

## Concise report

**International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients****Michaël Hofer<sup>1,2</sup>, Pascal Pillet<sup>3</sup>, Marie-Madeleine Cochard<sup>1</sup>, Stefan Berg<sup>4</sup>, Petra Krol<sup>5</sup>, Isabelle Kone-Paut<sup>6</sup>, Donato Rigante<sup>7</sup>, Véronique Hentgen<sup>8</sup>, Jordi Anton<sup>9</sup>, Riva Brik<sup>10</sup>, Bénédicte Neven<sup>11</sup>, Isabelle Touitou<sup>12</sup>, Daniela Kaiser<sup>13</sup>, Agnès Duquesne<sup>14</sup>, Carine Wouters<sup>15</sup> and Marco Gattorno<sup>16</sup>****Abstract**

**Objectives.** The aims of this study were to describe the clinical features of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) and identify distinct phenotypes in a large cohort of patients from different countries.

**Methods.** We established a web-based multicentre cohort through an international collaboration within the periodic fevers working party of the Pediatric Rheumatology European Society (PReS). The inclusion criterion was a diagnosis of PFAPA given by an experienced paediatric rheumatologist participating in an international working group on periodic fever syndromes.

**Results.** Of the 301 patients included from the 15 centres, 271 had pharyngitis, 236 cervical adenitis, 171 oral aphthosis and 132 with all three clinical features. A total of 228 patients presented with additional symptoms (131 gastrointestinal symptoms, 86 arthralgias and/or myalgias, 36 skin rashes, 8 neurological symptoms). Thirty-one patients had disease onset after 5 years and they reported more additional symptoms. A positive family history for recurrent fever or recurrent tonsillitis was found in 81 patients (26.9%). Genetic testing for monogenic periodic fever syndromes was performed on 111 patients, who reported fewer occurrences of oral aphthosis or additional symptoms. Twenty-four patients reported symptoms (oral aphthosis and malaise) outside the flares. The CRP was >50 mg/l in the majority (131/190) of the patients tested during the fever.

**Conclusion.** We describe the largest cohort of PFAPA patients presented so far. We confirm that PFAPA may present with varied clinical manifestations and we show the limitations of the commonly used diagnostic criteria. Based on detailed analysis of this cohort, a consensus definition of PFAPA with better-defined criteria should be proposed.

**Key words:** PFAPA, child, autoinflammatory disease, recurrent fever, cohort.

<sup>1</sup>Paediatric Rheumatology Unit of Western Switzerland, Department of Paediatrics, CHUV, University Hospital of Lausanne, Lausanne, <sup>2</sup>Department of Paediatrics, HUG, Geneva, Switzerland, <sup>3</sup>Paediatric Rheumatology, Department of Paediatrics, Hôpital Pellegrin, Bordeaux, France, <sup>4</sup>Paediatric Rheumatology, University of Gothenburg, Gothenburg, Sweden, <sup>5</sup>Paediatric Rheumatology, Department of Paediatrics and Adolescent Medicine, Charles University, Prague, Czech Republic, <sup>6</sup>Paediatric Rheumatology, Department of Paediatrics, CEREMAI, CHU de Bicêtre, APHP, Paris SUD, Faculty of Medicine, Le Kremlin-Bicêtre, France, <sup>7</sup>Paediatric Rheumatology, Department of Paediatric Sciences, Università Cattolica Sacro Cuore, Rome, Italy, <sup>8</sup>CEREMAI (National Centre for Auto-Inflammatory Diseases), Department of Paediatrics, Hôpital Mignot, Versailles, France, <sup>9</sup>Paediatric Rheumatology, Department of Paediatrics, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain, <sup>10</sup>Paediatric Rheumatology, Meyer Children's

Hospital of Haifa Rambam Medical Center, Faculty of Medicine, Technion Haifa, Israel, <sup>11</sup>Paediatric Rheumatology, Hôpital Necker-Enfants Malades, Paris, France, <sup>12</sup>Unité Médicale des Maladies Auto-Inflammatoires, Hôpital A de Villeneuve, Montpellier, France, <sup>13</sup>Paediatric Rheumatology, Kantonspital, Lucerne, Switzerland, <sup>14</sup>Paediatric Rheumatology, Hôpital Femme-Mère-Enfant, Lyon, France, <sup>15</sup>Paediatric Rheumatology, Department of Paediatrics, University Hospital Leuven, Leuven, Belgium and <sup>16</sup>UO Pediatria 2, Rheumatology Unit, G. Gaslini Institute, Genoa, Italy.

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Correspondence to: Michaël Hofer, Paediatric Rheumatology, Department of Paediatrics, BH11-CHUV, CH-1011 Lausanne, Switzerland. E-mail: Michael.Hofer@chuv.ch

## Introduction

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is a recurrent fever syndrome diagnosed according to previously published criteria (supplementary Table S1, available at *Rheumatology* Online) [1–5] and clinician usually rely on these criteria. However, because PFAPA is not a well-defined disease and there are no specific confirmatory tests, the power of these criteria remains limited.

Since the first description by Marshall in 1987 [6], 10 cohorts with >25 PFAPA patients per cohort (supplementary Table S2, available at *Rheumatology* Online) have been published [1, 2, 5, 7–13] with different sets of diagnostic criteria. The clinical manifestations differed in frequency between the studies [14], suggesting that these cohorts may not represent exactly the same population of patients. In 2007 we created an international cohort to describe the complete clinical and laboratory spectrum of PFAPA syndrome and identify distinct phenotypes.

## Methods

We established a cohort (<http://www.pfapa.net>) with the participation of 15 centres from eight countries (supplementary Table S3, available at *Rheumatology* Online). Only physicians with expertise in the field of recurrent fever syndromes and PFAPA (publication or participation in an international working group) were allowed to participate.

The PFAPA patients were divided in complete cluster (all three cardinal symptoms) and incomplete cluster (one or two cardinal symptoms) groups. Exclusion of monogenic autoinflammatory (MAI) diseases was performed according to the centres' policy on clinical evaluation or molecular analysis. The previously published diagnostic criteria [1] were applied to our cohort and three distinct phenotypes were described: complete vs incomplete cluster, disease onset before vs after 5 years of age and patients who underwent genetic testing or not. Consecutive PFAPA patients were included using a web-based form (Access, Microsoft Corporation, Redmond, WA, USA) asking for demographic and clinical information, laboratory investigations, treatment and outcome. Only anonymous (de-identified) retrospective clinical data were entered. The Commission cantonale (VD) d'éthique de la recherche sur l'être humain, CHUV, Lausanne, Switzerland approved the study and the parents/caregivers gave their informed consent according to the local ethical regulations.

### Statistical methods

Ninety-five per cent CIs were calculated based on the Poisson distribution for the relative risk (RR) of reported symptoms comparing subgroups of patients (three distinct phenotypes).

## Results

From January 2007 to October 2009, 301 PFAPA patients were included: 161 boys and 140 girls (1.15 male/1 female); median age at inclusion, 6.8 years (range 0.5–34); median age at disease onset, 1.7 years (range 0.1–12); median age at diagnosis, 4.0 years (range 0.8–32). The median interval between fever attacks was 4 weeks (range 1–12) and the median duration was 4 days (range 1–10). By definition, all patients presented with at least one cardinal symptom (Table 1): pharyngitis (271, exudative 113), cervical adenitis (236, bilateral 205) and oral aphthosis (171). Additional symptoms were reported by 228 patients (Table 2): abdominal pain, arthralgias, myalgias and headache were present during all or most flares in the majority of the patients who reported them; the other symptoms occurred only in some flares.

A positive family history was reported in 81/301 patients [recurrent fever, 47; recurrent tonsillitis, 15; PFAPA, 11; FMF, 8]. In the eight patients with a family history of FMF, the clinical picture and genetic testing were non-contributory for FMF. Parents originated mainly from countries participating in the study (88% of the mothers and 86% of the fathers; supplementary Table S4, available at *Rheumatology* Online), which corresponds to the rate of foreigners living in European countries, suggesting the absence of a specific ethnic background for PFAPA. We are aware that the rates of foreign origin are only an estimate of the rates of children with different ethnic backgrounds.

According to the first of the current criteria [1], onset of fever flares should occur before age 5 years (supplementary Fig. S1, available at *Rheumatology* Online), which was not the case in 31 patients. Most of them (21/31) experienced their first symptoms before age 6 years. In the 31 patients with later disease onset, pharyngitis, aphthae, abdominal pain, diarrhoea, arthralgias and headache were more frequent, and vomiting, nausea and cervical adenitis less frequent (Tables 1 and 2).

Fifty-four patients (17.9%) reported only one cardinal symptom, 115 (38.2%) two symptoms and 132 (43.9%) all three symptoms; the latter, considered as a complete PFAPA cluster, was more often found in patients with disease onset after 5 years (Table 1). Patients with the complete cluster were more often girls [73/132 (52%)] than boys [59/132 (45%), RR=1.88, 95% CI 1.6, 2.2,  $P < 0.001$ ] (supplementary Fig. S2, available at *Rheumatology* Online) and presented more frequently with myalgias (24.4% vs 16.6%, RR=1.63, 95% CI 1.25, 2.0,  $P < 0.01$ ), arthralgias (34.6% vs 26.9%, RR=1.44, 95% CI 1.1, 1.77,  $P < 0.05$ ), osteoarticular symptoms (46.2% vs 32.5%, RR=1.78, 95% CI 1.45, 2.11,  $P < 0.001$ ), diarrhoea (22.5% vs 11.5%, RR=2.23, 95% CI 1.84, 2.62,  $P < 0.001$ ), abdominal symptoms (66.4% vs 53.6%, RR=1.71, 95% CI 1.39, 2.04,  $P < 0.001$ ) and skin rash (19.4% vs 7.7%, RR=2.87, 95% CI 2.45, 3.28,  $P < 0.001$ ).

In 145/301 patients, exclusion of MAI diseases was done only on a clinical basis. Genetic testing was done on 111 patients (36.9%) and was negative in 97 patients

TABLE 1 Frequency of the cardinal symptoms

Symptom	All tested (n = 301)	Genetically tested (n = 111)	Non-genetically tested (n = 190)	P-value	<5 years (n = 270)	≥5 years (n = 31)	P-value
Pharyngitis	271 (90)	93 (85)	178 (94)	P < 0.001	241 (90)	30 (97)	< 0.001
Cervical adenitis	236 (78)	87 (80)	149 (78)	ns (P > 0.50)	213 (79)	23 (74)	< 0.05
Oral aphthosis	171 (57)	70 (64)	101 (53)	P < 0.01	151 (56)	20 (65)	< 0.01
All three symptoms (complete cluster)	132 (44)	56 (51)	76 (40)	P < 0.001	115 (43)	17 (55)	< 0.001

Values are the number of patients (%). The frequency of the cardinal symptoms is shown in all 301 patients, in genetically tested vs non-genetically tested patients and in patients with disease-onset < 5 years vs ≥ 5 years. ns: not significant.

(supplementary Table S5, available at *Rheumatology* Online). In some centres, mevalonic aciduria was measured during fever flares and mevalonate kinase (MVK) deficiency (MKD) gene mutation analyses were performed in patients with positive results. Genetic testing was more frequently performed in patients with disease onset after 5 years [15/31 (48.4%), RR = 1.70, 95% CI 1.37, 2.03,  $P < 0.001$ ] than in patients with earlier disease onset [96/270 (35.6%)]. We compared the clinical presentation in patients who had genetic testing and patients without genetic testing (supplementary Fig. S2, available at *Rheumatology* Online).

In our cohort, 24 patients (8%) presented at least one symptom between flares: malaise (4) and aphthous stomatitis (20). These patients did not present any other symptoms, suggesting an alternative diagnosis such as Behçet's disease. All patients but one (height at  $-3$  s.d.) had normal growth.

CRP and neutrophil count showed a marked increase during fever flares. CRP was >30 mg/l in 155 patients, >50 mg/l in 131 and >100 mg/l in 77; outside the flare the median value was 5 mg/l, and only 12 patients had a level >10 mg/l. After a single dose of steroids (average dose 1 mg/kg) at fever flare onset, resolution of the fever occurred in 93/147 patients (63%), 46 (32%) were partially improved and only 8 (5%) were non-responders.

## Discussion

We report the largest cohort of PFAPA patients so far described, aiming to describe particular PFAPA phenotypes and to evaluate how expert paediatricians applied the current diagnostic criteria on a large number of patients. The modified Marshall's criteria remain highly unspecific [15], and the lack of consensus on the PFAPA definition is illustrated by differences in the criteria used in previously published cohorts [16]. The diagnosis of PFAPA is generally based on a number of variables (dramatic onset of attacks, lack of response to antibiotics, repetitive presence of cardinal symptoms and prompt response to steroids) that are much more complex than the mere satisfaction of the current diagnostic criteria. For these reasons, in order to avoid possible bias of selection, we considered expert opinion as the gold standard.

Since the complete cluster (all three cardinal symptoms) could represent the true typical PFAPA, we were surprised to see more additional symptoms reported. We can explain it by a better awareness of additional symptoms, such as pain, presented by these children, or by the increase in systemic symptoms in patients with more systemic inflammation. Based on our findings, we cannot challenge the current criteria, and conclude that more than one cardinal symptom is needed for the diagnosis [15].

In our cohort we reported disease onset before 5 years of age in 90% of patients [15]. There is no reason not to believe that the 31 patients with later-onset disease have PFAPA. A recently published observation of a series of PFAPA patients with adult-age onset [17] challenges the rationale for an age cut-off as a criterion. To record the

**TABLE 2** Frequency of different symptoms during flares among the 301 patients

	Present	Always	Often	Sometimes	≥ 5 years	P-value	RR (95% CI)
Abdominal symptoms (at least one of below)	176 (59)	52	56	68	23 (74)		
Pain	136 (45)	47 (15.8)	40 (13.5)	49 (16.5)	19 (61)	<0.001	2.45 (2.13, 2.78)
Vomiting	53 (18)	3 (1.0)	16 (5.4)	34 (11.5)	2 (6)	<0.001	0.31 (0, 0.71)
Nausea	32 (11)	2	11	19	1 (3)	<0.01	0.28 (0, 0.75)
Diarrhoea	48 (16)	3 (1.0)	10 (3.4)	35 (11.9)	6 (19)	<0.001	1.74 (1.32, 2.15)
Osteoarticular symptoms (at least one of below)	118 (39)	23	48	47	16 (52)		
Arthralgias	90 (30)	13 (4.4)	37 (12.5)	40 (13.4)	14 (45)	<0.001	2.20 (1.85, 2.55)
Myalgias	56 (20)	12	23	21	8 (26)	<0.01	1.59 (1.19, 1.99)
Arthritis	8 (3)	0	2	6	1 (3)	ns (>0.50)	1.30 (0.51, 2.08)
Headache	85 (29)	19	35	31	12 (39)	<0.05	1.72 (1.36, 2.07)
Skin rash	38 (13)	6 (2.0)	10 (3.4)	22 (7.4)	4 (13)	ns (>0.50)	1.59 (1.19, 1.99)
Conjunctivitis	16 (5)	0	2	14	2 (6)	ns (<0.30)	1.35 (0.75, 1.95)
Neurological symptoms	11 (4)	1	1	9	0 (0)	ns (>0.50)	0.00 (−0.69, 0.69)

Values are number of patients (%). ns: not significant.

exact date of disease onset may be difficult in young children with recurrent infections, and because of the long diagnostic delay (median 2.3 years). In our study, late-onset PFAPA patients showed a higher frequency of some symptoms, such as abdominal and osteoarticular pain. A higher pain reporting capability in older children can explain this difference, but also a selection bias, as patients not meeting the age criterion would need to be more convincing to the doctor. Since FMF and TNF receptor-associated periodic syndrome (TRAPS) may have a later onset, genetic testing was more frequently performed in this subgroup of patients. Our observation shows similar clinical features in PFAPA patients with later disease onset compared with other PFAPA patients, suggesting that age is not a reason to exclude the diagnosis. In any case, in patients with disease onset after 5 years of age, we recommend intensifying the search for other diagnoses, such as MAI, autoimmune disorders and malignancies.

Because of the strict periodicity of fever attacks described by Thomas *et al.* [1], only cyclic neutropenia was considered as an exclusion in the criteria [15]. Since a significant percentage of patients with MAI show regularly recurrent attacks [7], they represent a relevant differential diagnosis [3, 8]. MKD has the highest degree of clinical overlap with PFAPA [8], however, a PFAPA-like phenotype can also be observed in children with FMF and TRAPS [8, 18]. The patients who underwent genetic testing presented more additional symptoms, which could be a good reason for more frequent genetic testing. One of our patients was affected by MKD and 14 patients showed heterozygosis or polymorphisms in the *MEFV* or *MVK* gene. In a recent study on 94 *MEFV* heterozygous patients (mainly of Jewish or Arabic origin) with recurrent fevers, only 4 patients presented a clear PFAPA phenotype [18]. We believe that the exclusion of MAI should be included in a new version of the criteria. Recently a

diagnostic score based on the high frequency of specific clinical manifestations was shown to be able to distinguish those PFAPA-like patients at higher risk of carrying mutation of genes associated with inherited periodic manifestations [8].

In our cohort, the frequency of the different symptoms was similar to previously published studies [3, 8]. In the current diagnostic criteria, the description of the fever episodes is rather vague and the characteristics of the cardinal symptoms are not defined. The frequency and duration of fever and a minimal number of episodes were described but were not included in the original criteria [1]. In our opinion, a more detailed description of these variables in the criteria would help to better identify PFAPA patients.

The presence of high CRP is uncommon in viral infections of the respiratory tract, another important differential diagnosis of PFAPA. As reported previously [19], our results showed high CRP values during PFAPA flares, with normalisation between fever episodes in the vast majority of the patients, which strongly suggests PFAPA and should be included in the criteria.

Symptoms (mainly aphthae) were reported outside flares in 24 patients. In these patients a careful differential diagnosis should be carried out, in particular Behçet's disease. A good response to steroids, as confirmed in our cohort, may be used as an additional criterion for diagnosis. However, other MAI such as MVK may also respond well to this treatment.

Due to lack of consensus on precise classification criteria and the absence of a definite diagnostic marker, our study presents some limitations. We had to rely on the expert interpretation of current PFAPA criteria as a gold standard for the diagnosis. Every centre had its own policy for exclusion of MAI, leading to great variability, but there is currently no evidence on this and at the time of collection no low-risk score was present.

The periodicity of fever attacks was not recorded, and it was not clearly required in the diagnostic criteria. Finally, our cohort was recruited retrospectively to collect a relevant number of patients.

With this study we report the largest cohort of PFAPA patients published so far and we describe three distinct phenotypes. Previous studies have suggested the low specificity of the present PFAPA diagnostic criteria [8], and we attempted to verify their possible pitfalls, identify possible sources of misunderstanding and propose modifications. Even if paediatricians are able to recognize PFAPA patients, the absence of a validated classification is problematic for further evaluation of treatment efficacy and outcome. A classification system for PFAPA syndrome based on a consensus among experts followed by a validation process should be undertaken until we have a better knowledge of the aetiology of PFAPA syndrome.

#### Rheumatology key messages

- The large cohort of patients describes different periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome phenotypes.
- This study emphasizes the need for validated classification criteria for periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome.

*Disclosure statement:* The authors have declared no conflicts of interest.

### Supplementary data

Supplementary data are available at *Rheumatology* Online.

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