10 **Abramson JS**, Givner LB, Thompson JN. Possible role of tonsillectomy and adenoidectomy in children with recurrent fever and tonsillopharyngitis. *Pediatr Infect Dis J* 1989;**8**:119–20.