Periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis

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ABSTRACT

INTRODUCTION: The periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a non-hereditary idiopathic febrile syndrome belonging to the group of autoinflammatory diseases. PFAPA does not cause long-lasting sequelae. An early diagnosis provides treatment possibilities for the patient and comfort to the family.

MATERIAL AND METHODS: This study is a retrospective review of the medical records of patients diagnosed with PFAPA and admitted to our clinic from January 1999 to January 2010 (n = 31).

RESULTS: The study population (n = 31) consisted of 21 males and ten females: 30 Caucasians and 1 Asian. Normal growth was seen in 30 patients. The median age at onset was 33 months. The mean duration of fever episodes was 4.45 days (95% confidence interval (CI): 3.92-4.98), and the mean duration of intervals between fever episodes was 29.66 days (95% CI: 25.31-34.01). Concomitantly with the fever, all patients had characteristic symptoms. All patients were asymptomatic in between their fever episodes. Prodromal symptoms were seen in 12 patients. Oral prednisolone was used in 24 patients and caused immediate fever reduction in 87.5%. A reduction in the duration of the asymptomatic interval after treatment was seen in 75.0%. Tonsillectomy was performed in 20 of the 31 patients causing cessation of fever episodes in 70%. Fever episodes continued in 15%, and the postoperative status remained unknown in the last 15%. Spontaneous resolution was seen in four patients. The diagnostic delay had a median duration of 28 months (range 2-160 months).

CONCLUSION: The long diagnostic delay of PFAPA gives cause for concern and it indicates a need for greater awareness of the disease so that the diagnosis may be made earlier.

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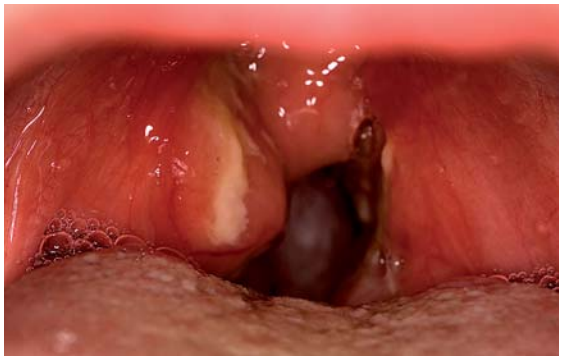
The periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome was first described as a clinical entity in 1987 [1]. PFAPA belongs to the group of autoinflammatory diseases and is thus characterised by fever episodes due to seemingly unprovoked inflammation. Unlike autoimmune diseases, neither antigen-specific antibodies nor antigen-specific auto-reactive T-cells are present in autoinflammatory diseases [2].



Pharyngitis.

PFAPA is an idiopathic febrile syndrome of non-hereditary origin. It has an early age of onset, one or more of the associated symptoms (aphthous stomatitis, cervical adenitis and pharyngitis) and an absence of respiratory tract infections and cyclic neutropenia [1, 3]. At present, no specific biomarkers are at hand to help with the diagnosis [4]. It is widely recognized that in order to make the diagnosis, it is necessary to rule out the monogenic periodic fever syndromes that may overlap clinically with PFAPA [5, 6]. Even though the syndrome has not been associated with long-lasting sequelae [7, 8], it has a great impact on the patient, and it is a cause for concern for the family. An early diagnosis provides treatment possibilities for the patient and comfort to the family. Thus the aim of this study was to describe PFAPA through a retrospective review of the medical records of patients seen in a paediatric rheumatology clinic to increase awareness of the disease.

MATERIAL AND METHODS

The study was performed as a retrospective review of the medical records of patients diagnosed with PFAPA admitted to our clinic from January 1999 to January 2010. Since no ICD code has been established for PFAPA, the patients were found using the diagnostic code for fever without specification. This provided a total of 186 patients. A total of 24 patients were selected on the basis of recurrent fever in cases where infectious causes and monogenic recurrent fever had been excluded. Selected were also another seven patients referred to our immunology clinic for recurrent fever during January

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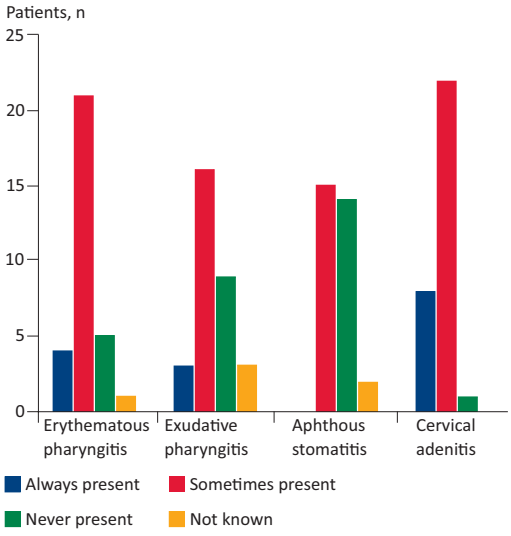
FIGURE 1

Characteristic symptoms concomitantly with fever episodes in 31 patients.



2009 to February 2010 who fulfilled the PFAPA criteria. In total, the study population consisted of 31 patients.

It was verified that the patients fulfilled the EuroFever PFAPA criteria: 1) periodic fever for a minimum of six months. Daily fever of at least 38.5 °C (axillar) for two to seven days. 2) Pharyngitis, cervical adenitis and/or oral aphthosis. 3) Exclusion of other causes of recurrent fever (clinical or by laboratory, depending on the history). 4) Exclusion of infections, immunodeficiency and cyclic neutropenia. 5) Full recovery between episodes and a normal linear growth [9].

Monogenic hereditary periodic fever syndromes were excluded in all patients. This exclusion was based on the patient's ethnicity, medical history and genetic mutation investigations, if found necessary. Infection was excluded by throat, blood and urine cultures. Immunodeficiencies were excluded by measuring immunoglobulin levels, leukocyte counts and more elaborated immunological investigations, if needed. Cyclic neutropenia was excluded by measuring the level of neutrophilic leukocytes during fever episodes and the intervals between fever episodes. None of the patients included had neutrophile counts below 1.5×10^9/l at any time measured.

For each patient, the following data were recorded: demographic and anthropometric data, duration of fever episodes, duration of intervals between fever episodes, laboratory results and clinical manifestations. The latter included: prodromal symptoms, symptoms associated with fever episodes, i.e. presence of pharyngitis (exudative/erythematous), cervical adenitis and oral aphthosis as well as any other symptom.

Laboratory results for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and leukocytes were only included if it had been noted whether the blood samples were taken during an asymptomatic interval or a febrile episode. If no such information was available, the result was excluded. Statistical calculations were made using SPSS and included Spearman's ranked correlation. A p value of < 0.05 was considered significant.

Trial registration: not relevant.

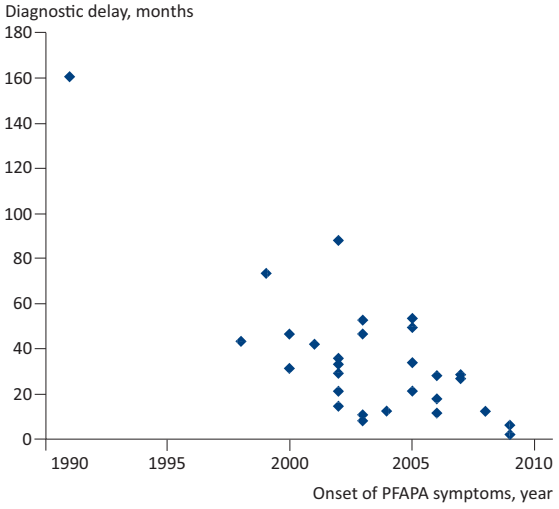
RESULTS

The study population consisted of 31 patients (21 males and ten females), 30 were Caucasian and one was Asian; 27 fulfilled the EuroFever criteria. The remaining four patients did not fulfil the EuroFever criteria due to the lack of growth charts or vague records of the characteristic symptoms. Normal growth was seen in 30 patients (96.8%). No growth details were available for the last patient.

The median age at onset of symptoms was 33 months (interquartile range: 19-65 months). The mean duration of fever episodes was 4.45 days (95% confidence interval (CI): 3.92-4.98), and the mean duration of intervals between fever episodes was 29.66 days (95% CI: 25.31-34.01). Seasonal variation in the frequency of fever episodes was seen in 45.2% (14/31) of the patients. All patients had characteristic symptoms (pharyngitis, cervical adenitis and/or aphthous stomatitis) concomitantly with fever (**Figure 1**). Furthermore, 30 patients had other symptoms associated with the fever episodes, including headache, stomach ache,

FIGURE 2

Diagnostic delay correlated with year of onset of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) symptoms. r = –0.584 (p = 0.001).



arthralgia, tiredness, rash, vomiting, diarrhoea or photophobia (**Table 1**). All patients were asymptomatic in the intervals between fever episodes. However, twelve patients experienced prodromal symptoms before fever episodes in the form of headache, fatigue or arthralgia.

CRP, ESR and leukocytes were elevated during fever episodes in 91%, 86% and 41%, respectively, of the patients tested (**Table 2**). All throat, blood and urine cultures were negative. Elevated immunoglobulin (Ig) D levels were seen in ten patients (32.3%). Genetic tests were done for *MVK* mutation (eight patients), *TNFRSF1A* mutation (three patients), *MEFV* mutation (one patient) and *NLRP3/CIAS1* mutation (one patient). All genetic tests were negative. All 31 patients had normal levels of IgA, IgM and IgG – including subclasses.

Oral prednisolone (dosage: 1-2 mg/kg/day) given at the start of fever episodes and for 1-3 days had been administered in 24 of the 31 cases. Fever reduction was seen in 87.5% (21/24) of patients after administration of oral prednisolone. However, 75.0% (18/24) experienced a reduction in the duration of the asymptomatic interval after treatment. Tonsillectomy was performed in 20 of the 31 patients. Four of the remaining eleven patients experienced spontaneous resolution of fever episodes during follow-up. The resolution occurred after two to seven years of fever episodes.

Tonsillectomy was followed by cessation of fever episodes in 70% (14/20) of the patients. These 14 patients were followed in our clinic between two and 14 months after surgery. Fever episodes at a decreased frequency continued in three patients (15%) during a follow-up of seven to 65 months after surgery. The postoperative status is not known for the last three patients (15%) as they withdrew from follow-up after surgery. Information regarding surgical complications was available for twelve patients. Of these patients two had complications – higher pitched voice in one patient and rhinolalia aperta in the other.

The time from onset of symptoms to diagnosis (diagnostic delay) was calculated for each patient. The diagnostic delay had a median duration of 28 months (interquartile range: 12.5-49 months). In order to investigate if the diagnostic delay had changed over time, it was correlated to the year of symptom onset. Spearman's rank of correlation (r) was –0.585 (p = 0.001) (**Figure 2**). The figure shows an "outlier". Disregarding this value, the new correlation coefficient was –0.541 (p = 0.002). The correlations indicate a decrease in the diagnostic delay over time.

TABLE 1

Distribution of symptoms other than pharyngitis, cervical adenitis and oral aphthosis associated with fever episodes in 30 patients. The values are n (%).

Symptom	Always present	Sometimes present
Headache	10 (33)	8 (27)
Stomach ache	9 (30)	5 (17)
Joint pain	6 (20)	5 (17)
Tiredness	6 (20)	5 (17)
Vomiting	4 (13)	3 (10)
Rash	1 (3)	3 (10)
Diarrhoea	1 (3)	2 (7)
Low appetite	1 (3)	1 (3)
Photophobia	0 (0)	1 (3)
Convulsions	0 (0)	1 (3)
Cough	1 (3)	1 (3)

DISCUSSION

This retrospective review aimed to describe the PFAPA syndrome. Our result for the median age at onset of PFAPA (33 months) is similar to results found in the studies by Thomas et al (2.8 years) [7] and Feder & Salazar (39.6 months) [10]. Still, other studies have found a much lower median age at onset. More specifically, 18 months (range 1-60 months), 12 months (range 2-60 months) and 22 months (range 1–120 months) [5, 11, 12]. The studies agree that the onset of PFAPA primarily occurs before five years of age.

The mean duration of fever episodes (4.45 days) and asymptomatic intervals (29.66 days) in our study resemble those first described by Marshall et al in 1987 [1] (5-day fever episodes, 4.5-week intervals), and our findings are in accordance with those of other studies [7, 10, 12, 13]. In summary, the studies agree that fever episodes last about 4-5 days separated by asymptomatic intervals lasting 30 days. However, it should be kept in mind that the duration of the intervals can vary. This was described in the original report by Marshall et al [1] and confirmed by Gattorno et al [5] and by the finding of seasonal variation in the present study.

Concomitantly with periodic fever, patients have at least one of the following characteristic symptoms: pharyngitis, aphthous stomatitis and/or cervical adenitis. As not all characteristic symptoms need to be present to

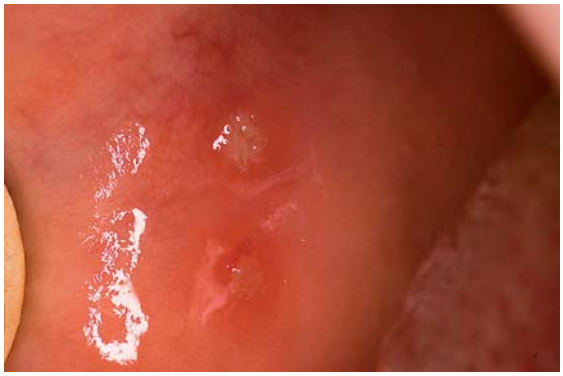
TABLE 2

Distribution of patients on normal or elevated laboratory values during fever episodes and asymptomatic intervals. Total number of patients investigated was 31.

	CRP, mg/l		ESR, mm/h		Leukocytes, × 10^9/l	
	≤ 10	> 10	≤ 13	> 13	≤ 12.5	> 12.5
Fever episodes, n (%)[a]	2 (9)	21 (91)	3 (14)	19 (86)	13 (59)	9 (41)
Intervals, n (%)[a]	15 (54)	13 (46)	12 (48)	13 (52)	28 (97)	1 (3)

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
a) % relate to the rows of the table.

Aphthous stomatitis.



make the PFAPA diagnosis, there will be variation in the patients' clinical presentation. This becomes apparent when our findings are examined for the distribution of patients according to characteristic symptoms and are compared with the findings of other studies. Erythematous pharyngitis was present in 80.6% of the patients in our study, and exudative pharyngitis in 61.3%. Other studies have reported pharyngitis in 65-96% of patients [5, 7, 10, 12]. We found that 48.4% of our study population had aphthous stomatitis. In other studies, this was the case in 38-67% of patients [5, 7, 10, 12]. Lastly, 96.8% had cervical adenitis in our study, but this was only the case for 61-77% of patients in other studies [7, 10, 12].

The high prevalence of patients who had associated symptoms (96.8%) other than the characteristic symptoms of PFAPA in the present study underlines the variation in the clinical presentation of the syndrome and the diagnostic challenge it poses. This is supported by the findings of other studies, which found that fever was associated with abdominal pain and headache in 18-65% of patients [5, 7, 10, 12, 13], vomiting in 27-30% [5, 10], diarrhoea in 29-30% and rash in 15-22% of patients [5, 7]. Patients who have prodromal symptoms also cause variation in the clinical presentation. This was the case for 38.7% of the patients in our study population, whereas other studies have reported that as many as 62-78% of cases experienced prodromal symptoms [7, 10].

The treatments used in our study population were oral prednisolone and tonsillectomy. Fever reduction after the administration of oral prednisolone was seen in 87.5% of the 24 patients treated in our study. Another study found that fever reduction occurred in 97% of the 72 patients treated with prednisolone [10]. Unfortunately, 75.0% (18/24) of the patients treated in our study experienced a reduction in the duration of the asymptomatic intervals afterwards. This was only the case for 50% (36/72) of the patients treated in the other study [10].

The role of oral prednisolone in the treatment of PFAPA is merely one of symptom relief, and as there is a risk of shortening the intervals between fever episodes as well as of not preventing future fever episodes, its use should be carefully considered. Nevertheless, the possibility to control fever episodes in specific situations of social importance is of great value. The role of tonsillectomy in the treatment of PFAPA has been investigated in study reviews and randomized controlled trials [14-16]. It was demonstrated that tonsillectomy is an effective method of PFAPA resolution as studies have shown that 64-100% of patients had cessation of fever episodes after tonsillectomy [7, 10]. In our study, we found that this was the case in 70% of cases. Despite the positive results associated with tonsillectomy in terms of PFAPA resolution, a meta-analysis on the effect of tonsillectomy recommends that it should be considered cautiously due to the general risks of operation, and given that treatment for symptom relief exists (in the form of prednisolone) and as many patients experience spontaneous resolution with time [17]. None of our patients received anakinra [18], which has recently been proposed as a treatment option.

Our correlation analysis showed an "outlier" patient with a longer diagnostic delay than the rest of the study population. This patient had onset of symptoms as early as 1991. Based on the clinical manifestations, medical history and the patient presenting with elevated IgD levels, the patient was initially suspected of having Hyper-IgD Syndrome (HIDS). HIDS was, however, later excluded by genetic mutation analysis (*MVK* mutation). Furthermore, the patient responded well to prednisolone.

Being a retrospective study, this investigation has limitations due to the variability of the data presented in the medical records. Another limitation is the missing data, e.g. the growth details of one patient and the follow-up status of another three patients after tonsillectomy, the withdrawal of patients from follow-up before cessation of fever episodes, as well as missing laboratory values. A third limitation is that the medical records do not indicate the set of PFAPA criteria used to make the diagnosis. However, we were able to retrieve sufficient data to describe the PFAPA syndrome, and our results are in accordance with the findings of other studies.

In conclusion, although PFAPA was first described more than 20 years ago and the diagnostic process in our material shortened over time, the considerable diagnostic delay of PFAPA gives cause for concern and it points to a need for greater awareness of the disease. Living with the PFAPA syndrome is bothersome, and early diagnosis is the key to understanding the repetitive disturbances in the child's development and to application of early, appropriate intervention.

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CONFLICTS OF INTEREST: none

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