ORIGINAL ARTICLE

PFAPA syndrome: new clinical aspects disclosed

D Tasher, E Somekh, I Dalal

Arch Dis Child 2006;**91**:981–984. doi: 10.1136/adc.2005.084731

See end of article for authors' affiliations

Correspondence to: I Dalal, Pediatric Infectious/Allergy/ Immunology Unit, E Wolfson Medical Center, POB 5, Holon 58100, Israel; ilandalal@hotmail.com

Accepted 16 March 2006
Published Online First 4 April 2006

Background: The recently described PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis) syndrome is characterised by periodic fever, aphthous stomatitis, pharyngitis and adenitis. However, there are currently relatively few data on the natural history of this syndrome.
Objective: To describe the presentation, clinical course, doctors' awareness, therapeutic response and long-term follow-up of children with PFAPA syndrome.
Methods: Children with PFAPA syndrome referred over a 5-year period (from January 1999 to January 2004) were enrolled in the study. Data were gathered from medical records, parents' interviews, physical examination and telephone calls.
Results: 54 patients with PFAPA syndrome were evaluated. Our patients had a higher rate of abdominal pain (65%) and a lower rate of aphthous stomatitis (39%) than those in previous reports. Four different patterns of disease evolution were identified, including the relatively common (n = 14, 26%) and newly described course of alternating remissions and relapses. The remissions lasted 8.5 months on average (range 4–36 months). Diagnosis was established by primary paediatricians in 30 of 54 (56%) patients. However, a substantial delay in diagnosis was apparent (mean 15 months). Episodes were curtailed by a much lower dose of prednisone or equivalent corticosteroid (mean 0.6 mg/kg/day, range 0.15–1.5 mg/kg/day) than reported previously. Tonsillectomy was successful in the prevention of recurrence of further episodes in all six patients who underwent the procedure.
Conclusions: We describe several new characteristics of PFAPA syndrome in children, contributing to our knowledge of this relatively unrecognised but troublesome syndrome. Early diagnosis and appropriate treatment can markedly improve the quality of life of both patients and families.

PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis) syndrome is characterised by recurrent episodes of fever associated with cervical adenitis, pharyngitis and aphthous stomatitis. The disease belongs to the group of periodic fever syndromes characterised by short episodes of illness that recur regularly for several years, alternating with healthy periods. The syndrome was first described in 1987[1] and the acronym PFAPA was subsequently coined in 1989.[2] Currently, most of the information gathered about the syndrome is based on only a few reports.[1–4]

This study was undertaken to investigate the epidemiological data, clinical course and long-term follow-up of children with PFAPA syndrome in central Israel. We were especially interested in aspects that were not described in previous reports, such as doctors' awareness of the syndrome, adherence to corticosteroid treatment, effective corticosteroid dosage, unique side effects of corticosteroid treatment and a possible correlation between childcare attendance and occurrence of PFAPA syndrome.

PATIENTS AND METHODS

Children with recurrent episodes of fever referred over 5 years (from January 1999 to January 2004) to the Pediatric Infectious/Immunology/Allergy Clinic, E Wolfson Medical Center, Holon, Israel, were evaluated for PFAPA syndrome. When the patients were seen for the first time in our clinic, all of them underwent a full assessment of their medical history and physical examination. Diagnosis of PFAPA syndrome was established according to the modified clinical criteria proposed by Marshall *et al*.[1 3] Criteria include regularly recurring fevers with early age of onset (<5 years of age) and symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs: aphthous stomatitis, cervical lymphadenitis or pharyngitis. Additional clinical criteria include completely asymptomatic intervals between episodes, normal growth and development, and exclusion of cyclic neutropenia.

After diagnosis, patients were seen during the subsequent febrile episodes (by ES and ID) for a few months, enabling us to further characterise the episodes, and then followed up on a regular basis every 3–6 months. The study took place during 2004. Relevant medical data were gathered from the medical records and from the patients and families.

The medical data included:

1. demographic data and medical history of patients and families,
2. characteristics of episodes,
3. laboratory evaluation,
4. how the diagnosis was determined and the time lapse until diagnosis and
5. drugs used, efficacy and side effects.

To complete missing medical data, parents were interviewed twice by telephone. The interviews were held 6 months apart (by DT). During the interviews, more information on patients, such as adherence to and satisfaction with corticosteroid treatment and long-term course of the syndrome, was also obtained.

Data analysis

Analysis of data was carried out using SPSS V.9.0. For continuous variables, such as age and laboratory parameters, descriptive statistics were calculated and reported as mean (standard deviation). Normalcy of distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared by

Abbreviation: PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis

disease severity using the t test for independent samples. Continuous variables with distributions deviating significantly from normal were compared by disease severity using the Mann–Whitney U test. Categorical variables such as sex and the presence of specific medical conditions were described using frequency distributions. The χ^2 test with 99% Monte Carlo confidence intervals was used to detect differences in categorical variables by disease severity. Associations between attitude, satisfaction and variables associated with corticosteroid treatment were described using correlation analysis with Spearman's r. All tests were two sided and considered significant at $p<0.05$.

RESULTS

A total of 62 children were suspected of having PFAPA syndrome. Seven families could not be traced, and in one case the parents refused to answer the questionnaire. A total of 54 patients were identified with well-documented, regularly recurring periodic febrile episodes. All patients fulfilled the criteria, except for three patients who did not fulfil the age criterion. Two of the patients had manifestations starting at 7 years of age and one patient at 10 years of age. They were diagnosed with PFAFA syndrome despite their older age at presentation. All of them had all the other features of PFAPA including pharyngitis, and did not have other clinical and laboratory manifestations suggesting other diseases (all underwent haematological, immunological tests and genetic analysis for familial Mediterranean fever). In addition, all of them had an excellent response to corticosteroid treatment.

Table 1 describes the demographic and epidemiological data in patients with PFAPA syndrome.

To investigate a possible correlation between daycare attendance and PFAPA occurrence, we compared the ages of entry to day care between patients and their healthy siblings. The difference was not significant.

Tables 2 and 3 describe the clinical characteristics of the febrile episodes.

Average duration of follow-up for the entire study population was 2.2 years (range 0.5–6 years), and the time elapsed from the first episode averaged 3.5 years (range 1–7.5 years).

Febrile episodes began at a mean age of 1.9 years (range 1 month to 10 years). One of our patients presented with features of PFAPA at the very early age of 1 month. At his first presentation, he underwent full examination for sepsis. The subsequent febrile episodes were typical, recurred regularly (every 2–3 weeks) and lasted 7–10 days. Immunological screening was normal and familial Mediterranean fever was excluded. The diagnosis was determined at 3 years of age by his primary paediatrician.

Table 1 Demographic and epidemiological data in patients with PFAPA syndrome

No of patients	54
Men, n (%)	33 (61)
Women, n (%)	21 (39)
Origin	
Sephardic, n (%)	41 (76)
Ashkenazi, n (%)	13 (24)
Age of entry to day care, years (range)	1.8 (0.25–4)
Age of entry of sibling to day care, years (range)	2.1 (0.25–4)
Medical history	
Atopic manifestations, n (%)	21 (39)
Family medical history	
Atopic manifestations, n (%)	16 (30)
FMF, n (%)	4 (7)
Autoimmune diseases, n (%)	4 (7)

FMF, familial Mediterranean fever; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis.

Table 2 Clinical characteristics of PFAPA episodes

Onset of PFAPA, years (range)	1.9 (0.08–10)
Duration of episode, days (range)	5.3 (2–14)
Maximal temperature, ℃ (range)	40.1 (38.5–41.2)
Days of temperature, 38.3˚C (range)	4.5 (1–14)
Frequency, every week (range)	3.7 (1–9)
Seasonality	
No seasonality, n (%)	47 (87)
More in the winter, n (%)	5 (9)
More in the summer, n (%)	2 (4)
Change in frequency of episodes	
No frequency change, n (%)	15 (28)
Gradually decreased frequency, n (%)	23 (42)
Gradually increased frequency, n (%)	2 (4)
Relapse after long-term remission, n (%)	14 (26)

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis.

Table 3 Symptoms reported by parents of children with PFAPA syndrome

Symptoms	Frequency, no of patients (%)
Pharyngitis	52 (96)
Abdominal pain	35 (65)
Cervical lymphadenopathy	33 (61)
Chills	33 (61)
Headache	25 (46)
Aphthous stomatitis	21 (39)
Nausea/vomiting	19 (35)
Rhinorrhoea	18 (33)
Cough	15 (28)
Myalgia	11 (22)
Diarrhoea	7 (13)
Rash	2 (4)
Classic cluster (fever, pharyngitis, lymphadenopathy, aphthous stomatitis)	15 (28)

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis.

His response to corticosteroid treatment was excellent, and episodes became less frequent and much shorter over time, but still occurred at the age of 5 years.

Seasonality was not found among our patients. In long-term follow-up, we were able to identify four different patterns in the course of the disease. In group I (n = 15, 28%), no change in frequency was reported. In group II (n = 23, 42%), the episodes recurred less frequently over time at different intervals (mean every 11.1 weeks, range 2–25 weeks). In group III (n = 2, 4%), the episodes became gradually more frequent. Group IV (n = 14, 26%) presented a unique pattern of disease characterised by remissions and relapses. The remissions lasted 8.5 months on average (range 4–36 months).

Table 4 shows the data related to diagnosis. The mean time required for diagnosis was 1.25 years (range 3 weeks to 7 years). Most of the cases (55%) were diagnosed by the primary paediatrician. However, the diagnosis was deferred in many cases (41%) until referral to an infectious disease or immunology expert.

Table 5 presents data related to treatment. In our study, episodes were curtailed by a much lower single dose of prednisone or equivalent corticosteroid (mean 0.59 mg/kg/day, range 0.15–1.5 mg/kg/day) as compared with the recommended dose of 1–2 mg/kg/day. In all, 51 of 54 patients required only one single dose of corticosteroid for each episode. The other three patients rarely needed a second dose within 24 h. Corticosteroid administration resulted in rapid resolution of fever (mean 10 h). Although corticosteroid treatment did not prevent subsequent episodes of fever, patients responded successfully on subsequent episodes. In most cases (48%), corticosteroid treatment did not change

Table 4 Diagnosing physicians of patients with PFAPA and laboratory investigations

	No of patients
Diagnosing physician	
Primary paediatrician, n (%)	30 (55)
Infectious disease or immunology expert, n (%)	22 (41)
ENT, n (%)	2 (4)
Time to diagnosis, years (range)	1.25 (0.06–7)
Investigations	
Genetic analysis for FMF, n (%)	12 (22)
Immunoglobulin battery, n (%)	12 (22)

ENT, ear, nose and throat specialist; FMF, familial Mediterranean fever; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis.

the course of the disease. In all, 15 (31%) families reported that the episodes of fever became less frequent after successful treatment with corticosteroids. However, 9 (19%) families described increased frequency of the subsequent episodes.

Most of the parents (65%) did not report any side effects of corticosteroid treatment. The most commonly reported side effect was restlessness (16 children, 33%).

The parents rated their satisfaction with corticosteroid treatment on a scale from 1 to 4. The score 4 represents maximal satisfaction. The mean score was 3.1. Despite the high rate of satisfaction, the fear of corticosteroids resulted in poor compliance. In all, 22 (46%) parents avoided corticosteroid treatment in some of the episodes.

No significant associations were detected between the dosage of corticosteroids and the following parameters: time to defervescence, satisfaction with corticosteroid treatment and the frequency of subsequent febrile episodes.

Tonsillectomy was successful in the prevention of recurrence of further episodes in all 6 (11%) patients who underwent the procedure at an average follow-up of 1.6 years (range 1–4 years). The average age of the patients at the time of tonsillectomy was 4.8 years (range 2.2–6 years), and a mean period of 3.6 years (range 1.5–5.5 years) had elapsed from diagnosis until surgery.

In an attempt to further characterise a subgroup of patients with a more severe course, we defined disease severity according to frequency of episodes (occurring at intervals of $\leqslant$14 days) or prolonged fever (lasting $\geqslant$7 days). This group of patients (n = 13) was not found to have unique characteristics predicting the clinical course.

Table 5 Treatment of PFAPA episodes

	No of patients
Treatment	
Antibiotic, n (%)	41 (76)
Effectiveness of antibiotic treatment, n (%)	1 (2)
Corticosteroid treatment, n (%)	48 (89)
Dose of corticosteroid treatment (prednisone equivalent; mg/kg/day (range))	0.6 (0.15–1.5)
Time to defervescence, h (range)	10 (0.5–96)
Change of frequency after corticosteroid treatment	
No change, n (%)	24 (50)
Increased frequency, n (%)	9 (19)
Decreased frequency, n (%)	15 (31)
Side effects of corticosteroid treatment	
No documented side effects, n (%)	31 (65)
Restlessness, n (%)	16 (33)
Increased appetite, n (%)	1 (2)
Satisfaction of corticosteroid treatment (1–4)	3.1
Adherence to corticosteroid treatment, n (%)	26 (54)
Tonsillectomy, n (%)	6 (11)
Time to tonsillectomy, years (range)	3.6 (1.5–5.5)
Recurrence of the disease after tonsillectomy	0

PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis.

DISCUSSION

Although the clinical manifestations of PFAPA syndrome episodes are well known,[3–11] there are several characteristics that are still unclear, such as awareness of the primary physicians, attitude towards corticosteroid treatment and the temporal course of the illness. To shed light on these important parameters, we investigated a large cohort of patients referred to our centre over 5 years.

Most of our patients (n = 33, 61%) were males. This male predominance has been previously described.[3 4 8] Most of the children were of Sephardic or mixed ethnic background, reflecting the local population distribution. Previous studies failed to show ethnic background influence.[2–4] Recent studies[12 13] showed inverse association between early exposure to infectious agents and susceptibility to autoimmune and allergic diseases. Therefore, we checked whether the age of entry to day care, representing early exposure to infectious diseases, is different in children with PFAPA as compared with their healthy siblings. Assuming that both patients and healthy siblings were from the same genetic background and were raised in the same environment, we found it reasonable to use this group as a control group. No significant difference was found.

Atopic manifestations were reported by 39% of our patients. This observation has not been described previously. Further studies have to be carried out to clarify whether there is a clear association between atopic manifestations and PFAPA syndrome. Family history of autoimmune and atopic diseases was found in 7% and 30% of patients, respectively. Similar prevalence in the normal population was reported previously.[14 15]

The febrile episodes started at a younger mean age than reported previously, but the range is wider.[4 11 16] The mean duration of the febrile episodes (5.3 days), frequency of episodes (every 3.7 weeks) and mean maximal temperature were similar to those described previously.[1 3 8 11 16]

Clinical presentation that included all the typical symptoms (periodic fever, aphthous stomatitis, pharyngitis and adenitis) was reported in only 15 (28%) children. Almost all the patients (96%) had pharyngitis; 33 (61%) had lymphadenopathy (as compared with 72–88% described elsewhere).[2–4] The frequency of aphthous stomatitis was relatively low (39%); previous studies reported frequencies of 67–71%.[2 3] The second most common symptom in our study was abdominal pain (65%), the prevalence of which in previous reports was only 18–49%.[3 17]

The course of the disease has been previously characterised only in a small number of patients reporting that remissions seemed to be preceded by attacks with decreasing frequency.[3] We identified four different patterns in disease evolution. The most common pattern (n = 23, 42%) is characterised by episodes becoming gradually shorter and less frequent over time. A unique, common and newly described course of remissions and relapses was reported in 14 (26%) children. Remissions lasted up to 3 years. No change in frequency was reported in 15 (28%) children. The least common pattern (n = 2, 4%) is characterised by episodes becoming gradually more frequent over time.

The primary paediatrician diagnosed 55% of the cases. However, the diagnosis was deferred in many cases (41%) until referral to an expert on infectious disease or immunology. We believe that despite increased awareness of the syndrome (at least in our region), it is still suboptimal.

Most of our patients received antibiotic courses before the diagnosis was established, even though it was found to be ineffective.[1 3 8 11 18] The use of oral corticosteroids resulted in a

What is already known on this topic

- The clinical manifestations of PFAPA syndrome episodes are well known.
- The PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome belongs to the group of periodic fever syndromes characterised by short episodes of illness that recur regularly for several years, alternating with healthy periods.

What this study adds

- We describe the clinical course, doctors' awareness, therapeutic response and long-term follow-up of children with PFAPA syndrome.

dramatic resolution of febrile episodes; however, it did not prevent their recurrence. In our study, episodes were curtailed by a much lower dose of prednisone or equivalent than reported previously in the literature.[3 4 11] The fear of corticosteroids caused parents to skip the recommended treatment or to try much lower doses than we recommended. Some of the families (n = 9, 19%) reported that the intervals between the episodes became shorter after successful treatment with corticosteroids. However, more often, the corticosteroid treatment did not change the course of the disease. No significant association was found between the corticosteroid dosage and the time elapsed to defervescence. Our data indicate that a lower dosage of corticosteroids is probably adequate for aborting the episodes.

The role of tonsillectomy in the management of PFAPA syndrome has been discussed previously, with a wide range of success in aborting the symptoms after the procedure.[3 8 11 16 19 20] In our study, tonsillectomy was successful in the prevention of recurrence of further episodes in all six patients who underwent the procedure.

In this study, we describe several new characteristics of PFAPA syndrome in children, contributing to our knowledge of this relatively unrecognised but troublesome syndrome. Early diagnosis and appropriate treatment can significantly improve the quality of life of both patients and families.

Authors' affiliations
D Tasher, Department of Pediatrics, E Wolfson Medical Center, Holon, Israel
E Somekh, Pediatric Infectious/Allergy/Immunology Unit, E and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
I Dalal, E Somekh, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Competing interests: None declared.

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