İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2024;24(2):124-127
DOI: 10.26650/jchild.2024.1329799

CASE REPORT

Paediatric PFAPA Syndrome: an Easily Missed Diagnosis

Nada Boutrid[1,2], Ahmed Samaouel Chehad[3,4], Hakim Rahmoune[3,5]

[1]Setif-1 University, Faculty of Medicine, LMCVGN Research Laboratory; Setif , Algeria
[2]EHS El-Eulma, Department of Pediatrics, El Eulma, Algeria
[3]Constantine-3 University, Faculty of Medicine, El Khroub, Algeria
[4]University Hospital of Constantine, Department of Dermatology, Constantine, Algeria
[5]University Hospital of Setif, Department of Pediatrics, Setif , Algeria

ORCID ID: N.B. 0000-0002-9697-2773; A.S.C.0000-0003-4228-3443; H.R.0000-0002-9604-3675

Citation: Boutrid N, Chehad AS, RahmouneH. Paediatric PFAPA syndrome: an easily missed diagnosis. Çocuk Dergisi - Journal of Child 2024;24(2):124-127. https://doi.org/10.26650/jchild.2024.1329799

ABSTRACT

PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) syndrome is an autoinflammatory condition characterised by recurrent febrile episodes associated with aphthous stomatitis, pharyngitis, and cervical adenitis. It typically presents before the age of 5 years, with over 60% of cases occurring in males. The prevalence of PFAPA is unknown, but over 500 cases have been reported. The syndrome is diagnosed on the basis of clinical manifestations and is a diagnosis of exclusion. It is characterised by episodes of fever lasting for 3–6 days, with recurrences every 3–8 weeks. Patients are usually asymptomatic between episodes and show normal growth. The aetiology of PFAPA is unknown, it is considered an immune-mediated disease characterised by cytokine dysfunction. Genetic factors may also play a role, as suggested by the strong familial clustering of the syndrome. There is no specific treatment for PFAPA, and its management is based on controlling the symptoms and preventing future episodes.

Keywords: PFAPA syndrome, Periodic fever, Auto-inflammatory, Child

INTRODUCTION

PFAPA (Periodic fever-aphthous stomatitis- pharyngitis - adenopathy) syndrome is an autoinflammatory disorder that typically occurs in preschoolers and is characterised by periodic fever, aphthous stomatitis, pharyngitis, and adenitis. It typically presents before the age of 5 years, with over 60% of cases occurring in males. The prevalence of PFAPA is unknown, but over 500 cases have been reported (1)

The diagnosis of PFAPA syndrome is based on clinical findings, which include at least three febrile episodes lasting up to 5 days and occurring at regular intervals, pharyngitis plus adenopathy or aphthous ulcers, good health between episodes, and elevated acute-phase reactants during a febrile episode but not between episodes. Blood tests may be performed to measure substances that indicate inflammation (2).

PFAPA syndrome is easily missed by practitioners when dealing with recurrent pharyngitis, aphthosis, or stomatitis, which would delay appropriate management. Treatment of PFAPA syndrome is optional and depends on the frequency and severity of flare-ups; it can include glucocorticoids, such as a single dose of prednisone or betamethasone, which, when administered at the onset of an episode, can dramatically abort fever attacks in a few hours. Tonsillectomy may also be considered in some cases (3).

CASE REPORT

An 8-year-old male child presented to the dermatology outpatient clinic with recurrent aphthous stomatitis since the age of 5 years. He was the first child of consanguineous Algerian parents, and his pregnancy, labour, and postnatal development were uneventful. The episodes occurred almost regularly, every 4 weeks, and lasted 8-10 days, accompanied by fever and pharyngitis. Upon admission, physical examination revealed superficial, aphthous lesions on the inner side of the cheeks, tongue, and lips, cervical adenitis, tonsillitis, concomitant elevated temperature at 39°C, vague abdominal pain, and diffuse arthralgia (Figures 1 and 2).

Laboratory findings showed elevated inflammatory biomarkers (high C-reactive protein > 18 mg/l, no exact titration provided and elevated erythrocyte sedimentation rate > 30 mm at the first hour), whereas blood count and smear did not show any

Corresponding Author: Hakim Rahmoune **E-mail:** rahmounehakim@gmail.com

Submitted: 19.07.2023 • **Revision Requested:** 14.11.2023 • **Last Revision Received:** 04.01.2024 • **Accepted:** 05.02.2024

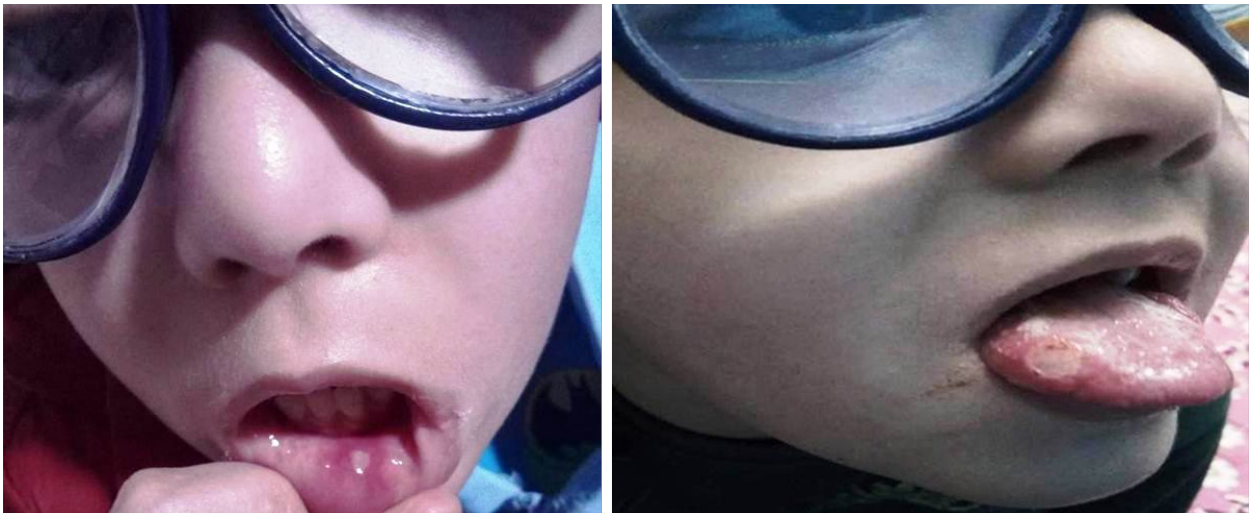

Figure 1,2: Recurrent aphthous ulcers in two episodes. Left: on the lower lip; Right: on the tongue

haematological abnormality. A further biopsy to rule out any underlying condition such as atypical infections or other rare pathologies that may present with symptoms similar to those of recurrent tonsillitis. It revealed a non-specific, lymphocytes-histiocytes infiltration.

The modified Marshall's criteria were used to finally diagnose the patient with PFAPA syndrome.

Following a short course of steroids (two days of Prednisone, 2mg/kg/day), colchicine was initiated to prevent attacks, and tonsillectomy was scheduled with ENT surgeons.

DISCUSSION

PFAPA syndrome is a periodic fever syndrome of unknown cause that was first described in 1987 by Marshall et al. (4).

It is an autoinflammatory disorder characterised by recurrent, abrupt episodes of fever that resolve spontaneously within a few days, along with pharyngitis, oral aphthous lesions, and cervical lymphadenitis. Other symptoms, such as abdominal pain, arthralgia, arthritis, headache, rash, diarrhoea, and nausea/vomiting, have also been reported during attacks (2).

Moreover, the syndrome's aetiology is unknown, and the proposed contributors to pathogenesis include infection, abnormal host immune responses, or a combination of both. The presence of variants in inflammasome-related genes, mostly in NLRP3 and MEFV, suggests a possible role of these genes in PFAPA pathogenesis. However, none of these variants alone seem to be relevant to the disease aetiology, suggesting an oligogenic or polygenic background (5).

Approximately 90% of cases of PFAPA syndrome manifest before the age of five, as was the case with our patient. Recurrences of symptoms occur periodically, with intervals of 3–8 weeks initially, and then with longer intervals as the child ages (6).

Our patient's odyssey is not uncommon: due to the complex non-specific presentation of PFAPA, patients often undergo multiple diagnostic tests and procedures, including intravenous perfusions of antibiotics(7); which can lead to a delay in diagnosis and inappropriate treatment strategies (8,9).

The diagnosis of PFAPA syndrome can be challenging because of its diverse clinical presentation and lack of specific diagnostic criteria. Typically, diagnosis is made by exclusion, and the differential diagnosis should include disorders depicting a periodic fever, such as recurrent tonsillitis, streptococcal infection, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, familial Mediterranean fever, TRAPS syndrome, and mevalonate kinase deficiency (1,10) . Less common autoinflammatory diseases, such as Cryopyrin-Associated Periodic Syndrome (CAPS) and Tumour Necrosis Receptor-Associated Periodic Syndrome (TRAPS), must also be excluded (11).

The diagnostic criteria for PFAPA syndrome have low specificity, and the adoption of new, more specific criteria is crucial to better identify the syndrome and provide a correct and rapid diagnosis. The lack of gold standard criteria for PFAPA syndrome has led to difficulties in establishing classification criteria (5,10,11) . To address this, the Eurofever Registry and the Paediatric Rheumatology International Trials Organisation have published a modified set of criteria for PFAPA syndrome, which has been validated and shown to have high specificity and sensitivity (12). The new criteria provide a more specific and evidence-based approach to the diagnosis of PFAPA syndrome (Table 1).

The management of PFAPA eases symptoms, shorten the duration of fever, and prevent recurrence. Various treatment strategies have been used and demonstrated variable efficacy for treating attacks. The different therapeutic options for PFAPA syndrome encompass the following (5,13) :

1. Corticosteroids: Glucocorticoids are considered the mainstay of treatment for PFAPA syndrome and are frequently used in managing fever episodes. A short course of steroids, with a single dose of prednisone (1–2 mg/kg) or betamethasone (0.1–0.2 mg/

Table 1 : New criteria for PFAPA diagnosis according to Gattorno et al (12).

Criteria	Description
Regularity	Recurrent fevers with a duration of 3-6 days and a frequency of at least one episode every 4-8 weeks
Aphthous stomatitis	Oral ulcers that occur during fever episodes or within 24 to 48 hours of fever onset
Pharyngitis	Sore throat or redness of the pharynx during fever episodes or within 24 to 48 hours of fever onset
Cervical adenitis	Tender or enlarged cervical lymph nodes during fever episodes or within 24 to 48 hours of fever onset
Exclusion of other diseases	Exclusion of other periodic fever syndromes, autoimmune diseases, and infections
Response to the treatment	Complete resolution of symptoms within 24 to 48 hours of treatment with corticosteroids

kg) administered at the onset of an episode, can dramatically resolve symptoms, shorten or even end the episode

2. Colchicine has shown efficacy in some patients and may help prevent future episodes in some children

3. Cimetidine has been suggested as an effective prophylactic treatment for PFAPA and has relieved symptoms in a subset of patients

4. Tonsillectomy may prevent future episodes in some children: in more than 80% of children, tonsillectomy has been reported to cure PFAPA, but the best timing for this treatment is unclear.

5. Nonsteroidal anti-inflammatory drugs have poor results in amending PFAPA symptoms and are not considered a primary treatment option.

6. Biologics like interleukin-1 inhibitors have been efficient in some studies but require further confirmation.

Even if such treatments are useful for managing PFAPA episodes, there is no evidence that treatment can modify the natural history of PFAPA syndrome. The main goal of treatment is to ease symptoms, shorten the duration of fever, and prevent recurrence

CONCLUSION

PFAPA syndrome is a periodic fever, autoinflammatory disorder characterised by recurrent, abrupt episodes of fever that resolve spontaneously within a few days, along with pharyngitis, oral aphthous lesions, and cervical lymphadenitis. The challenges in diagnosing PFAPA syndrome include its diverse clinical presentation, lack of specific diagnostic criteria, and unknown aetiology.

Treatment for PFAPA syndrome is primarily symptomatic, with the goals of easing symptoms, shortening the duration of fever, and preventing recurrence

Acknowledgment: The authors thank the patient and his parents for their kind collaboration.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.S.C., N.B., H.R.; Data Acquisition- A.S.C.; Data Analysis/Interpretation- A.S.C., N.B., H.R.; Drafting Manuscript- A.S.C.; Critical Revision of Manuscript- H.R.; Final Approval and Accountability- A.S.C., N.B., H.R.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

1. Orphanet: PFAPA syndrome [Internet]. [cited 2024 Jan 2]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=42642&lng=EN
2. Wekell P. Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome – PFAPA syndrome. Presse Médicale. 2019 Feb;48(1):e77–87.
3. Lazea C, Damian L, Vulturar R, Lazar C. PFAPA Syndrome: Clinical, Laboratory and Therapeutic Features in a Single-Centre Cohort. Int J Gen Med. 2022 Aug;Volume 15:6871–80.
4. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr. 1987 Jan;110(1):43–6.
5. Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome. Pediatr Rheumatol. 2016 Dec;14(1):38.
6. Ali NS, Sartori-Valinotti JC, Bruce AJ. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Clin Dermatol. 2016 Jul;34(4):482–6.
7. Semianchuk VB. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (pfapa) syndrome in children. Wiadomosci Lek Wars Pol 1960. 2017;70(1):144–7.
8. Spivakovskaya A, Spivakovskiy Y, Cnernenkov Y, Dushanova A. AB1057. Difficulties in the diagnosis of the PFAPA syndrome in the real clinical pediatrician practice. In: Abstracts Accepted for Publication [Internet]. BMJ Publishing Group Ltd and European League Against Rheumatism; 2019 [cited 2024 Jan 2]. p. 1992.2-1992. Available from: https://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2019-eular.4296
9. Costagliola G, Maiorino G, Consolini R. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome (PFAPA): A Clinical Challenge for Primary Care Physicians and Rheumatologists. Front Pediatr. 2019 Jul 5;7:277.
10. Crimi F, Mejbri M, Hentgen V, Dingulu G, Koné-Paut I, Georgin-Lavialle S, et al. SAT0507 Evaluation of the new classification criteria for PFAPA syndrome. In: Saturday, 15 June 2019 [Internet]. BMJ Publishing Group Ltd and European League Against Rheumatism; 2019 [cited 2024 Jan 2]. p. 1343.1-1343. Available from: https://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2019-eular.8057
11. Vanoni F, Caorsi R, Aeby S, Cochard M, Antón J, Berg S, et al. Towards a new set of classification criteria for PFAPA syndrome. Pediatr Rheumatol Online J. 2018 Sep 21;16(1):60.

12. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis. 2019 Aug;78(8):1025–32.
13. Gaggiano C, Rigante D, Sota J, Grosso S, Cantarini L. Treatment options for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in children and adults: a narrative review. Clin Rheumatol. 2019 Jan;38(1):11–7.