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Concise report

PFAPA syndrome is not a sporadic disease

Marie Cochard[1,2], Johanna Clet[3], Lan Le[1,2], Pascal Pillet[3], Xavier Onrubia[4], Thierry Guéron[4], Mohammed Faouzi[5] and Michaël Hofer[1,2]

Abstract

Objectives. To determine whether PFAPA (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) patients have a positive family history (FH) for recurrent fever syndromes.

Method. For all patients with PFAPA seen in two paediatric rheumatology centres (Romandy, Switzerland and Bordeaux, France), parents were interviewed to record the FH for periodic fever. As controls, we interviewed a group of children without history of recurrent fever.

Results. We recruited 84 patients with PFAPA and 47 healthy children. The FH for recurrent fever (without an infectious cause and recurring for at least half a year) was positive in 38/84 (45%), and was positive for PFAPA (diagnosis confirmed by a physician) in 10/84 (12%) of the PFAPA patients. For 29 of the 38 patients with positive FH, the affected person was a sibling or a parent. None of the healthy children had a positive FH for recurrent fever or PFAPA. A positive FH for rheumatological diseases was seen in both groups of children.

Conclusion. These data show that a significant percentage of PFAPA patients present a positive FH of recurrent fever and PFAPA. This familial susceptibility suggests a potential genetic origin for this syndrome.

Key words: Heredity, Child, Auto-inflammatory disease, Periodic fever.

CLINICAL SCIENCE

Introduction

PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) is a recurrent febrile disease first described in 1987 by Marshall *et al.* [1]. It is characterized by fever episodes, lasting for 3–6 days with a recurrence every 3–8 weeks, and accompanied by aphthous stomatitis, pharyngitis or cervical adenitis [2]. No specific diagnostic test for PFAPA is available and the diagnosis is based on published diagnostic criteria [2, 3]. The patient should not present any upper respiratory tract infection, must be totally asymptomatic between the episodes and present normal growth and development. Various febrile diseases should be excluded, like recurrent infections, immunodeficiency, Still's disease, haematological diseases and monogenic auto-inflammatory diseases [3].

Since the first description of PFAPA, no clear aetiology has been found and it is considered a sporadic disease [3–5]. The exact prevalence of this syndrome is not known but PFAPA seems to be far more frequent than other auto-inflammatory diseases [2, 3].

To better understand PFAPA syndrome, in 2007 we established a European registry with the participation of 8 countries and 14 rheumatological centres [6]. A preliminary analysis of the data showed a surprisingly high number of patients with a positive family history (FH) for recurrent fever. Based on this observation, we decided to investigate more precisely the FH of PFAPA patients in order to determine whether there is a familial predominance in this syndrome.

Patients and methods

From centres participating in the European PFAPA registry, we included all patients from Romandy ($n = 46$) and Bordeaux ($n = 39$). The patients were diagnosed according to previously published diagnostic criteria [2, 3].

[1]Pediatric Rheumatology, Department of Pediatrics, CHUV, Lausanne, [2]Department of Pediatrics, HUG, Geneva, Switzerland, [3]Pediatric Rheumatology, Department of Pediatrics, Hôpital Pellegrin, Bordeaux France, [4]Pediatric Practice, Châtel St-Denis and [5]Centre d'Epidémiologie Clinique, University Hospital Lausanne, Lausanne, Switzerland.

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Correspondence to: Michaël Hofer, Pediatric Rheumatology, Department of Pediatrics, BH11- CHUV, CH-1011 Lausanne, Switzerland. E-mail: michael.hofer@chuv.ch

All patients had recurring fever episodes with a median maximum temperature of 40°C, and at least one of the cardinal symptoms (pharyngitis, cervical adenitis and oral aphthosis); 35/84 presented all three symptoms. All patients were in a good general condition between the fever attacks and they showed normal growth and development. Monogenic auto-inflammatory diseases were excluded by clinical presentation, completed by laboratory tests if necessary. Genetic testing for common periodic fevers was performed by DNA sequencing of the most clinically relevant exons.

All parents were asked for the FH of the patient during a 5- to 10-min phone interview. Questions were asked following a questionnaire with a list of items: FH for recurrent fever (without an infectious cause and recurring for at least half a year), PFAPA syndrome (diagnosis confirmed by a physician), chronic inflammatory rheumatological diseases and psoriasis. When a question was answered positively, we asked for the family rank of the affected person and if the diagnosis was confirmed by a physician. We performed the same interview on children without a history of recurrent febrile attacks or chronic disease and who attended the consultation of one of the three paediatricians participating in the study. These children were randomly selected among those consulting for regular control of their development or an acute illness. The study was approved by our local ethics committee (Commission d'Éthique de la Recherche Clinique du CHUV) and the parents gave their informed consent for the study.

Statistical methods

Analyses were conducted using STATA 10.1 (Stata Corp., College Station, TX, USA). To examine bivariate associations between two variables, we used Fisher's exact test when the two variables were categorical, and a non-parametric Wilcoxon test if one was continuous and the second was categorical. The difference between FH-positive (FH^+) and FH-negative (FH^-) patients was analysed using logistic regression. Significant bivariate predictors ($P < 0.1$) were included in a multivariate logistic regression.

Results

We were able to contact the parents of 84 out of our 85 PFAPA patients and all agreed to answer the questions. The mean age at the time of the interview was 7.5 years (2–25 years) with a girl to boy ratio of 1 : 1.4 for the PFAPA patients; 6.9 years (4–13 years) and 1 : 1.35 for the 47 healthy children. Monogenic auto-inflammatory diseases were excluded by the clinical presentation in 64 patients and by genetic testing in 20 patients [Tumor necrosis factor receptor-associated periodic syndrome (TRAPS): 12; FMF: 14; HyperIgD syndrome: 3; Cryopyrin-associated periodic syndrome: 1].

A positive FH for recurrent fever was found in 38/84 (45%) of the PFAPA patients. In 29/38 (76%) of the patients, the affected family member was a sibling or parent. In 10/38 (26%) patients, the recurrent fever syndrome in the family member was diagnosed as PFAPA by a physician. In 3/38 (8%) patients a FMF was reported, and in 2 of them the father was affected and the PFAPA patient was heterozygous for M694V. In one of the patients with positive FH for FMF, the affected father and uncle were followed in childhood by the same paediatric rheumatologist, and the diagnosis was confirmed by genetic testing. In 25/38 (66%), the affected family member reported recurrent fever without an established diagnosis. Seven PFAPA patients had two family members with recurrent fever (PFAPA: one, FMF: two, recurrent fever: four). Among the 64 patients with PFAPA diagnosed by clinical presentation, the percentage of FH^+ 26/64 (41%) was lower than in the group of patients who had genetic testing, 12/20 (60%).

In the group of healthy children, the FH was completely negative for recurrent fever and PFAPA. A positive FH for rheumatological diseases (RA: 8; seronegative arthritis: 11; rhizomelic pseudopolyarthritis: 1; lupus: 2; scleroderma: 1; Hashimoto: 1) was found more frequently in the PFAPA patients [19/84 (23%)] than in the healthy children group [5/47 (11%)] (cf. Fig. 1), but the difference was not statistically significant. Psoriasis was found in equal proportion in both groups of children.

We analysed the origin of the parents of the FH^+ and FH^- patients and the healthy children: for the majority both parents originated from the country of living (France or Switzerland) in the three groups of children. We then evaluated whether FH^+ and FH^- patients could correspond to two distinct subsets of PFAPA (Fig. 2). Bivariate logistic regression did not show any significant difference in the age of onset, symptom duration, sex ratio, maximal

Fig. 1 Percentage of children with positive FH for PFAPA, recurrent fever and rheumatological diseases in PFAPA patients and in healthy children.

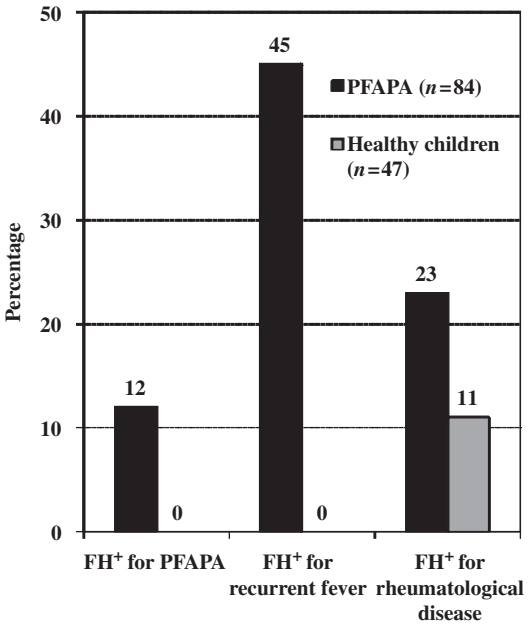
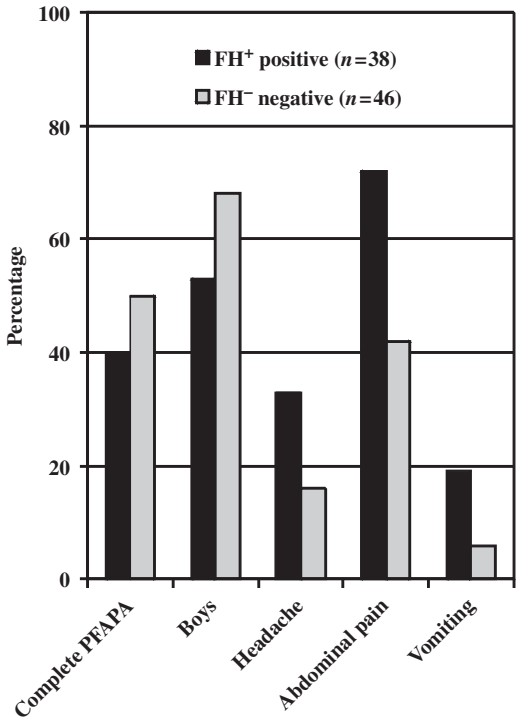


FIG. 2 Frequency of clinical features in FH^+ and in FH^- PFAPA patients. FH^+: patient with a FH of recurrent fever; FH^-: patient without FH of recurrent fever.



temperature during the fever episodes or presenting symptoms except for headache [Odds Ratio (OR) = 2.54, $P = 0.076$], abdominal pain (OR = 3.38, $P = 0.011$) and vomiting (OR = 3.46, $P = 0.089$). In the multivariate analysis, only abdominal pain was still significantly associated with FH^+. The frequency of the complete PFAPA cluster (presence of all three main clinical symptoms: pharyngitis, cervical adenitis and aphthous stomatitis) was similar in FH^+ (44.1%) and in FH^- (42.2%) patients.

Discussion

With this study, we show that nearly half of our PFAPA patients have a positive FH for recurrent fever. Most of these family members reported a recurrent fever of unknown origin similar in clinical presentation to the affected child, but in 10 patients the family member had an established diagnosis of PFAPA. In previous series of PFAPA patients no familial tendency for periodic fever was mentioned [3, 7], but three families with two siblings diagnosed with PFAPA were recently reported [8, 9]. The FH for recurrent fever was always negative in the healthy children suggesting that recurrent fever and PFAPA are not frequently found in the general population. Since in 76% of the FH^+ patients the affected relative was a parent or a sibling, it is very unlikely that a positive FH would have been missed in the healthy children. In contrast to recurrent fever, a FH for rheumatological diseases and psoriasis was positive in both PFAPA patients and healthy children. For rheumatological diseases, we found a trend of more frequent positive FH in PFAPA patients, but without a significant difference between the two groups. This observation may suggest that PFAPA patients show an increased susceptibility to inflammatory diseases, as we could also describe in an adult patient with both PFAPA and SpA (Cochard M *et al*., 2010, data not published).

PFAPA syndrome is one of the auto-inflammatory diseases with recurrent fever like TRAPS, FMF, Hyper-IgD syndrome, cryopyrin-associated periodic syndrome. A genetic origin was found for these diseases except for PFAPA, where no clear aetiology has been found so far [3]. In most of our patients, the clinical presentation was clear enough to confirm the diagnosis of PFAPA and genetic testing was performed in only a minority of the patients. The rate of positive FH was higher for this group of patients than for the group of clinically diagnosed patients, showing that despite laboratory exclusion of monogenic auto-inflammatory diseases there is still a high familial predominance for recurrent fever in PFAPA syndrome.

Our study showed some methodological limitations, because the diagnosis of PFAPA is based on clinical criteria and the low prevalence did not allow us to perform the study prospectively. Furthermore, FH has to rely on the memory of the person asked and may be incomplete owing to insufficient knowledge about the diseases presented by other family members. In our study, the FH was taken by a limited number of physicians and based on phone interviews performed in a limited period of time, ensuring data consistency. As discussed above, the majority of the affected family members were closely related to the patient, limiting the risk of inaccurate data. PFAPA syndrome usually has a benign long-term outcome; thus, expensive genetic testing in all patients is not justified. As positive FH is also markedly present in the patients tested genetically, we believe that the way in which patients were diagnosed did not bias the results of our study.

Interestingly, three of our PFAPA patients reported family members with FMF. In these patients, FMF could be excluded by the clinical presentation, genetic testing and outcome. The possible predisposition for PFAPA in the case of a heterozygous mutation of the *MEFV* gene has already been studied [10]. In a first paper, MEFV mutations were searched in for six unrelated children with PFAPA and the results argued against the involvement of MEFV in PFAPA syndrome [5]. Recently, Kone-Paut *et al.* [11] reported the clinical spectrum of 94 MEFV heterozygous patients with recurrent fever: 4 patients had typical features for PFAPA syndrome and 3 of them responded well to colchicine. The familial predominance of PFAPA was not related to a specific ethnic background in our cohort, suggesting that the origin of the family did not play a role in the susceptibility for the disease. We examined the profile of both FH^+ and FH^- PFAPA patients, to evaluate whether they correspond to two different subsets of PFAPA syndrome. For clinical presentation, gender repartition, and age of disease onset, both FH^+ and FH^- groups were similar; we only found a significant difference

for abdominal pain, which is a common symptom in PFAPA syndrome [12].

With this study, we show for the first time a familial susceptibility to PFAPA syndrome, suggesting a potential genetic origin. Therefore, our study reinforces the interest of further investigations on a genetic marker for PFAPA syndrome, which would represent a great help for diagnosis. Furthermore, if such a marker were available, studies on the effect of different therapies and on the long-term outcome could be performed on patients with a clear diagnosis of PFAPA.

Rheumatology key messages

- PFAPA syndrome is not a sporadic disease.
- A genetic origin for PFAPA syndrome is suspected.

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

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