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CASE REPORT

PFAPA Syndrome: A Case report and literature review

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Abstract

PFAPA syndrome is an autoinflammatory disease stemmed from immune system deregulation diagnosed by exclusion. The authors discussed the relevance of diagnosis and the unnecessary prescription of antibiotics in patients with the disease.

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INTRODUCTION

PFAPA (periodic fever - aphthous stomatitis- pharyngitis - adenopathy) syndrome is an autoinflammatory disease characterized by recurring episodes of inflammation stemmed from innate immune system deregulation[1]. Gary Marshall et al. described the syndrome in 1987.

According to the diagnostic criteria for PFAPA syndrome include the following [2,3]:

1. Relapsing fever in regular intervals in children younger than five years.
2. Symptoms despite the absence of upper respiratory tract infection and at least one of the following clinical signs:

a) aphthous stomatitis
b) cervical lymphadenopathy
c) pharyngitis

3. Ruling out cyclic neutropenia
4. Asymptomatic period between episodes
5. Normal growth and development

Absence of neutropenia at the onset of fever episodes excludes cyclic neutropenia.

Constant set of symptoms during episodes[3].

Patients of any age must meet all criteria.

Modified diagnostic criteria (Lawton et al 2008)[4,5]

1. Three or more well documented episodes of fever lasting for up to five days in regular intervals ranging from three to six weeks.
2. Pharyngitis and/or painful cervical adenopathy and/or aphthous mouth ulcers.
3. Absence of symptoms and normal growth and development between episodes.
4. Resolution of symptoms with one single dose of prednisolone or other equivalent drugs.

CASE REPORT

An eight-year-old boy arrived at the allergy and immunology ward of the Bonsucesso Federal Hospital accompanied by his mother. She reported he was “constantly sniffing” and had recurrent tonsillitis. Sneezing and nasal pruritus were observed preferentially in the morning or when the boy was close to “strong odors” or dust. She said he did not snore, and added that he had more than six episodes of tonsillitis, all treated with antibiotics, the last of which three weeks prior to his arrival at the hospital. The boy took azithromycin for hives associated with amoxicillin and cephalexin.

The patient did not have a history of asthma or atopic dermatitis. He was followed by a pediatric nephrologist for reflux nephropathy and was not prescribed prophylactic antibiotics. His parents did not have a history of atopy. The family lives in a brick house, does not have pets, and the parents said they did not smoke in the house. His psychomotor and neural development was normal and he had an up-to-date vaccination record. His mother had hyperemesis gravidarum and type 1 diabetes mellitus during gestation and in the perinatal period. He was born well, weighing 2,830 grams, and was discharged 48 hours after birth. He was given only breast milk until six months of age.

Physical examination revealed that his psychomotor and neural development status matched his age. He weighed 22.8 Kg and his stature was 126 cm (25th percentile). Anterior rhinoscopy showed a pale nasal mucosa with hyaline nasal discharge and nasal congestion in an otherwise normal examination. His tonsils were of normal size for his age.

The patient was followed quarterly at first and then monthly in the outpatient ward. He had fever and tonsillitis every month. His clinical signs were indicative of acute tonsillitis in some visits, and included submandibular lymphadenopathy, hyperemia of the tonsils, and fever. The patient took azithromycin for five days in some episodes and clarithromycin for ten days in some of his bouts. He has been on regular nasal budesonide 50mcg twice a day to manage persisting rhinitis. An otolaryngologist signed the prescription of the drug, a medication used in the treatment of allergies. The patient was not prescribed a tonsillectomy. His skin test was positive for the more common types of mites, and he was referred to immunotherapy.

His initial test results were as follows: radiographs of the facial sinuses were normal; his complete blood count (CBC) came back normal, with 11,300 white blood cells per mm^3. Another CBC run a month later during a course of infection showed he had 10,700 white blood cells per mm^3 (65% neutrophils; 25% lymphocytes) and 220,000 platelets/mm^3; his C-reactive protein was normal and his ESR was 54 mm/h. An oropharyngeal swab revealed growth of alpha-hemolytic Streptococci. The patient’s IgA, IgM, and IgG levels were 373 mg/dl, 181mg/dl, and 1080 mg/dl, respectively, all within normal range for his age.

He was suspected for PFAPA syndrome and was prescribed prednisolone 1mg/kg/day for three days during episodes. On the following month, he had another bout of fever and throat pain lasting for three days treated successfully with oral prednisolone. His fever went away soon after the second dose of medication. He was prescribed cimetidine 30mg/kg/day in December 2016 in an attempt to prevent further episodes.

Epidemiology

PFAPA (periodic fever - aphthous stomatitis- pharyngitis - adenopathy) syndrome starts during childhood between the ages of two and five years. The disease is slightly more prevalent in males, but no difference has been reported for ethnicity or race. It is usually a self-limiting condition that resolves around the age of ten, but cases in adults have been described[5].

Immune pathophysiology

The cause of innate immune system deregulation and the ensuing bouts of inflammation within regular intervals is still unknown. The levels of a number of inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and interleukin-6 (IL-6), IL-1, and IL-18 are increased during bouts. The levels of pro-inflammatory mediators such as IL-1beta are increased even between episodes of fever. The lack of seasonality, regional incidence, and contagion between individuals living in the same household, in addition to negative oropharyngeal swab cultures, rule out infection[5].

Differential diagnosis

Differential diagnosis includes recurrent respiratory tract infections, which do not reoccur within regular time intervals. Other conditions include cyclic neutropenia, in which patients have neutropenia for three to five days every 21 days in the typical cycle; and familial Mediterranean fever, in which patients suffer from periodic bouts of fever, however not within regular intervals and without pharyngitis and aphthous stomatitis. Systemic juvenile idiopathic arthritis, Behçet's disease, hyper IgD syndrome, tumor necrosis factor receptor 1 associated periodic syndrome (TRAPS), and Muckle-Wells syndrome must be ruled out.

GENERAL COMMENTS

In light of the clinical presentation including fever, throat pain, and painful cervical lymphadenopathy, the patient was initially diagnosed with recurrent tonsillitis. The regularity of symptoms, the prompt response to steroid therapy, and the patient's good growth and development status were relevant factors in considering PFAPA syndrome. Tonsillectomy is indicated only to subjects refractory to drug therapy, whose symptoms interfere with quality of life, although its outcomes have been challenged in the literature[7]. PFAPA is diagnosed by exclusion, and delays lead to injudicious use of antibiotics and significant anxiety among patient family members. Although benign and self-limiting, the condition produces significant discomfort to affected individuals and precludes attendance to school and enjoyment of leisure activities.

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