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PFAPA syndrome: a case report of a challenging diagnosis

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RESUMO

Introduction: PFAPA syndrome (Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis) is the most common cause of periodic fever in childhood. Typically, it occurs in children up to five years old and is characterized by sudden and recurrent episodes of high-spiking fever accompanied by at least one of the other eponymous features. This case report enhances the importance of its recognition, to prevent unnecessary tests and/or treatments.

Case description: We present a case of a four-year-old boy, with no relevant background, observed multiple times in primary and secondary care settings due to fever. His parents reported monthly episodes of high fever, usually along with pharyngitis, oral aphthosis, and/or cervical adenitis. He was completely asymptomatic between crises and showed normal growth and psychomotor development. Several oropharyngeal and nasal swab tests were performed, with negative results. After some investigation and articulation with his pediatrician, a diagnosis of PFAPA syndrome was made and he started oral corticosteroids, a single dose on the first day of every episode, obtaining fast and complete symptomatic relief.

Comment: PFAPA syndrome diagnosis is challenging, and its process can trigger anxiety in the patient, his family, and even in healthcare professionals. However, this relatively common and benign condition tends to be self-limited, usually with spontaneous resolution before adolescence. Its recognition by the medical community is essential, particularly in primary care settings since family physicians are usually the first point of medical contact within the healthcare system. This case report enhances the family physician's core competence to manage illness with nonspecific presentations and the importance of the interface with other specialties to provide the best care to the community.

Keywords: PFAPA syndrome; Periodic fever; Tonsilitis; Cervical adenitis; Aphthous stomatitis; Case report.

INTRODUCTION

PFAPA syndrome (Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis) represents the most common cause of periodic fever in childhood.[1-4] It is an autoinflammatory disease characterized by clockwork regular episodes of fever, pharyngitis, oral aphthosis and/or cervical lymphadenopathy.[1-4] Since its first description by Marshall *et al.* in 1987, this condition has become better understood, although there are a lot of unsolved issues regarding the precise etiopathogenesis.[5] Its incidence remains unclear and probably underestimated; however, a Norwegian study reported an incidence of 2,3 per 10,000 children up to five years old.[1,3,5-6] Most cases occur by the age of five years, with a slight male predominance.[3-5]

Patients present with recurrent episodes of high spiking fever (39-40 °C) lasting three to seven days, every two to eight weeks, usually along with at least one of the other associated eponymous features.[1-5] In up to 60% of the cases, children experience a prodrome of nausea, abdominal discomfort, irritability, headache and/or myalgia.[3] Apart from fever, pharyngitis is the most common symptom, being present in over 90% of patients, and it can be either erythematous or exudative.[3,5] Adenitis is a finding in 53-94% of patients, and typically there are bilateral nodes in the anterior cervical chains, with two to three centimeters of largest diameter, elastic consistency, and moderately tender during palpation.[3,5] Approximately half of the cases present with small-sized oropharyngeal aphthae located in non-masticatory surfaces of the mucosa.[3,5] The symptoms often have a duration of four to six days, with a benign course and spontaneous resolution.[3,5]

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The diagnosis relies on clinical criteria, as described by Marshall and Vanoni *et al.*[4-5,7-8] Nonetheless, due to the challenge of its recognition, it remains an underdiagnosed syndrome. Besides, the lack of awareness of its benign nature leads to unnecessary auxiliary tests and unsuccessful treatments.[2-5] This case report highlights the importance of recognizing PFAPA syndrome to avoid unnecessary tests and treatments, from the perspective of quaternary prevention.

CASE DESCRIPTION

The case presents a four-year-old Caucasian boy from a nuclear family in stage V of Duvall's family life cycle. There was no relevant familiar background, and the parents denied any allergies or regular medications. The child was seen on multiple occasions in both primary and secondary care settings presenting with fever, frequently accompanied by pharyngitis, aphthous stomatitis, and/or cervical adenitis.

The initial episode occurred in 2019, by the age of two, characterized by a sudden onset of high spiking fever (38.5-39.7 °C) along with aphthous stomatitis and cervical adenitis. The child was observed in the primary care setting and was treated with paracetamol and nystatin. The symptoms completely resolved within five days.

After the first episode, the child experienced multiple recurrences requiring acute care consultations in both primary care and pediatric emergency departments, with an approximately monthly pattern. These episodes manifested with variable combinations of fever, pharyngitis, aphthous stomatitis, and adenitis. Often, a diagnosis of tonsillitis or other upper respiratory tract infections was presumed, leading to treatment with various antibiotics.

In May 2022, the child presented to primary care with a new episode of fever accompanied by odynophagia lasting three days. Parents reported axillary temperatures above 38.5 °C (maximum of 39.3 °C), with partial response to antipyretics. There were no other associated symptoms such as cough, rhinorrhea, nasal congestion, or diarrhea, and the parents denied any relevant epidemiological context or seasonal pattern. Physical examination revealed tonsillar hyperemia and hypertrophy, along with cervical adenitis characterized by two elastic and tender nodes, each measuring approximately two centimeters in the left anterior cervical chain. Other clinical findings such as exanthema or signs of respiratory distress were absent. A nasal swab for SARS-CoV-2 and an oropharyngeal swab for group A *Streptococcus*, as well as a urinalysis reagent strip, yielded negative results. Considering the clinical presentation, blood tests were ordered, demonstrating mild elevation of inflammatory markers (erythrocyte sedimentation rate: 55 mm/h; C-reactive protein: 10.05 mg/dL) alongside a normal white blood cell count. Serological tests for Epstein-Barr virus and cytomegalovirus were also negative, ruling out infectious etiologies.

Based on the recurrent monthly episodes of sudden high fever lasting three to six days, often accompanied by pharyngitis, aphthous stomatitis, and/or adenitis, resolving spontaneously, and associated with inter-episode asymptomatic intervals as well as normal growth and psychomotor development, a presumptive diagnosis of PFAPA syndrome was established. Following a discussion of the case with the children's pediatrician, a trial of oral betamethasone at a single dose of 0.2 mg/kg was initiated, resulting in rapid and effective resolution of symptoms, further supporting the diagnosis.

The child continued to be monitored by both the family physician and pediatrician, with the frequency of flares gradually decreasing and easily managed with corticosteroids.

COMMENT

PFAPA syndrome is a relatively common disease yet remains frequently unfamiliar within the medical community.[4] The key to its diagnosis relies on clinical criteria, despite not being universally accepted; usually, it is based on modified Marshall's criteria, proposed in 1999.[4-5,7] However, a new set of criteria was proposed by Vanoni *et al.* in 2018, which includes more detail concerning fever crises and conditions to be excluded (Table 1).[5,8] These criteria establish the fever as a cardinal symptom as it must be present and accompanied by, at least, one of the other eponymous features.

There are no specific laboratory tests for PFAPA syndrome diagnosis, although lymphopenia, neutrophilia, and monocytosis may be observed during the flares, as well as slight increases in nonspecific inflammatory markers, such as C-reactive protein.[5] It is

TABLE 1. Modified Marshall's and Vanoni's criteria set for PFAPA syndrome diagnosis/classification

Criteria set	Modified Marshall's Criteria (1999)	Vanoni's Criteria (2018)
Age of disease onset	Before 5 years of age	Before 6 years of age
Recurrent fever definition	Regular fever episodes	Periodic fever for at least 6 months: a. Daily fever of at least 38.5 °C (axillary) for 2 to 7 days b. At least 5 regularly recurring fever episodes with maximum of 2 months interval between them
Symptoms	At least one of: a. Pharyngitis b. Aphthous stomatitis c. Cervical lymphadenitis	At least one in every episode and two in the majority of episodes: a. Pharyngitis b. Aphthae c. Cervical adenitis
Between-flares periods	Asymptomatic Normal development and growth	Full recovery Normal linear growth
Exclusion	Cyclic neutropenia Upper respiratory tract infection	Infections Immunodeficiency Cyclic neutropenia Other causes of recurrent fever

necessary to exclude conditions such as cyclic neutropenia, chronic infections, or immunodeficiency, making PFAPA an exclusion diagnosis.[5] Some patients, who may present with atypical symptoms, may need genetic testing for monogenic autoinflammatory diseases as well as other specific exams, upon suspicion.[4,9]

Currently, there are different management strategies and a lack of evidence-based treatment guidelines since there is also a lack of clinical trials.[1,5] Depending on the disease severity and flares' frequency, the decision to treat is optional and must be individualized since there is no evidence that medical treatment modifies the outcome.[4,10] According to the Childhood Arthritis and Rheumatology Research Alliance PFAPA work group, there are four treatment strategies: 1) antipyretics during episodes; 2) abortive treatment with corticosteroids; 3) prophylaxis with colchicine or cimetidine and 4) tonsillectomy.[1] Antipyretics can be effective in some children, making it a reasonable management strategy, especially for parents who are reluctant to use daily medication, are concerned about corticosteroids' side effects, or refuse surgical treatment.[1] Low-dose corticosteroids at the disease's onset are the first line of treatment, with a suggested single dose of 1 mg/kg of prednisone (maximum of 60 mg) or 2 mg/kg of prednisone (maximum of 60 mg) in cases of partial response or higher frequency of episodes (intervals ≤14 days).[1,4] Oral betamethasone in a dose of 0.1-0.2 mg/kg at the disease's onset, as used in this patient, is another option.[4] It is possible to repeat treatment on day two if the fever persists.[4] The effectiveness and duration of pro-phylaxis with colchicine or cimetidine have limited evidence in the literature and are considered as options after the failure of other treatments.[1] Tonsillectomy is an option in selected patients, being typically reserved for more severe cases.[1,4]

As a benign condition, PFAPA syndrome tends to be solve spontaneously within three to six years after disease onset and before adolescence, with favorable outcomes. Flares' frequency and duration decrease over time and there are no long-term sequelae.[2-5,10] However, a minority of cases continue to have episodes into adulthood and some experience relapses after complete resolution.[3,11-12]

Recognition of PFAPA syndrome is crucial to avoid unnecessary interventions in children, given its considerable impact on both the child's quality of life and that

of their caregivers.[3] Its diagnosis is often challenging in clinical practice and can cause anxiety in patients, their families, and healthcare professionals. Family physicians play a crucial role in diagnosing this condition as they have knowledge of the patient's background and are in a unique position to coordinate with secondary care professionals for accurate diagnosis, treatment, and follow-up.

Future goals include defining more specific classification criteria and establishing evidence-based management guidelines based on higher-quality studies, with more homogeneous patient groups.

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AUTHORS CONTRIBUTION

Conceptualization, TA; methodology, AM, CL, DB, MF, and TA; validation, AM, CL, DB, MF, and TA; investigation, MF, and TA; resources, AM, CL, DB, MF, and TA. TA wrote the original draft. All the authors reviewed, revised and approved the final manuscript.

CONFLICT OF INTEREST DISCLOSURE

All authors declare that they have no conflicts of interest.

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ABSTRACT

SÍNDROMA PFAPA: UM RELATO DE CASO COM DIAGNÓSTICO DESAFIANTE

Introdução: O síndroma PFAPA (Febre Periódica, Estomatite aftosa, Faringite e Adenite) é a causa mais comum de febre periódica na infância. Ocorre tipicamente em crianças até aos cinco anos de idade e caracteriza-se por episódios recorrentes de febre alta acompanhada por pelo menos mais uma característica típica. Este caso clínico releva a importância do seu reconhecimento, com o objetivo de prevenir a realização de meios complementares de diagnóstico e terapêuticas desnecessários.

Descrição do caso: Criança do sexo masculino, de quatro anos de idade, sem antecedentes pessoais de relevo, observada múltiplas vezes em contexto de cuidados de saúde primários e secundários por febre. Os pais referiam episódios de febre alta, geralmente acompanhada por faringite, aftose oral e/ou adenite cervical. Entre crises encontrava-se completamente assintomática e apresentava desenvolvimento estaturo ponderal e psicomotor normal. Foram realizadas várias zaragatoas orofaríngeas e nasais, sempre com resultados negativos. Após investigação e articulação com o seu pediatra estabeleceu-se o diagnóstico de síndroma PFAPA. A criança iniciou corticoterapia oral em dose única no primeiro dia de cada episódio, obtendo-se alívio sintomático rápido e completo.

Comentário: O diagnóstico de síndroma PFAPA é desafiante e o seu processo pode ser ansiogénico para o doente e sua família, mas também para os profissionais de saúde. No entanto, trata-se de uma condição relativamente comum e benigna, tendencialmente autolimitada e com resolução espontânea antes da adolescência. É fundamental o seu reconhecimento pela comunidade médica, em particular nos cuidados de saúde primários, uma vez que o médico de família constitui geralmente o primeiro contacto médico nos serviços de saúde. Este caso clínico reforça a competência nuclear do médico de família na gestão da doença que se apresenta de forma inespecífica e a importância da multidisciplinariedade, no sentido de providenciar os melhores cuidados à comunidade.

Palavras-chave: Síndroma PFAPA; Febre periódica; Amigdalite; Adenite cervical; Estomatite aftosa; Relato de caso.