

## ORIGINAL PAPER

# Clinical features and diagnosis of PFAPA syndrome: approach of the primary care physician

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## ABSTRACT

**Introduction:** Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), described for the first time in 1987 by Marshall, is an inflammatory disease that is characterized by febrile episodes with a specific symptoms. PFAPA syndrome is the most frequent among autoinflammatory diseases. The purpose of this study was to evaluate the clinical features of PFAPA syndrome in children in Western Ukraine and its timely diagnosis by the primary care physicians.

**Material and methods:** The medical records of 28 children with PFAPA syndrome referred to the inpatient and outpatient departments of Ternopil Regional Children's hospital (tertiary pediatric care hospital) between 2015 and 2020 were reviewed.

**Results:** The mean age of disease onset was  $2.9 \pm 1.5$  years, ranged from 1 to 6 years. The disease occurred more often in male (71.4%,  $p = 0.0013$ ). Besides fever, the majority of patients were presented with pharyngitis (100%), adenitis (64.3%) and aphthous stomatitis (53.6%). The effectiveness of steroid drugs occurred in all patients: in 25 (89.3%) – full response, in 3 (10.7%) – partial response. Tonsillectomy was performed in 2 cases (7.1%) and only in one of them PFAPA symptoms have passed. PFAPA syndrome was diagnosed  $1.2 \pm 0.5$  years from the onset of the first symptoms, mainly by the specialists of tertiary pediatric care.

**Conclusions:** The combination of recurrent fever with pharyngitis, adenitis, and aphthous stomatitis may be a clue to the suspicion of PFAPA by primary care physicians who need to seek professional help to rule out other (genetic, metabolic, self-inflammatory, etc.) causes, as this diagnosis is an exclusion diagnosis. There is a need to raise awareness among primary care physicians about PFAPA, which can improve timely diagnosis and treatment, and avoid unnecessary testing and treatment.

## KEY WORDS:

PFAPA syndrome, children, diagnosis.

## INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), described for the first time in 1987 by Marshall, is an inflammatory disease that is characterized with febrile periodic episodes with a specific symptoms [1-3]. The disease begins more often in healthy children 2-5 years of age and presents with regular (mostly once every 4 or more weeks) episodes of febrile fever in combination with at least one of the following

signs: aphthous stomatitis, cervical lymphadenitis, pharyngitis [4-5]. The exacerbation lasts several days, usually 3-6 days [4].

PFAPA syndrome is the most frequent among autoinflammatory diseases. Its prevalence in the world is exactly unknown, however, some publications show that among Norwegian children, the annual incidence is 2.3 per 100 thousand children [6], and Italian researchers indicate 0.4 cases per 1000 children per year [7]. The prevalence of PFAPA syndrome in Ukraine is un-

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known due to the lack of a complete registry of such patients, although the prognostic number, according to the number of population, should be at least several thousand cases.

The episodes of fever in patients with PFAPA syndrome may precede by short-term irritation, fatigue, headache, decreased motor activity, abdominal pain, nausea and diarrhea [8]. Commonly these symptoms occurred 24 hours before the episodes of fever. Children are completely asymptomatic between the episodes of fever and other symptoms [4, 5]. The disease lasts for several years, passes by adolescence without impairing the physical development of the child. However, in some cases periodic fever remains in adult age or even can have an adult onset [9].

The pathogenesis of PFAPA syndrome remains unknown, although it is now recognized that innate immunity and cytokine dysfunction play a major role. [10-12]. A family history of recurrent fever or recurrent tonsillitis suggests a genetic basis for the syndrome. [3, 8, 9]. Genetic testing for monogenic periodic fever syndromes in 111 patients with PFAPA was negative in 97 of them. [13]. However, the contribution of *NLRP3* and *MEFV* genes to the etiology of PFAPA disease was previously described [3, 4, 12]; the role of *PIK3AP1* and *SPON2* was detected recently [14, 15].

Oral corticosteroids are the first-line choice to control symptoms, although they do not prevent new episodes [8]. Moreover, after their use interval between flares can become shorter. Tonsillectomy also demonstrated a good result in the majority of cases [16]. If flare episodes are frequent and / or tonsillectomy is ineffective, colchicine may be used to increase the interval between episodes [17].

Thus, the diagnosis of PFAPA syndrome mainly based on clinical criteria [1] and they may differ depending on country, ethnicity due to epigenetic or environmental factors [18].

The purpose of this study was to evaluate the clinical features of PFAPA syndrome in children in Western Ukraine and its timely diagnosis by the primary care physicians.

## MATERIAL AND METHODS

The medical records of 28 children with PFAPA syndrome referred to the inpatient and outpatient departments of Ternopil Regional Children's hospital (tertiary pediatric care hospital) between 2015 and 2020 were reviewed. In total, there were 31 children with unexplained fever. In two during the follow-up examination, cytomegalovirus infection was detected, and in one – acute leukemia. The patients ( $n = 28$ ) were classified as having PFAPA if they fulfilled Thomas diagnostic criteria for PFAPA syndrome [4].

Structured face-to-face interviews with parents and clinical laboratory examinations of children were conducted during hospital visits. The questionnaire for parents provided a complete collection of anamnesis of illness and life and made it possible to reproduce a detailed picture of the disease, as well as its dynamics in each case.

Written consent to the processing and publication of the analysis results was obtained from the parents of all study participants.

The study was conducted in accordance to the basic principles of the Helsinki Declaration of 1975, as revised in 2000.

The data was analyzed using the statistical package STATISTICA 10.0 and Microsoft Excel 2007 to determine the main characteristics (mean, standard deviation). The comparison of frequency parameters was performed using the  $\chi^2$  test.

## RESULTS

Most of the observed patients were rural residents (17/60.7%); boys predominated (20/71.4%,  $p = 0.0013$ ). The age required for inclusion in the study should not exceed 8 years. The average age at the time of the study was  $5.9 \pm 1.7$  years, ranged from 2 to 8 years. The mean age at disease onset was  $2.9 \pm 1.5$  years, ranged from 1 to 6 years.

The first and the dominant symptom of the disease was fever (Table 1). It was the main reason to refer to medical care. Usually (26/92.9%) the fever was higher than  $38^\circ\text{C}$ .

The mean duration of the fever episodes was  $4.4 \pm 1.0$  days, ranged from 2 to 7 days. The fever repeated from every 2-3 weeks to every 2 months.

Symptoms preceding the episodes of fever were reported by only six parents (21.4%). They include runny nose, cough, arthralgia and weakness. The possibility of any infectious disease was also excluded.

The second frequent symptom was pharyngitis. It occurred in all patients. Cervical lymphadenitis was detected in 11 (39.3%) children, in one case in combination with an enlargement of the submandibular lymph nodes. We also observed adenoiditis in 7 (25.0%) patients.

Aphthous stomatitis during the episodes was observed in 15 (53.6%) patients.

Other signs, such as abdominal pain, arthralgia, headache, nausea were less common (Table 1). However, in one patient, fever and pharyngitis were combined with severe abdominal pain, acute appendicitis was diagnosed and urgent surgery was performed.

The physical and mental development of all surveyed matched their age. There were no symptoms related to the disease between episodes of fever. Comorbidities were observed in 8 (28.5%). Commonly they were presented by biliary tract dysfunction (5 patients) and hereditary disorder of connective tissue with skeletal involvement (4 patients). Laboratory data was nonspecific.

TABLE 1. Symptoms of PFAPA syndrome in the observed children

Symptom	Observed children	
	<i>n</i>	%
Fever	28	100.0
Recurrence of fever attacks	28	100.0
Pharyngitis	28	100.0
Cervical lymphadenitis	11	39.3
Adenoiditis	7	25.0
Aphthous stomatitis	15	53.6
Abdominal pain	5	17.6
Arthralgia	3	10.7
Headache	6	21.4
Nausea	3	10.7

Clinical and laboratory examination allows to exclude other diseases with periodic fever, such as cyclic neutropenia, autoinflammatory and autoimmunity disorders, viral and bacterial infections.

One boy was observed to have an increase in episodes of fever with pharyngitis up to 1 time in 2 weeks after Epstein-Barr virus infection, that was confirmed by serological testing. Autoinflammatory diseases were also suspected, and sequence analysis identified variant of uncertain significance in *NLR4* gene that is associated with autosomal dominant familial cold autoinflammatory syndrome and autosomal dominant macrophage activation syndrome.

Recurrent fever with tonsillitis/pharyngitis or tonsillectomy in parents was reported in 7 (25%) cases.

PFAPA syndrome was diagnosed 1.2 ± 0.5 years from the onset of the first symptoms. All patients were referred by primary care physicians to the tertiary pediatric care hospital where diagnosis was set, only in 4 (14.4%) cases patients were referred with suspected PFAPA syndrome. In 20 (71.4%) PFAPA syndrome was diagnosed by pediatric immunologists, in rest cases – by other specialists (otolaryngologist, infectious disease specialist, and rheumatologist).

The majority of parents reported about partial efficiency (10/35.7%) or complete inefficiency (9/32.1%) of antipyretic drugs (Ibuprofen in a single dose of 10 mg/kg three times a day or paracetamol in a single dose of 12 mg/kg three times a day). In 5 (17.9%) cases, the effectiveness of antipyretic drugs ranged from resistance to a tendency to decrease in fever, depending on each exacerbation, and only in 4 (14.3%) cases, parents reported full effectiveness. Instead, the effectiveness of steroid drugs occurred in all patients, however, in 25 (89.3%) we observed full efficacy and in 3 (10.7%) – partial response. Glucocorticoids at a dose of 1 mg/kg for prednisolone mostly interrupted the cascade of clinical symptoms. However, 15 (53.6%) observed children needed the second doses of glucocorticoids.

Tonsillectomy was performed in 2 cases (7.1%), and only in one of them the symptoms of PFAPA were eliminated. An adenoidectomy was performed in 3 children and mothers reported that flares became less frequent after this surgery.

## DISCUSSION

The diagnosis of PFAPA is based mainly on clinical criteria [1]. There are no specific laboratory findings to confirm diagnosis [19]. On the other hand, PFAPA is a diagnosis of exclusion, therefore other causes of recurrent fever should be ruled out [19].

Fever of infectious or noninfectious genesis is one of the most common causes to seek for medical advice in preschool children. Mostly fever is caused by the upper respiratory tract infections, and usually is accompanied by regional lymphadenitis, and sometimes by aphthous rash on the oral mucosa. Therefore, primary care physicians treated first episodes of PFAPA as an acute respiratory disease and, in its recurrence, as a relapse.

Cluster recurrence of symptoms led to unnecessary laboratory and instrumental examinations, multiple consultations by doctors of related specialties, such as: otolaryngologist, dentist, hematologist, rheumatologist, infectious disease specialist, immunologist. Accordingly this leads to polypragmasia. As recurrent infections are the main signs of primary immunodeficiency [20], these patients often were referred to the immunologist, and as a result the PFAPA syndrome in our study mostly was diagnosed by the immunologists (71.4%). The small number of cases suspected of PFAPA by primary care physicians, despite all criteria for diagnosis and the delay in diagnosis, indicates a need for increased awareness of this syndrome, especially among primary care physicians [21, 22]. According to the PFAPA criteria, the first manifestations are determined before 5 years of age [5]. In children from our study, the average age also ranged 2.9 ± 1.5 years. But in 7.1% (*n* = 2) children the first manifestations were recorded at 5.5 years and 6 years. This was also noted in the Hofer *et al.* study (2014), where they reported that 10.3% of the cases had late onset [13].

The incomplete cluster of PFAPA obviously affects the timeliness of diagnosis and makes the average age of diseases onset variable according to the data of various studies [9, 23].

Multicentre study revealed that the classic combination of symptoms of PFAPA is more common in boys [13] that was also observed in our study.

Only 21.4% of patients had predictors of PFAPA flares, however, other studies reported them in the vast majority of cases and noted variability of additional symptoms in their patients [13, 24]. A quarter of the children in our study had adenoiditis, although other studies did not allocate adenoiditis separately, but in some studies both tonsillectomy and adenoidectomy were performed [25].

The efficacy of steroid therapy (complete in 89.3% of cases) is in accordance with EUROFEVER registry data, which confirms the widespread use of steroids for disease outbreaks with 90% efficacy in those receiving treatment [24]. However, in another study, rapid cancellation of a fever episode after a single dose of steroids was observed only in 63% of patients, whereas 32% found partial response and 5% did not respond at all [13].

The need of tonsillectomy in patients with PFAPA syndrome is disputable [19]. It was performed in two of our patients (7.1%), and only in one of them it was successful, although other publications reported more frequent use of this method of treatment (45-93% of patients) with good results [3, 6, 16, 26].

However, genetic testing was performed in our study only in one case, it identified variant of uncertain significance in *NLR4* gene, that need further investigation of its role in autoinflammation, as even carriers of *MEFV* and *NLRP3* genes were susceptible to autoinflammation [3].

Thus, all children in our study had a complete cluster of PFAPA syndrome with a frequency of individual symptoms similar to those as reported by other researches [3, 6, 8]. In all observed patients, the reaction of lymphoid tissue was combined in time with the onset of fever, in which only 14.3% of patients responded to the use of antipyretics. The effectiveness of steroid drugs occurred in all patients. A good response to the steroids can be used as an additional criterion to confirm the disease along with generally accepted clinical criteria. Tonsillectomy is not as popular strategy for treating the PFAPA syndrome among our physicians as in other populations, which may be due to a lack of knowledge among otolaryngologists about its effectiveness and the disagreement of parents who know about the favorable course of the syndrome and its resolution with age. Noteworthy is the use of the alternative colchicine cimetidine or anakinra to prevent recurrent episodes of the disease [27].

Delayed establishment of this diagnosis after 1.2 ± 0.5 years from the appearance of the first symptoms in the presence of classic cluster reproduction of the symptom complex reflected the need to increase the professional level of doctors of the first contact.

## CONCLUSIONS

In the cases of recurrent fever that is accompanied by pharyngitis, adenitis, and aphthous stomatitis primary care physicians should suspect PFAPA syndrome and refer to a specialist to exclude other (genetic, metabolic, auto-ignition, etc.) reasons, since this diagnosis is a diagnosis of exclusion. The diagnosis of PFAPA requires a longer observation of the patient and the use of special laboratory tests, including genetic ones. Corticosteroids are an effective treatment strategy and its efficacy can be used as additional criterion to diagnose PFAPA syndrome.

Raising awareness of PFAPA among primary care physicians can improve timely diagnosis and treatment by avoiding unnecessary testing and treatment.

## DISCLOSURE

The authors declare no conflict of interest.

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