PFAPA syndrome: clinical characteristics and treatment outcomes in a large single-centre cohort

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Abstract

Objective

This paper aims to describe clinical and laboratory features and disease outcome in a single-centre cohort of patients with PFAPA syndrome (Periodic Fever, Aphtous stomatitis, Pharyngitis, and Adenitis) and to test performance of diagnostic and therapeutic algorithms.

Methods

Patients fulfilling criteria were selected from the fever clinic population. Prospective follow-up together with recruitment of newly diagnosed patients followed pre-defined guidelines. Diagnostic and therapeutic algorithms and definitions of outcome and therapy response were formulated. Paired blood samples during febrile and afebrile periods were compared.

Results

Out of 176 patients referred for suspected periodic fever 125 children fulfilled criteria. Their age at onset was 23 months, median episode duration 3.5 days at 4-week intervals. Fever was associated with pharyngitis (91%), cervical adenitis (78%) and aphtae (41%). Among therapeutic options, episodic prednisone proved to be the most common first-line treatment. Administered to 77 patients, it reduced symptoms in 94%. Tonsillectomy led to the full symptom resolution in all 18 patients. Forty-six patients reached disease remission.

Conclusion

Distribution of typical symptoms, response to therapies and disease outcome in a large patient cohort were documented. We offer diagnostic and therapeutic algorithms that have proven effective during this prospective trial. Our findings support the general belief of benign nature of this aetiologically unclear condition, despite proportion of patients having persistent disease for years. Maintenance of normal findings in afebrile intervals, striking response to a single dose of prednisone and normal growth and development together with spontaneous tendency towards prolongation of afebrile intervals are important confirmatory features of PFAPA syndrome.

Key words

periodic fever, aphtous stomatitis, pharyngitis and cervical adenitis syndrome, diagnostic algorithm, outcome

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Introduction

Recurrent fever in childhood often presents a differential diagnostic puzzle. Besides well-recognised entities such as infections, immune deficiencies, idiopathic inflammatory and neoplastic disorders, autoinflammatory diseases have become an important player. While monogenic periodic fevers can be confirmed by molecular-genetic analysis, syndrome of Periodic Fever, Aphtous stomatitis, Pharyngitis and cervical Adenitis (PFAPA) is a clinical entity diagnosis which requires exclusion of other potential causes of recurrent fever (1-3). In a preschool child, regular short (3–6 days) febrile episodes are accompanied by at least one of: culture-negative tonsillopharyngitis, oral aphthae and cervical lymphadenitis. Additional features such as fatigue, headache, nausea, vomiting, abdominal pain or arthralgia may occur (4-6). Affected children are healthy between attacks (5). Elevation of non-specific inflammatory parameters during attacks can barely differentiate PFAPA syndrome from infections as well as other inflammatory and neoplastic disorders. Its diagnosis is based on clinical symptoms according to the Marshall's criteria, later modified by Hofer *et al*. (Table I) (2, 5, 7). Antibiotics do not change the course of the febrile attack which is typically aborted by a single dose of prednisone (4, 5, 8). Other treatment options include cimetidine, colchicine and tonsillectomy (9-13).

In this study, we aimed to analyse clinical and laboratory features as well as disease outcome of patients attending our fever clinic with a diagnosis of PFAPA syndrome. Testing the performance of pre-defined diagnostic and therapeutic algorithms was our secondary objective.

Patients and methods

Patients

Consecutive patients referred to the fever clinic of Paediatric Rheumatology Unit, General University Hospital in Prague for suspected periodic fever were considered for recruitment. In the retrospective part of the study charts of patients referred during 2004–2007 were reviewed. Prospective data collection was conducted from January 2008 to July 2011. In order to become eligible to enter the prospective part, patients must have had at least 3 fever episodes over the previous 6 months. Clinical diagnosis of PFAPA syndrome was the main inclusion criterion. The study was approved by the institutional Ethics Committee and informed consent was obtained from parents/guardians of all participants.

Diagnostic algorithm

– Medical history

Patient and family history was a major diagnostic component. Data were collected by 2 means. A questionnaire was administered to parents at the first clinic visit or via email prior to the appointment. Parents were advised to consult their child's primary care physician for data they were not able to supply. Family history of recurrent fevers, reaction to vaccinations, overall infectious morbidity, age at onset of periodic fevers, detailed description of typical presentations and duration of afebrile interval were of particular importance.

– Initial clinical evaluation

Existing modified diagnostic criteria (7) were applied in order to establish the working diagnosis of PFAPA syndrome (Table I). Where neutrophil count (to exclude cyclic neutropenia) and throat culture results (at least 2 negative) were not available they became part of the investigations list. Acute inflammatory parameters included ESR, CRP and serum amyloid A (SAA), screening for immune deficiencies consisted of the full blood count with differential, serum immune globulins and antibodies against vaccination antigens. Serum IgD and A concentrations and mevalonic acid in urine collected on the first day of the febrile episode were used as a screening for Hyper-IgD Syndrome (HIDS). Where appropriate, further laboratory tests and imaging were applied to exclude other diseases. When the child displayed features suggestive of a monogenic fever, DNA analysis was requested. An experienced physician (PD, PK) confirmed the final diagnosis of PFAPA syndrome upon review of all above information.

– Laboratory tests

In the prospective part of the study, blood sampling was performed twice: during the typical fever episode and at afebrile interval. Timing of the "febrile" blood test was within 48 hours from fever (≥38.5°C) onset, prior to the corticosteroid administration. "Afebrile" tests were performed at least 14 days after the most recent fever detected. For detection of mevalonate and its metabolites urine was collected over 12–24 hours of the first day of the episode. CRP, ESR, full blood count (FBC) and SAA were measured using routine methodologies. Mevalonaturia was quantified using capillary gas chromatography/mass spectrometry, the commonly used method for profiling urinary organic acids, with cut-off values for mevalonolacton and mevalonate/creatinine ratio of 0.01 and 0.001 mg/g, respectively.

Therapeutic algorithms and disease assessment

At the time of diagnosis patients were offered the following options: a) watch-and-wait with antipyretics as required; avoidance of antibiotics was recommended; b) prednisone in a single dose of 1 mg/kg or its equivalent administered within up to 24 hours from fever onset; c) other conservative treatment options (cimetidine, colchicine); and d) tonsillectomy. Parents received the printed form ("fever diary") and were instructed to record fevers, associated symptoms and treatments administered. Assessment of the drug treatment efficacy was based on the interval from administration to symptom resolution and on duration of the upcoming afebrile interval. Full response was defined as a complete resolution of all symptoms within up to 12 hours. In partial responders the full effect was reached within 24–48 hours with or without the need for an additional prednisone dose. Responders (both full and partial) must have remained symptom-free for at least 2 weeks following treatment and a similar response must have been noticed in the majority of typical attacks. Patients in whom full resolution was not achieved or who had an early fever recurrence in a minimum of 2 treated PFAPA episodes or who had differing responses in more than 50% of typical episodes were considered non-responders.

For the purpose of clinical status and outcome evaluation the following definitions were applied: active disease, characterised by typical recurrent fever attacks at least every 2–6 weeks over the 3 months prior to the assessment; and full remission, with a minimum of 12-month fever-episode free interval (10). Infections with features different from prior PFAPA episodes were not considered.

Statistical analysis

Descriptive statistics for the characterisation of the population was expressed in median (range). The nonparametric Mann-Whitney U-test was used for comparisons between febrile episodes and afebrile intervals. *p*-values of <0.05 were considered statistically significant.

Table I. Modified diagnostic criteria for PFAPA syndrome (7).

1) Regularly recurring fevers with an early age of onset (<5 years of age).

2) Constitutional symptoms in the absence of upper respiratory tract infection with at least 1 of the following clinical signs:
   a) aphthous stomatitis;
   b) cervical lymphadenitis;
   c) pharyngitis;

3) Exclusion of cyclic neutropenia.

4) Completely asymptomatic interval between episodes.

5) Normal growth and development.

6) Exclusion of monogenic periodic fevers mainly in patients with gastrointestinal symptoms and rash.

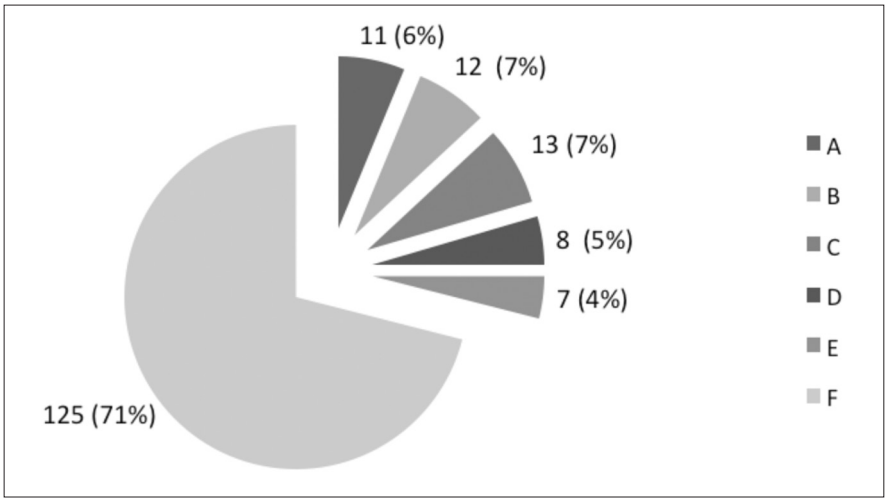

Fig. 1. Distribution of patients with periodic fever syndromes in our cohort: n (%):
A: Genetically confirmed monogenic periodic fevers
B: Suspected monogenic fevers with negative DNA analysis
C: Suspected monogenic fevers with pending genetic results
D: Low serum IgA
E: Recurrent infections
F: PFAPA syndrome

Results

Patients with periodic fever syndromes

Total of 176 patients were referred for suspected periodic fever. The distribution of their diagnoses is shown in Figure 1. Only 125 patients with the final diagnosis of PFAPA syndrome underwent further analysis.

Clinical characteristics of children with PFAPA syndrome

All children with PFAPA syndrome (n=125; 63 boys) were Caucasians of the Czech origin. Of 59 patients (47%) with positive family history, recurrent fevers and/or tonsillitis in pre-school age were reported mainly in one of the parents (49/59), in remaining 10 patients their siblings or grandparents

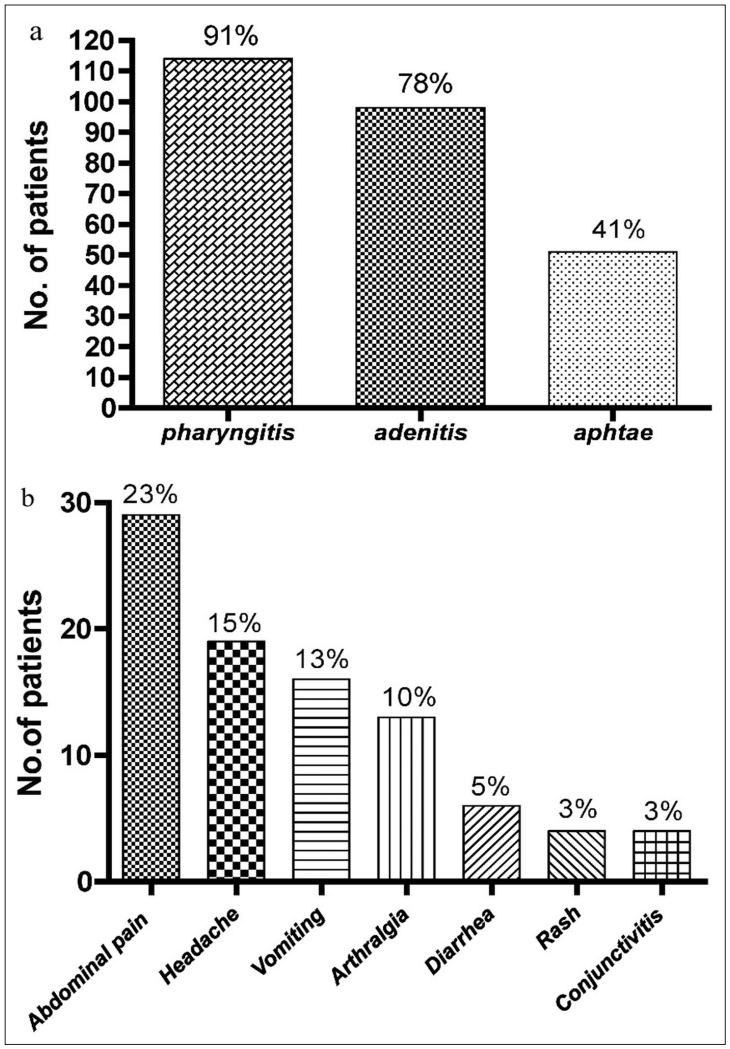

Fig. 2.
Presence of the (**a**) main and (**b**) other symptoms in 125 patients with PFAPA syndrome.

were affected. In 11 parents, tonsillectomy in early childhood lead to complete resolution of symptoms, while 38 parents reported spontaneous remission during childhood. None of family members displayed features suggestive of ongoing periodic syndrome.

In 31 patients, diagnosis was made prior to the onset of prospective data collection, 94 were enrolled prospectively. From the prospective cohort, 70% of patients were seen at least once during both febrile episode and afebrile interval at our clinic. Remaining patients were seen at afebrile interval and brought results of their physical examination and laboratory tests in febrile episode from their local physician. Clinical findings as reported by parents were systematically recorded during the follow-up visits together with growth and developmental data. Patients were usually seen in 3–6-month intervals during the first year and then in prolonged intervals until their disease fully subsided.

Median age at the first manifestation was 23 months (range 6–60), with median interval between attacks of 4 weeks (range 2–6) and fever duration 3.5 days (range 3–6), with maximal fever 39.5°C. Regularity of episodes (predictability within ±1 week) was reported in approximately 58% of patients. Median age at diagnosis was 27 months (range 18–58), interval between onset and diagnosis ranged between 6 to 64 months (median 20). Distribution of individual clinical features is shown in Figure 2a. In the majority of cases, throat findings were described as "exudative" tonsillopharyngitis. Cervical lymphadenopathy was defined as the size of upper anterior cervical lymph nodes ≥1 cm in diameter and/or significant enlargement from the previous examination. A minority of patients in whom pharyngitis was not observed (9%) had either cervical lymphadenopathy or oral aphtae or combination of both usually with non-specific symptoms such as mood change, fatigue or decreased appetite. The presence of other than the main diagnostic features noticed in the majority of episodes is shown in Figure 2b. At afebrile intervals, all patients had normal physical findings, including physiological appearance of tonsils with no signs suggestive of chronic tonsillitis. Normal linear growth and development were noticed during the follow-up in all children.

All 125 PFAPA patients had elevated non-specific inflammatory parameters – median CRP 73 mg/l (range 10–359), ESR 35 mm/hour (range 7–95) and WBC 13.10^9/L (range 3.8–24) – at febrile episodes and reported their subsequent normalisation. Figure 3 illustrates a drop in these parameters as well as SAA in 35 patients, where paired blood samples in fever episode and in afebrile interval were prospectively collected.

Therapy

Episodic prednisone administration in a single dose of 0.8–1.2 mg/kg at fever onset was the most frequently used therapeutic option. Out of 77/125 patients (62%) treated, 72 (94%) were responders. Full response was noticed in 60 (83%), while 12 patients had partial response. A second prednisone dose was needed in 5 of these patients. About 10% of patients receiving prednisone observed mood change or fatigue lasting 2–3 days after prednisone administration, despite resolution of fever and mucosal symptoms. Shortening of afebrile intervals (to no less than 2 weeks) following prednisone administration occurred in 11 children (14%) and led to discontinuation of this treatment in 3 of them. Two subsequently received colchicine (0.5 mg/day), which reduced severity and frequency of febrile attacks but was not able to induce remission. Of 5 prednisone non-responders, 2 children did not attain full symptom resolution and in 3 cases after initial resolution typical PFAPA symptoms returned within 1 week from the administration. In

these cases, clinical re-assessment of possible infectious cause was always performed and it was negative (Fig. 4). None of the patients received cimetidine. In addition, from two fever episodes in two different patients, pyogenic streptococcus was cultured from the throat swab performed just before prednisone administration in one case and at the recurrence of low-grade fever the day after prednisone administration in the other. In both cases, penicillin treatment was then given with full resolution of symptoms. In other 8 patients, single episodes of insufficient prednisone response were subsequently re-assessed as a consequence to the parents' incorrect evaluation of that particular fever episode which subsequently evolved features of upper respiratory tract infection (URTI). The majority of parents who opted for episodic prednisone administration used it on the basis of their own decision. In the majority of cases, prednisone was not administered in all typical episodes, mainly when parents had doubts about the possible presence of URTI. Children with a higher frequency of typical episodes often received prednisone in every other episode in order to avoid any potential risk of corticosteroid side effects. Our general recommendation was to avoid regular long-term dosing in intervals shorter than 3–4 weeks.

Parents of 48/125 patients (38%) opted for other treatment modalities. In the majority of them, the "watch-and-wait" approach with episodic antipyretic treatment was an agreement between the family and the treating physician based on the mild disease course (short-lasting attacks up to 3 days, afebrile intervals >6 weeks). The parents of 3 patients refused prednisone treatment in principle. The response to antipyretics was short-lived requiring repeated dosing. The natural course of episodes remained unchanged.

In a total of 18 children (14%) tonsillectomy was performed after median of 34 months (range 5–48) from the diagnosis. In 8 of them, overall disease duration and/or episode frequency were considered a significant burden hardly acceptable for the family. In 4 patients, the surgical option was chosen because

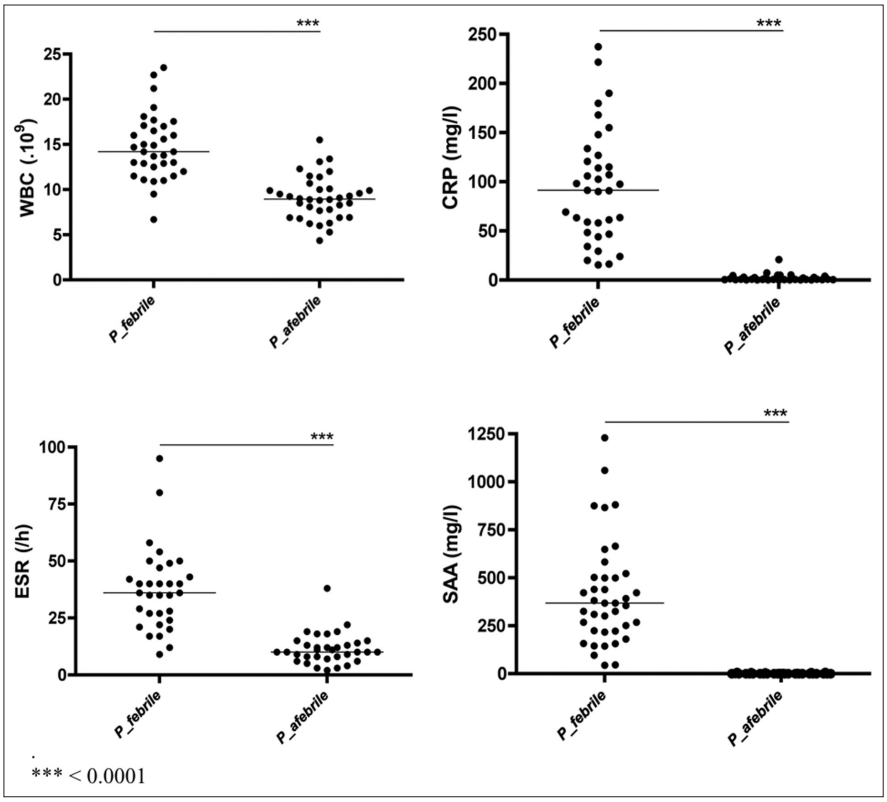

Fig. 3. Inflammatory parameters in patients with PFAPA syndrome (P) in febrile *vs*. afebrile condition.

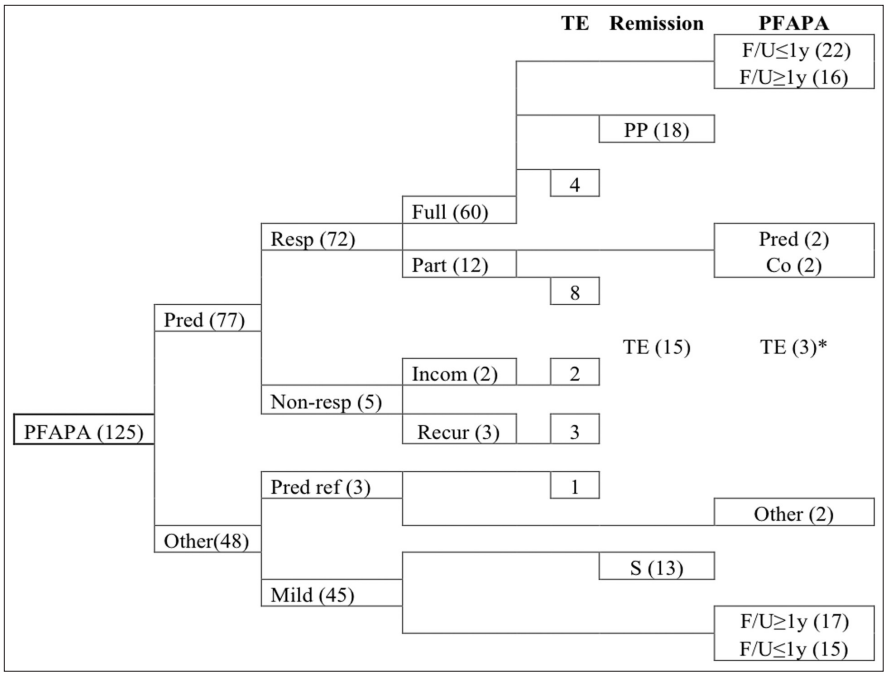

Fig. 4. Overview of distribution of patients according to the therapy effect and disease outcome. Pred: prednison; Co: colchicine; Other: other therapy; Resp: responders; Non-resp: non-responders); Pred ref: prednison refusal; Mild: mild fenotype; Part: partial; Incom: incomplete; Recur: early recurrence; PP: post-prednisone remission; TE: post-tonsillectomy remission; S: spontaneous remission; F/U≥1y: follow-up more than one year; F/U≤1y: follow-up less than one year.

afebrile intervals shortened after prednisone administration. All 5 prednisone non-responders opted for tonsillectomy while one family preferred tonsillectomy, as a first line treatment. In all 18 patients, tonsillectomy led to the full

resolution of symptoms immediately after the procedure. Fifteen patients (83%) reached the full remission, while 3 were followed for less than one year after tonsillectomy at the time of the data analysis. In 2 cases, recurrent fevers similar to the previous PFAPA episodes re-appeared after 12 and 14 months post tonsillectomy. The first patient had 8 febrile attacks over 16 months that differed from the pre-tonsillectomy episodes by the presence of abdominal symptoms. Originally, prednisone non-responder, in post-tonsillectomy relapse he responded fully to episodic prednisone administration. In the second patient, PFAPA-like episodes of lower frequency than before were managed successfully with antipyretics and occasional prednisone administration. At the most recent clinic visit 21 and 10 months from the relapse onset, respectively, both children had a prolonged afebrile period (5 and 6 months, respectively), suggesting upcoming remission.

Overview of the outcome

The median follow-up time was 25 months (2–60). The median disease duration at the time of the last follow-up was 8 months (6–57). Ninety-four patients (75%) were followed for longer than 12 months. Out of these, 46 patients (49%) reached the full remission, in 15 cases after tonsillectomy. There was no difference in the remission rate between patients who were untreated (n=13) and those who were taking episodic prednisone (n=18). Median disease duration prior to the PFAPA resolution was 17 months (8–58) in the whole remission group. Clinical characteristics of patients who reached remission did not differ from the rest of the cohort.

The remaining 48 patients followed for over 1 year continued to have recurrent PFAPA episodes. Their median disease duration was 45 months (range 18–72) from the onset to the last visit. Their clinical characteristics, namely the presence of other than oropharyngeal symptoms, did not differ from the remission group (data not shown). During the follow-up, none of them developed other diseases explaining their symptoms.

Discussion

The number of publications have raised awareness of PFAPA syndrome among paediatricians of various subspecialties and led to its better recognition. Although its aetiopathogenesis remains unclear and laboratory confirmation is not available, existing modification of clinical criteria and careful history have become the most important diagnostic factors. Since the establishment of the "fever clinic" as a part of the paediatric rheumatology service at our Department in 2004, the number of patients referred for recurrent fevers increased more than 10 times.

Unlike other studies, we report the so far largest single-centre experience with this generally most common periodic fever on the background of the wider spectrum of diseases. Since genetic testing had not been available in the Czech Republic, it was performed only in highly suspicious clinically cases at European laboratories mostly as a part of the EUROFEVER project (http://www.printo.it/eurofever/). Although we did not apply the recently suggested Gaslini diagnostic score (14), the genetic analysis in patients clinically suspected of hereditary disease yielded 48% positive results.

The diagnosis of PFAPA syndrome was based on the meticulous analysis of the medical history, clinical and laboratory data. Data were collected systematically as a part of a prospective study in patients attending our clinics. Patients were followed long-term, until achievement of disease remission. Therefore, the clinical data represent first-hand information. Majority of published series either combine retrospective chart review, physician or parent questionnaires and prospective clinic and/or telephone follow-up or do not fully describe data collection methodologies (15-18). Our report shows laboratory data in the paired fashion (febrile *versus* afebrile). In order to create as homogeneous as possible cohort, we excluded patients with PFAPA phenotype who exhibited features that might have suggested presence of other diseases. Therefore, children with, for example, abnormal concentration of IgA and/or IgD were excluded. Additionally, in all our patients, urine mevalonic acid was assessed in order to further reduce the risk of misdiagnosing HIDS. Immunoglobulin concentration is not systematically reported in the published series (14, 18) or has been performed in part of the patients only (5, 16, 17), while mevalonaturia is not mentioned in any of them.

Our patients exhibited similar age at onset as well as distribution of the main clinical features as in published series (Table II) (5, 6, 15-18). Abdominal pain was present in a relatively lower proportion of our patients (23%) than in others (5, 14). Also reports on headaches and arthralgia varied. This heterogeneity may be explained by the problematic reliability of reporting and interpreting pain and its localisation in toddlers. Normalisation of SAA levels in afebrile interval supported the idea of the benign nature of PFAPA syndrome in terms of the risk of amyloidosis (19). Our patients had similar extent of elevation of inflammatory parameters as in other studies. (5, 20-22).

Among therapeutic options reported in the literature, single-dose prednisone appears the most popular. In our cohort, it was used in over 60% of cases with generally high success rate. Its use in the published reports is summarised in Table II. We applied objective measures of efficacy assessment that were based on the interval to fever resolution and its subsequent maintenance. Based on these evaluations, the extent of response was defined as "full" or "partial". Methodology of efficacy evaluation varies among the published series. Our cut-off point for considering prednisone "fully effective" was fever decline within 12 hours from ingestion and maintenance of symptom-free period for at least 2 weeks and this was achieved by 83% of patients treated. This result cannot be directly compared to the published data where means and/or range of the time to fever resolution are presented. Nevertheless, prednisone led to fever defervescence within the mean of 10 (range 0.5–96) (16) or 2–24 hours (17). Some authors report the use of additional prednisone doses in case of insufficient response (5, 16, 17). The majority of our patients required only one prednisone dose to achieve the full response. We generally did not recom-

Table II. Characteristics of febrile episodes in children with PFAPA syndrome in different studies.

	Publication year	Study	n	Onset (m)	Time from O to R	F/U	Therapy						FH (n)
							Pred		TE		C	I	/
CO							n/%	Effect+	n/%	Effect+	n/%	Effect+	
Wurster *et al*.	2011	R	60	32	6.3 years	12–21 years	44/73	42	2/3	NA	CI 25/42 CO 2/3	12/1	6
Feder *et al*.	2010	R	105	39.6	33.2 months	NA	72/69	70	11/10	11	CI 26/25	7	NA
Tasher *et al*.	2006	R	54	23	NA	2.2 years	48/89	48	6/11	6	NA	NA	NA
Thomas *et al*.	1999	R/P	83	34	4.5 years	3.3 years	49/59	44	11/39	7	CI 8/29 CO 1/4	8/0	5
Padeh *et al*.	1999	R	28	50.4	⋆8 years	5.0 years	23/82	23	3/11	3	CI 10/36	◆10	NA
Król *et al*.	2013	P/R	125	23	17 months	25m (2.1 years)	77/62	72	18/14	18	CO 2/2	2	59

n: number of patients; Onset (m): age at disease onset in months; Time from O to R: time from onset to remission; F/U: follow-up; Pred: prednisone; TE: tonsillectomy; CI/CO: cimetidine/colchicine; n/%: number of patients/percentage of patients; Effect+: positive effect; FH (n): number of patients with positive family history.
⋆in 9 patients; ◆heterozygote for FMF.

mend repeated dosing without prior medical re-assessment in order to exclude infection. The well-known heterogeneity of the type and rate of corticosteroid side-effect occurrence does not allow to predict the highest safe long-term prednisone dosing in an individual patient. As PFAPA syndrome is a benign condition, the side-effect risk should be close to zero. Therefore, we believe that one single dose of prednisone around 1mg/kg at the typical PFAPA episode onset should be recommended in the frequency not exceeding 3–4 weeks. Using this regimen, none of our patients exhibited corticosteroid side-effects. Proportion of patients with shortening of afebrile intervals after prednisone (14%) was similar in some studies (16, 17), while others reported even a higher rate of increased febrile attack frequency (4).

The use of both colchicine and cimetidine has been reported in small numbers of children with variable efficacy difficult to interpret (5, 9, 17, 18). Only two of our prednisone non-responders received colchicine with promising results. The rate of disease resolution after tonsillectomy was very high, similar to published reports (5, 10, 15-17). The recently published meta-analysis has showed comparable effectiveness of both corticosteroids and tonsillectomy, but in long-term only tonsillectomy was effective (23).

Nearly half of the patients followed for over 1 year reached the full remission, suggesting favourable outcome, similarly to the reported series (18, 23). Proportion of spontaneous remission (28%) also did not differ from the published reports, where it ranged between 20–30%. Nevertheless, after the mean follow-up ranging between 2 and 6 years, there remained 57–63% of patients whose disease had not resolved (4, 5, 17), while our relevant number was 51%. The longest follow-up information published by Wurster *et al*. reported complete disease resolution in 50/59 patients whose disease lasted for the mean of 6.3 years (18). In 9 patients, symptoms persisted for up to 18.8 years, although these patients experienced remissions longer than 1 year and the overall frequency of episodes decreased. A few recent reports suggest possibility of PFAPA syndrome onset in adult patients (24, 25).

In comparison to other series (Table II) we observed a higher proportion of patients with positive family history. This result might support the possibility of yet unknown genetic background of PFAPA syndrome (26-28).

The results of this as well as other recent studies further support the common belief that PFAPA syndrome is a condition of benign nature. In case of typical presentation and sensible exclusion of other possible causes, the diagnosis of this relatively common syndrome appears straightforward. Nevertheless, conditions like immune deficiencies as well as inflammatory disorders and malignancies presenting with recurrent fever have to be carefully evaluated. A high degree of suspicion is needed in order to identify rare monogenic periodic syndromes, mainly in association with mevalonatekinase mutations and R92Q mutation of TNFRSF1A gene that can both present with PFAPA-like phenotype (14, 29).

Clinically sensible diagnostic algorithm of PFAPA syndrome includes careful medical history, detailed analysis of the disease presentations and laboratory tests to exclude other conditions and to confirm the full normalisation of inflammatory parameters. Prospective follow-up supplied with data from the parent-reported diary helps to evaluate treatment response as well as the overall disease outcome. Single-dose episodic prednisone should be offered as a first-line treatment with tonsillectomy as a second-line option in prednisone non-responders. Maintenance of normal findings in afebrile intervals, normal growth and development together with spontaneous tendency towards lowering episode frequency belong to the most important confirmatory features of PFAPA syndrome.

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