
Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis in Chinese adult patients

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ABSTRACT

Objective. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a multifactorial autoinflammatory disease (AID), which mainly affects children. There have been hardly any cases reported concerning the Chinese population. We aimed to describe the first cohort of adult PFAPA patients in China.

Methods. We evaluated all the adult patients suffering from PFAPA syndrome diagnosed in our centre from April 2015 through March 2018. The patients were diagnosed clinically, and whole exome sequencing was performed in each patient to rule out monogenic AIDs.

Results. During the study period, a total of 9 adult patients (8 men, 1 woman) with PFAPA syndrome were diagnosed. They all had disease onset in adulthood, and the mean age at onset was 25.2 ± 9.5 years. The mean duration of attacks was 4.1 ± 1.0 days, and the mean interval between attacks was 6.2 ± 2.7 weeks. Apart from periodic fever, which was present in all patients, pharyngitis, cervical adenitis and aphthous stomatitis were present in 89%, 67% and 44% patients, respectively. Other common symptoms included fatigue (100%), headache (56%), and myalgia (55%). Inflammatory markers, except ferritin, increased during attacks and returned to normal afterwards. Glucocorticoids given at onset of attacks were effective, while colchicine and tonsillectomy were of no effect.

Conclusion. Our study is the first to suggest the presence of PFAPA syndrome in the Chinese adult population. Clinicians should take into account PFAPA syndrome when diagnosing patients suffering from recurrent fevers of unknown origin, especially those with pharyngitis, cervical adenopathy and aphthous stomatitis.

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a multifactorial autoinflammatory disease (AID), characterised by spontaneous flares of fever and cardinal signs described by the PFAPA acronym (1-4). The diagnosis is currently based on the modified Marshall's clinical criteria proposed in 1999 (1, 4, 5). Increasing evidence has shown that the disease can also arise during adulthood (1, 3, 6-10). However, Chinese cases of PFAPA syndrome have not been reported in the English literature so far. In this study, we described the clinical and laboratory features of the first cohort of adult patients with PFAPA syndrome in China.

Materials and methods

A total of 86 adult (>16 years old) patients suffering from recurrent fever of unknown origin were referred to our hospital from April 2015 to March 2018, who were diagnosed as having PFAPA syndrome according to the modified Marshall's criteria (5). The first item of this set of criteria requiring a disease onset before the age of 5 was neglected, and the last item requiring a normal growth and development was retrospectively met, as in previous studies (3, 11). Complete medical records were documented at diagnosis. Extensive workups were performed to rule out alternative diagnoses such as infections, autoimmune diseases and malignancy. Whole exome sequencing by Next Generation Sequencing was performed in each patient to rule out monogenic AIDs. This research was approved by the Institutional Review Board of Peking Union Medical College Hospital and performed according to the Declaration of Helsinki. Informed consent was obtained from all participants.

Table I. Summary of the clinical characteristics of the patients.

No.	1	2	3	4	5	6	7	8	9
Gender	M	F	M	M	M	M	M	M	M
Age at onset (years)	16	29	27	46	22	16	31	18	22
Age at diagnosis (years)	27	32	29	53	31	17	32	24	24
Ethnicity	Han	Han	Han	Han	Han	Han	Han	Han	Han
Family history	-	-	-	-	-	-	-	-	-
Duration of febrile attacks (days)	3	4.5	2	3.5	4	4.5	5	5	5
Frequency of attacks per year	6	20	12	5	12	12	8	6	12
Interval duration (weeks)	8.5	3.0	4.5	11.0	4.5	4.5	6.5	9.0	4.5
Peak temperature (°C)	39.0	39.5	38.5	40.0	39.5	40.0	39.0	39.5	40.0
Pharyngitis	+	+	+	+	+	-	+	+	+
Cervical adenitis	+	+	+	-	+	-	+	-	+
Aphthous stomatitis	+	-	-	-	+	+	-	-	+
WBC ($\times 10^9/L$)	11	15.3	18.6	12.1	15.4	15	13.1	10.3	12.4
ESR (mm/h)	30	94	16	38	23	37	19	25	10
hsCRP (mg/L)	131	75.9	74	25.3	9.3	23.8	90.2	85.8	13.3
TNF- α (pg/ml, normal range <8.1)	83.2	19.6	63.2	9.1	7.6	99.2	14.7	40.2	57.9
IL-6 (pg/ml, normal range <5.9)	8.1	26.1	27.7	6.5	2	34.3	2	10.5	23
Ferritin (ng/ml, normal range 24-336)	104	404	193	239	170	118	220	210	120

Results

Among the 86 patients, 9 were diagnosed as having PFAPA syndrome. For the remaining 77 patients, a diagnosis of monogenic AID was reached in 39 patients, including 13 familial Mediterranean fever, 10 NLRP12-autoinflammatory disease, 7 NLRP3-associated autoinflammatory disease, 5 tumour necrosis factor-receptor associated periodic syndrome, 1 Blau syndrome, and 3 Yao syndrome. Because all of these 39 patients had irregularly recurring fevers, none of them fulfilled the diagnostic criteria for PFAPA syndrome.

Among the 9 patients diagnosed as having PFAPA syndrome (Table I), 8 of them were male. All patients had disease onset in adulthood with no history of recurrent fever in childhood, and the mean age of onset was 25.2 ± 9.5 years. At the time of diagnosis, the mean age was 29.9 ± 9.9 years. All patients were of Chinese Han ethnicity and denied family histories of AIDs. Cultures of throat swabs during flares were negative for all patients with pharyngitis. No patient presented cyclic neutropenia and all were negative for mutations related to monogenic AIDs, including *MEFV*, *MVK*, *TNFRSF1A*, *NLRP3*, *NLRP4*, *NLRP12*, *TNFAIP3* and *NOD2* genes. None of the patients with aphthous stomatitis satisfied the 1990 or 2014 criteria for Behçet's disease.

In our cohort, the mean duration of febrile attacks was 4.1 ± 1.0 days, and the

mean number of attacks per year was 10.3 ± 4.7 episodes. The mean duration between attacks was 6.2 ± 2.7 weeks. All patients were asymptomatic during the inter-flare intervals. Apart from periodic fever, which was present in all patients, the three cardinal symptoms, pharyngitis, cervical adenitis and aphthous stomatitis, were present in 8, 6 and 4 patients, respectively. Three patients had all the 3 cardinal symptoms, another 3 patients had a combination of 2 symptoms, and the remaining 3 patients had only 1 symptom. Among the 8 patients with pharyngitis, physical examination during attacks showed erythematous pharyngitis in 6 patients and exudative pharyngitis in the other 2 patients. Two patients with cervical adenitis underwent lymph node biopsy, both of which revealed reactive hyperplasia. Other common symptoms included fatigue (100%), headache (56%), myalgia (56%), conjunctivitis (22%) and arthralgia (22%). No patient developed chest pain, abdominal pain or diarrhoea, periorbital oedema, skin rash, genital ulcer, or uveitis.

Laboratory investigations performed during attacks showed that all patients had mild leukocytosis; 6 patients had elevated erythrocyte sedimentation rate (ESR); all patients had elevated hypersensitive C-reactive protein (hsCRP); 8 patients had elevated tumour necrosis factor (TNF)- α ; 7 patients had elevated interleukin (IL)-6; Only 1 patient had

elevated ferritin. All the inflammatory markers were normal during the inter-flare intervals in every patient.

These 9 patients were prospectively followed up at our centre for a median of 35 months (25-46). All patients, except two, showed poor response to non-steroidal anti-inflammatory drugs. Therefore, glucocorticoids starting at onset of attacks (prednisone 1 mg/kg/day either as one dose or tapered in 3-5 days) were given in these 7 patients, which achieved rapid control of fever in 6 patients and partial response in 1 patient, without obvious increase in attack frequency. Colchicine was administered to 2 patients without response. Tonsillectomy had been performed after the disease onset in 2 patients with pharyngitis without effect.

Discussion

PFAPA syndrome has been considered a paediatric disease since the initial report by Vanoni *et al.* (5). However, numerous adult patients have been identified during the last decade, mainly in Italy (3, 9, 11), Israel (6) and Japan (8). Herein, we report the first Chinese adult cohort of PFAPA syndrome.

Besides the modified Marshall's criteria, we also applied three sets of recently published classification criteria to our cohort (3, 4, 12). In terms of the criteria proposed by Cantarini *et al.* (3) and by Gattorno *et al.* (12), only 1 patient, who solely suffered from aph-

thous stomatitis, could not be classified as PFAPA syndrome, highlighting the good applicability of both sets of criteria to the adult population. When the criteria by Vanoni *et al.* were applied (4), 3 patients could not fulfill the criteria, suggesting that this set of criteria might be too restrictive (4).

While there seems to be a slight male predominance in patients with PFAPA syndrome (2-5), the gender difference in our cohort was very striking. Whether this difference was due to the small sample size, more adult patients are needed. The age of onset in our cohort was about 25 years of age, which was very similar to the previous large cohorts (3, 6), suggesting that PFAPA syndrome might have a bimodal age distribution, one big peak around 2 years of age and the other small peak around 25 years of age (2). Although PFAPA syndrome is not the leading cause of recurrent fever of unknown origin in adults, it still constitutes a significant proportion both in our center (10.5%) and in an adult reference center (15.6%) in Spain (7).

The duration of attacks in our patients was similar to the adult cohort from Israel (6) and the paediatric cohorts, which was about 4 days (2, 5, 13), emphasising the transient nature of attacks in adults as well as in children. The durations of intervals between attacks in all large cohorts, both adult and paediatric were all ranging from 4-6 weeks, but many patients had symptom-free intervals for months (6, 8), possibly reflecting different stages of the disease. Regarding the 3 cardinal symptoms, pharyngitis was the most common and aphthous stomatitis was the least common, which was consistent with previous reports (2, 3). As a result, only a minority of patients (33%) presented all the 3 symptoms in our cohort, which was not significantly different from previous cohorts [40% (6)-47% (14)]. Erythematous pharyngitis was much more common than exudative pharyngitis (6 vs. 2) in our patients. This ratio

was higher than that of the paediatric cohort (158 vs. 113) (2), but much lower than that of an Italian cohort (23 vs. 0) (13). Indeed, Cantarini *et al.* found a protective role of exudative pharyngitis against the diagnosis of PFAPA syndrome (3). On the contrary, no patient in the adult cohort from Israel had erythematous pharyngitis (0 vs. 15) because their diagnostic criteria made exudative tonsillitis essential (6). More data are needed to explain this discrepancy. In terms of other symptoms, compared with a recent large Italian cohort (3), only the occurrences of arthralgia (22% vs. 72%) and abdominal pain (0% vs. 45%) were significantly different in our cohort. The use of whole exome sequencing to rule out monogenic AIDs as thoroughly as possible might partly explain the decreases in these frequencies.

During the attacks, all patients had at least 3 elevated inflammatory markers among white blood cell count, ESR, hsCRP, TNF- α , IL-6. However, the majority of them (89%) had normal ferritin level, suggesting that ferritin might serve as a useful marker to distinguish PFAPA syndrome from adult onset Still's disease. The efficacy of glucocorticoid is great across patients in different age groups (88-99%) (13), probably indicating the last common pathway in pathogenesis. The response rate of tonsillectomy was poor in our cohort, which was similar to previous reports in the adult population (14). During our follow-up, no other morbidities were identified in our cohort, suggesting a fairly good prognosis similar to paediatric patients (9).

In conclusion, we reported the first Chinese cohort of adult patients suffering from PFAPA syndrome. Their phenotypes were generally similar to the previous adult cohorts. The emerging population of adult-onset PFAPA syndrome calls for both increased clinical awareness and for enhanced clinical research leading to a unified classification criteria.

References

1. VIGO G, ZULIAN F: Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA). *Autoimmun Rev* 2012; 12: 52-5.
2. HOFER M, PILLET P, COCHARD MM *et al.*: International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. *Rheumatology* (Oxford) 2014; 53: 1125-9.
3. CANTARINI L, VITALE A, SICIGNANO LL *et al.*: Diagnostic criteria for adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. *Front Immunol* 2017; 8: 1018.
4. VANONI F, CAORSI R, AEBY S *et al.*: Towards a new set of classification criteria for PFAPA syndrome. *Pediatr Rheumatol Online J* 2018; 16: 60.
5. THOMAS KT, FEDER HM, LAWTON AR *et al.*: Periodic fever syndrome in children. *J Pediatr* 1999; 135: 15-21.
6. PADEH S, STOFFMAN N, BERKUN Y: Periodic fever accompanied by aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome) in adults. *Isr Med Assoc J* 2008; 10: 358-60.
7. HERNÁNDEZ-RODRÍGUEZ J, RUÍZ-ORTIZ E, TOMÉ A *et al.*: Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center. *Autoimmun Rev* 2016; 15: 9-15.
8. KUTSUNA S, OHMAGARI N, TANIZAKI R *et al.*: The first case of adult-onset PFAPA syndrome in Japan. *Mod Rheumatol* 2016; 26: 286-7.
9. VITALE A, ORLANDO I, LOPALCO G *et al.*: Demographic, clinical and therapeutic findings in a monocentric cohort of adult patients with suspected PFAPA syndrome. *Clin Exp Rheumatol* 2016; 34 (Suppl. 102): S77-81.
10. CAVUOTO M, BONAGURA VR: Adult-onset periodic fever, aphthous stomatitis, pharyngitis, and adenitis. *Ann Allergy Asthma Immunol* 2008; 100: 170.
11. CANTARINI L, VITALE A, BARTOLOMEI B *et al.*: Diagnosis of PFAPA syndrome applied to a cohort of 17 adults with unexplained recurrent fevers. *Clin Exp Rheumatol* 2012; 30: 269-71.
12. GATTORNO M, HOFER M, FEDERICI S *et al.*: Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis* 2019; 78: 1025-32.
13. RIGANTE D, VITALE A, NATALE MF *et al.*: A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. *Clin Rheumatol* 2017; 36: 463-8.
14. CATTALINI M, SOLIANI M, RIGANTE D *et al.*: Basic characteristics of adults with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome in comparison with the typical pediatric expression of disease. *Mediators Inflamm* 2015; 2015: 570418.