Demographic, clinical and therapeutic findings in a monocentric cohort of adult patients with suspected PFAPA syndrome

A. Vitale[1], I. Orlando[1], G. Lopalco[2], G. Emmi[3], M. Cattalini[4], B. Frediani[1], M. Galeazzi[1], F. Iannone[2], D. Rigante[5], L. Cantarini[1]

[1]*Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy;*
[2]*Interdisciplinary Department of Medicine, Rheumatology Unit, University of Bari Aldo Moro, Bari, Italy;*
[3]*Department of Experimental and Clinical Medicine, University of Florence, Italy;*
[4]*Paediatric Clinic, University of Brescia and Spedali Civili di Brescia, Italy;*
[5]*Institute of Paediatrics, Università Cattolica Sacro Cuore, Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy.*

Antonio Vitale, MD
Ida Orlando, MD
Giuseppe Lopalco, MD
Giacomo Emmi, MD, PhD
Marco Cattalini, MD, PhD
Bruno Frediani, MD, PhD
Mauro Galeazzi, MD, PhD
Florenzo Iannone, MD, PhD
*Donato Rigante, MD, PhD**
*Luca Cantarini, MD, PhD**

**These authors equally contributed to this manuscript.*
Please address correspondence to:
Luca Cantarini, MD, PhD,
Rheumatology Unit,
Policlinico "Le Scotte",
University of Siena,
viale Bracci 1,
53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com

Received on December 19, 2015; accepted in revised form on June 1, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 102): S77-S81.

Key words: PFAPA syndrome, autoinflammation, prednisone, tonsillectomy.

Competing interests: none declared.

ABSTRACT

Objective. *Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome is a non-Mendelian autoinflammatory disorder until now considered to be specifically limited to paediatric age. Recently, an increasing number of reports seems to suggest that PFAPA syndrome, diagnosed by the Marshall criteria revised by Thomas et al., can also affect adults.*

Methods. *The Marshall/Thomas criteria have been applied to 989 adult patients presenting for recurrent fever episodes: all patients enrolled were reviewed for demographic, clinical, and therapeutic data. Infectious, neoplastic, autoimmune and other autoinflammatory diseases were ruled out.*

Results. *We identified 30 adult patients (19 males, 11 females) with a suspected PFAPA syndrome: their mean age at disease onset was 33.75±14.01 years, mean age at diagnosis 39.1±14.39 years, and mean body temperature peak 39.5±0.7°C. In addition, the mean frequency of febrile episodes was 11.58±8.97 per year. More precisely, patients complained of pharyngitis (77%), cervical adenitis (73%), asthenia (63%), arthralgia (67%), oral aphthosis (50%), myalgia (54%), cephalalgia (43%), abdominal pain (27%), nausea/vomiting (17%), periorbital pain (17%), and arthritis (10%). Six out of 30 (20%) patients had suffered from PFAPA syndrome also during childhood, and the disease had reappeared in adulthood.*

Conclusion. *We provide the largest monocentric cohort of patients diagnosed with a suspected PFAPA syndrome in adulthood confirming that this syndrome can occur also during adulthood; moreover, due to the medical history of our patients and based on our experience, PFAPA syndrome might relapse during adulthood after a temporary remission reached in the course of paediatric age.*

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome is a clinical entity firstly recognised in 1987 by Marshall *et al*. (1). To date, PFAPA syndrome has been included among polygenic autoinflammatory diseases along with other systemic inflammatory conditions such as Still's disease and Behçet's disease (2).

From a clinical point of view, PFAPA syndrome is characterised by self-limited febrile inflammatory flares, typically occurring before the age of five years. Fever episodes arise abruptly every 3–8 weeks with temperatures reaching 40°C, and lasting from 3 to 6 days. In addition to symptoms identified by the acronym PFAPA, also headache, joint pains, myalgia, nausea, vomiting and abdominal discomfort can be encountered (3-5). Notably, subjects are typically healthy between PFAPA episodes and growth is not involved in children. Since there are no laboratory diagnostic tests, the clinical diagnosis of PFAPA syndrome is established according to the Marshall criteria, which were modified by Thomas *et al.,* when other causes of recurrent fevers have been excluded, such as infections, immune deficiencies, neoplasms, autoimmune, and other monogenic autoinflammatory diseases. The overall prognosis is excellent, as the syndrome usually resolves during puberty (1, 6).

PFAPA clinical manifestations promptly respond to single doses of corticosteroid. Nevertheless, the use of steroids can increase the frequency of attacks in some patients. Cimetidine can represent an additional therapeutic choice, while tonsillectomy has proved to be a feasible option when the described pharmaceutical approach is unsatisfactory (7). In the past, PFAPA syndrome has been relegated to the paediatric world, so much that the onset before

the age of five years counted for a diagnostic item. However, an increasing number of cases arisen in adulthood have been recently described, suggesting that this syndrome could also affect adults (8-10).

To the best of our knowledge, to date, 43 patients with adult-onset PFAPA syndrome have been described, with an average age at onset ranging between 21 and 26 years. Although similarities between paediatric and adult patients are evident, some differences have been occasionally identified and discussed: myalgias, arthralgias and asthenia appear to have a higher rate in adults, while aphthae and chills are less common. Moreover, corticosteroids seem to be less effective in adult patients, although in most subjects they lead to a complete response (11-14). However, high rates of musculoskeletal complaints and low occurrence of oral aphthosis have also been reported in large series of paediatric patients, making less clear the identification of clinical differences between children and adults (6, 15).

We herein describe a cohort of 30 adult patients fulfilling the Marshall/Thomas criteria (1, 6), pointing up their demographical, clinical and therapeutic features.

Patients and methods

The Marshall criteria modified by Thomas *et al*. (1, 6) were applied to 989 consecutive patients presenting for recurrent fever episodes in the Interdepartmental Research Centre of Systemic Autoimmune and Autoinflammatory disease of the University of Siena in the period between January 2007 and September 2015. In order to apply the Marshall criteria in adults, we neglected the item of disease onset before the age of five, and investigated whether patients had presented normal growth and development during childhood.

Based on these assumptions, after all causes of periodic fevers were excluded, the Marshall criteria adapted for adults were applied to 989 consecutive patients visited in our Centre. In addition to the Marshall criteria, patients with no other fever-related diseases had to meet the following criteria: i) at least 6 months of disease duration; ii) at least 5 recurrent flares during the last year; iii) minimum body temperature of 38.5 C during febrile episodes; iv) duration of flares between 4 and 12 days. Table I shows the clinical criteria for diagnosing PFAPA syndrome in paediatric patients. All adult patients were over 16 years.

Patients fulfilling inclusion criteria were reviewed for demographic, clinical and therapeutic data collected at the first visit and during subsequent follow-up evaluations. Among other data, we searched for the age at disease onset, fever characteristics, the presence of cardinal signs (oral aphthosis, pharyngitis, and cervical adenitis) or additional clinical manifestations, the occurrence of PFAPA-related symptoms during childhood, the response to different treatments (corticosteroids, nonsteroidal anti-inflammatory drugs or NSAIDs, paracetamol/acetaminophen, colchicine, anti-interleukin-1 or anti-IL-1 agents), dosages employed, and the response to tonsillectomy, if performed.

Infectious, autoimmune, and neoplastic diseases were ruled out. In addition, these selected patients did not meet criteria for other autoinflammatory diseases, and were negative for mutations related to *MEFV* (exons 2, 3, 5, 10), *TNFRSF1A* (exons 2, 3, 4, 6), *NLRP3* (exon 3), and *MVK* (exons 2-11) genes, respectively responsible for familial Mediterranean fever (FMF), tumour necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic fever syndrome, and mevalonate kinase deficiency. Mutations were searched by amplification of genomic DNA using polymerase chain reaction and then performing direct sequencing.

Regarding the definition of response to treatments, complete response was defined as temporary total fever control for NSAIDs or paracetamol and total and sustained disappearance of all symptoms within a few hours for corticosteroids and anti-IL-1 agents. For colchicine, complete response was defined as the lack of recurrences following chronic administration at the dose of 1 mg/day. Instead, partial response was defined as partial reduction of fever within a few hours for NSAIDs and paracetamol and remarkable improvement of all symptoms with no complete disappearance of clinical manifestations within a few hours after corticosteroids and anti-IL-1 agents. For colchicine, partial response indicated lengthening of asymptomatic intervals and reduction in symptom severity. Failure of treatment was defined as no amelioration after drug administration.

Results

Thirty out of 989 (19 males and 11 females) patients met the Marshall criteria and showed a clinical picture resembling PFAPA syndrome. Twenty-nine patients were Italians, 1 patient came from Morocco. No patient had a positive family history for recurrent fevers of unknown origin. Fever episodes lasted less than five days in 10 patients (33%), between five and ten days in 9 cases (30%), and more than ten days in 11 (37%).

In all, except 1 patient, onset of symptoms occurred after the age of 16 years. The only patient with paediatric onset reported start of symptoms when he was 14-year-old; however, when the patient was enrolled in the study he was 25-year-old and PFAPA manifestations still persisted. Notably, this patient had complained with PFAPA symptoms also during his infancy, which temporarily disappeared after tonsillectomy. Based on medical history, further 5 out of 30 patients had complained from PFAPA-related symptoms also during childhood, later followed by a long-term resolution (about 10 years). Table II provides further clinical and demographic data of the enrolled cohort of patients.

With regard to clinical manifestations, 9/30 patients (30%) had all three cardinal PFAPA signs, 11/30 (37%) complained from a combination of two out of three signs, and 10/30 (33%) showed only one cardinal sign during fever episodes. Among patients with pharyngitis, no one presented exudative pharyngitis. Clockwork periodicity was identified in only 2 patients (7%). No symptoms were reported during the inter-febrile periods. None of the patients had complained any growth delay during childhood. Table II shows the frequency of each cardinal sign and additional symptoms reported by patients.

Table I. Diagnostic criteria for PFAPA syndrome created by Marshall *et al*. and revised by Thomas *et al*. in children. The first item was ignored in our adult patients; the fifth item was investigated retrospectively.

1) Regularly recurring fevers with an early age of onset (<5 years of age)
2) Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
   a) Aphthous stomatitis
   b) Pharyngitis
   c) Cervical lymphadenitis
3) Exclusion of cyclic neutropenia
4) Completely asymptomatic interval between episodes
5) Normal growth and development

Table II. Clinical manifestations observed in our cohort of patients and in previously reported cohorts of paediatric patients. Abbreviation: SD, standard deviation.

Clinical manifestations	Frequency (%) in the present study	Frequency (%) in Hofer's study (5)	Frequency (%) in Thomas' study (6)
Age at inclusion (years), mean±SD	39.1 ± 14.4	6.8	8.9
Age at disease onset (years)	33.75 ± 14.01	1.7	-
Age at diagnosis, mean±SD (years)	39.1 ± 14.39	4.0	-
Frequency of febrile episodes per year, mean±SD	11.58 ± 8.97	-	10.0
Body temperature peak (°C), mean±SD	39.5 ± 0.7°C	-	40.3
Oral aphthosis	15 (50)	57	67
Pharyngitis	23 (77)	90	65
Cervical adenitis	22 (73)	78	77
Asthenia	19 (63)	-	-
Abdominal pain	8 (27)	59	45
Nausea/vomiting	5 (17)	11	52
Thoracic pain	6 (20)	-	-
Cephalalgia	13 (43)	29	-
Arthralgias	20 (67)	30	-
Arthritis	3 (10)	3	-
Myalgia	16 (53)	20	-
Periorbital pain	5 (17)	-	-
Conjunctivitis	4 (13)	5	-
Skin rash	5 (17)	13	-
Genital aphthosis	0 (0)	-	-

Overall, 6/30 patients (20%) had presented PFAPA-related symptoms during childhood: the PFAPA picture disappeared in 5, being followed by long-term resolution (about 10 years); the remaining patient with paediatric onset of PFAPA manifestations continued to have recurrent symptoms until diagnosis of PFAPA syndrome at 25 years. Two out of these 6 patients had undergone tonsillectomy in the paediatric age, obtaining the disappearance of symptoms in 1 case. Three further patients with onset in adulthood underwent tonsillectomy during adulthood, and disease resolution was obtained in 1 case (33%). Additional 8/30 patients (47%) had suffered from recurrent tonsillitis during childhood, but establishing in an unambiguous way whether they suffered from PFAPA syndrome during childhood was not possible by our retrospective data collection. However, 4 of them required tonsillectomy (with success in half of them). Laboratory investigations showed increased eritrocyte sedimentation rate, C-reactive protein, and serum amyloid-A during flares, which turned to normal values during interfebrile periods.

Fever episodes had been treated with NSAIDs in 12 patients (40%), leading to complete response in 5 patients (42%), partial fever control in other 5 cases (42%), and failure in 2 (16%). Paracetamol (acetaminophen) also allowed complete fever control in all 4 patients treated. In addition, colchicine, administered in 3 patients (10%), brought about symptom control in 2 cases (67%). Low-to-medium dose corticosteroids (prednisone up to 0.5 mg/kg/day and methylprednisolone up to 0.6 mg/kg/day) were administered to 18 patients (60%), bringing about complete response in 9 patients (50%) and partial response in 6 (33%). One patient had been treated with IL-1 inhibitors, proving a complete and sustained clinical response with both anakinra and canakinumab (12, 16). Table III provides detailed information about therapies administered to these patients.

Discussion

Although PFAPA syndrome has a typical onset during childhood, an increasing number of reports has recently shown that onset may potentially occur during adulthood (5, 8, 9). We have herein confirmed the occurrence of adult-onset PFAPA-like syndrome, providing the largest cohort of patients from a single centre. In particular, during the last 8 years we identified 30 patients fulfilling Marshall criteria adapted for adulthood and not meeting other clinical criteria for fever-inducing disorders, such as Still's disease, Behçet's disease, or any idiopathic febrile disorder. Noteworthy, all patients had undergone genetic testing in order to rule out mutations in the *MEFV*, *TNFRSF1A, NLRP3*, and *MVK* genes and no patient fulfilled the Livneh or Tel Hashomer criteria for a clinical diagnosis of FMF (17, 18). Consequently, the age criterion pointed out in the Marshall criteria (1, 6) should be scaled down, and physicians should take into account PFAPA syndrome also when PFAPA-like manifestations occur after the age of 5.

Although in some studies arthralgia and myalgia are reported more frequently in adults, while aphthosis more frequently in children (6, 8), to date the identification of differences between children and adults has not been definitely clarified. Comparing our data to some previously reported data on children, we highlight that oral aphthosis, cervical adenitis, abdominal pain, nausea, and skin rash seem to be more frequent in children, while pharyngitis, arthralgia and myalgia more frequent in adults (6, 8, 19). Clockwork periodicity, a nodal point for diagnostic purposes in children (6),

Table III. Treatments used and clinical outcome in patients with PFAPA syndrome. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol efficacy was evaluated in relationship with fever control; conversely, efficacy of colchicine, corticosteroids, and anti-interleukin-1 agents was evaluated with clinical control of all symptoms and inhibition of relapses.

	Drug administered (dosage)	Number of patients	Clinical output (%)
NSAIDs	Ibuprofen 400 mg OD	1	CFC (100)
	Ketoprofen 80 mg OD	1	CFC (100)
	Indomethacin 50 mg OD	2	CFC (100)
	Acetylsalicylic acid 400 mg OD	1	CFC (100)
	Other NSAIDs not determined	7	5 PFC (42) 2 F (16)
Antipyretic	Paracetamol 1000 mg OD	4	CFC (100)
Cytoskeleton inhibitor	Colchicine (1 mg/day)	3	2 CR (67) 1 PR (33)
Corticosteroids	Prednisone (25 mg/day)	9	3 CR (38) 4 PR (50) 1 F (13) 1 Not determined
	Methilprednisolone (16-40 mg)	8	5 CR (63) 2 PR (25) 1 Not determined
	Betamethasone (1 mg)	1	1 CR (100)
Anti-interleukin-1 agents	Anakinra (100 mg/day)	1	CR for 24 months
	Canakinumab (150 mg/8 weeks)	1	CR

CFC: complete fever control; CR: complete response; F: failure(s); OD: on demand; PFC: partial fever control; PR: partial response.

has been identified only in a few adults, while exudative pharyngitis, another frequent manifestation of PFAPA syndrome in children, has never been described in our cohort of patients. These findings induce to speculate that regular periodicity is not so typical when PFAPA syndrome occurs in adults.

Regarding treatment approaches, prednisone (1–2 mg/kg) or betamethasone (0.1–0.2 mg/kg) were successfully used during febrile episodes, leading to fever abortion in a few hours and representing the most effective therapy for PFAPA patients. Although corticosteroids did not bring about the complete response in all cases, this was probably related to the insufficient doses administered that were far from the optimal dosage required according to body weight. Accordingly, the only patient unresponsive to prednisone administration was obese; moreover in this case we could not increase steroid dose because of uncontrolled hypertension and palpitations while on corticosteroids. Nevertheless, 7 out of 9 patients treated with 25 mg/day of prednisone showed either a complete or a partial response, and similar results were obtained administering methylprednisolone. Instead, in 2 patients who received corticosteroids the response was not determined because of loss at follow-up and poor compliance, respectively.

NSAIDs and paracetamol (acetaminophen) were often effective in controlling fever in our adult patients, but other accompanying symptoms were less responsive to NSAIDs. These findings are in accordance with previously reported data in paediatric patients: Wurster *et al*. noted that NSAIDs are characterised by slight-to-high effectiveness in 44 out of 52 PFAPA patients, while complete inefficacy was observed in only 15.4% of cases (19). Also, according to the Eurofever Registry, a complete effectiveness of NSAIDs as monotherapy was proved in only 1 patient, while they induced a partial response in 21 out of 28 patients (20).

Notably, in our experience, chronic administration of colchicine prevented from disease recurrences in 2 out of 3 patients, though it induced lengthening of asymptomatic intervals as well as reduction of symptom severity in the third patient. Of note, similar results were obtained in the Eurofever Registry that identified a complete response in 3 out of 5 patients treated with colchicine and a partial response in 2 (20). A prophylactic effect of colchicine has been hypothesised, as it has shown to increase the interval between febrile episodes in 8 out of 9 PFAPA patients (21).

Noteworthy, in order to avoid corticosteroid-induced side effects, we administered anti-IL-1 agents in 1 patient with PFAPA flares occurring twice monthly and responsive to short courses of prednisone, but not to tonsillectomy: this patient showed a prompt and sustained clinical remission, and inflammatory markers dropped down to normal values. Specifically, after 24 months of treatment anakinra showed a loss of efficacy following a temporary withdrawn. Nevertheless, the introduction of canakinumab was able to induce a complete disease control again (12, 16).

In this context, we confirm that therapy for PFAPA patients should be tailored according to the specific clinical history and picture, and that treatment should firstly include less toxic and cheap choices. However, in selected cases IL-1 inhibition might represent a potential option to try.

Among treatments, tonsillectomy has been considered useful in PFAPA patients, especially if unresponsive to medical treatment: however, the role of tonsillectomy in this syndrome remains controversial, as wide differences have been highlighted in terms of efficacy among different studies and efficacy has also been found comparable to the standard medical treatment (22). To date, actual data suggest that surgery should be taken into account in patients with steroid-induced side effects or in the absence of drug alternatives (14). In adult patients current evidences seem to suggest that tonsillectomy is less useful than in childhood. Indeed, basing on the 43 PFAPA patients to date reported, the response to surgery was prompt and complete in only 1/17 patients undergoing tonsillectomy, while other 2 patients showed simply a partial response. In our cohort of patients, complete effectiveness was observed in 1 out of 3 patients undergoing surgery during

adulthood. Conversely, 2 out of 6 patients with PFAPA-related symptoms during childhood required tonsillectomy, and only 1 experienced a complete resolution after surgery. Nevertheless, despite a long-term benefit, the disease relapsed over time. This seems to corroborate the recent hypothesis according to which tonsillectomy can be provisionally effective on one hand, but may lead to transient efficacy on the other, with the reappearance of disease years later (14, 23).

Regarding the question of reoccurrence of PFAPA syndrome over time, we also identified 8 additional patients with recurrent tonsillitis during childhood; we could not however establish whether they had a real PFAPA syndrome because of the lack of reliable data. Therefore, the possible PFAPA reoccurrence in adulthood is an interesting issue deserving further investigation by means of long-term prospective studies based on *ad hoc* registries.

The retrospective design of our investigation and the application of the Marshall criteria represent the most relevant limitations of this present study. In particular, the Marshall criteria are tailored for paediatric patients, and the design of the present study required ignoring the first item of these criteria, investigating whether patients had presented any type of growth impairment during childhood (1, 6). For these reasons a new set of classification criteria should be created and validated for adult patients in order to identify more precisely PFAPA syndrome.

In conclusion, we provide the largest monocentric cohort of patients diagnosed with a suspected PFAPA syndrome in adulthood, confirming previous data on the possible onset of this clinical entity in adults. In addition, we speculate that PFAPA syndrome might relapse during adulthood after a temporary remission reached in the paediatric age. On this issue and on the role of tonsillectomy as a provisional therapeutic solution further long-term prospective studies based on *ad hoc* registries are needed. However, based on current knowledge and experience, we cannot definitely assert that paediatric and adult-onset PFAPA syndrome represent the same clinical entity. For this reason, future studies should clarify pathogenetic mechanisms sustaining adult-onset PFAPA and identify similarities and differences with paediatric patients.

References

1. MARSHALL GS, EDWARDS KM, BUTLER J, LAWTON AR: Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. *J Pediatr* 1987; 110: 43-6.
2. KRASZEWSKA-GŁOMBA B, MATKOWSKA-KOCJAN A, SZENBORN L: The pathogenesis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome: a review of current research. *Mediators Inflamm* 2015; 2015: 563876.
3. TASHER D, SOMEKH E, DALAL I: PFAPA syndrome: new clinical aspects disclosed. *Arch Dis Child* 2006; 91: 981-4.
4. FEDER HM, SALAZAR JC: A clinical review of 105 patients with PFAPA (a periodic fever syndrome). *Acta Paediatr* 2010; 99: 178-84.
5. 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.
6. THOMAS KT, FEDER HM JR., LAWTON AR: Periodic fever syndrome in children. *J Pediatr* 1999; 135: 15-21.
7. BURTON MJ, POLLARD AJ, RAMSDEN JD, CHONG LY, VENEKAMP RP: Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). *Cochrane Database Syst Rev* 2014; 9: CD008669.
8. 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.
9. CANTARINI L, VITALE A, BARTOLOMEI B, GALEAZZI M, RIGANTE D: Diagnosis of PFAPA syndrome applied to a cohort of 17 adults with unexplained recurrent fevers. *Clin Exp Rheumatol* 2012; 30: 269-71.
10. KUTSUNA S, OHMAGARI N, TANIZAKI R *et al.*: The first case of adult-onset PFAPA syndrome in Japan. *Mod Rheumatol* 2016; 26: 286-7.
11. CAZZATO M, NERI R, POSSEMATO N, PUCCINI R, BOMBARDIERI S: A case of adult periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome associated with endocapillary proliferative glomerulonephritis. *Clin Rheumatol* 2013; 32: S33-6.
12. CANTARINI L, VITALE A, GALEAZZI M, FREDIANI B: A case of resistant adult-onset periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome responsive to anakinra. *Clin Exp Rheumatol* 2012; 30: 593.
13. 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.
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 paediatric expression of disease. *Mediators Inflamm* 2015; 2015: 570418.
15. BERKUN Y, LEVY R, HURWITZ A *et al.*: The familial Mediterranean fever gene as a modifier of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome. *Semin Arthritis Rheum* 2011; 40: 467-72.
16. LOPALCO G, RIGANTE D, VITALE A, CASO F, IANNONE F, CANTARINI L: Canakinumab efficacy in refractory adult-onset PFAPA syndrome. *Int J Rheum Dis* 2015.
17. LIVNEH A, LANGEVITZ P, ZEMER D *et al.*: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40: 1879-85.
18. SOHAR E, GAFNI J, PRAS M, HELLER H: Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53.
19. WURSTER VM, CARLUCCI JG, FEDER HM JR, EDWARDS KM: Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *J Pediatr* 2011; 159: 958-64.
20. TER HAAR N, LACHMANN H, ÖZEN S *et al.*: Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85.
21. TASHER D, STEIN M, DALAL I, SOMEKH E: Colchicine prophylaxis for frequent periodic fever, aphthous stomatitis, pharyngitis and adenitis episodes. *Acta Paediatr* 2008; 97: 1090-2.
22. VIGO G, MARTINI G, ZOPPI S, VITTADELLO F, ZULIAN F: Tonsillectomy efficacy in children with PFAPA syndrome is comparable to the standard medical treatment: a long-term observational study. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S156-9.
23. COLOTTO M, MARANGHI M, DURANTE C, ROSSETTI M, RENZI A, ANATRA MG: PFAPA syndrome in a young adult with a history of tonsillectomy. *Intern Med* 2011; 50: 223-5.