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Marshall's Syndrome – A Review

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ABSTRACT

Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is a pediatric periodic disease characterized by recurrent febrile episodes associated with head and neck symptoms. The origin of this syndrome, which can last for several years, is unknown. During healthy periods, patients grow normally. Differential diagnosis includes other diseases characterized by periodic fevers such as recurrent tonsillitis, several infectious diseases, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, familial Mediterranean fever, familial Hibernian fever, and hyperglobulinemia D syndrome. Many treatments have been used with various results including antibiotics, non-steroid anti-inflammatory drugs, acetylsalicylic acid, colchicine, antiviral medicines, steroids, cimetidine, and tonsillectomy. Based on our experience and analysis of the literature, surgery (tonsillectomy with or without adenoidectomy) is likely to guarantee the best results in the management of PFAPA syndrome.

1. Introduction

Fever is a common sign of infection in the pediatric population. The most frequent causes of acute fever in children are otitis media and respiratory infections. Periodic fever syndromes, however, have a more complex presentation and pose a diagnostic dilemma for physicians. A periodic fever usually lasts only a few days, followed by asymptomatic periods. Clinical findings in periodic fever syndromes include mucous membrane involvement, involvement of the peritoneum and pleura (clinically presenting as acute abdominal distension), muscle guarding (as in acute appendicitis), and acute pleuritis with breathing difficulty), and reduced breathing sounds. Arthralgia and dermatologic changes might accompany the clinical onset of these disorders. A particular fever syndrome characterized by a relapsing (periodic) fever accompanied by aphthous stomatitis, pharyngitis, and cervical adenitis is classified as the PFAPA syndrome and was initially described by Marshall et al.1

Knowledge regarding the etiology of PFAPA is still limited, although possible causative factors have been explored in the last 20 years. Certain infectious vectors have been linked to recurrent fevers. Furthermore, viral infections such as those caused by herpetic viruses (HSV, HHV6, and HHV7) include fever as a presenting sign2.Most PFAPA cases, however, have had extensive evaluation to rule out these conditions as part of the diagnostic workup. Additional evidence toward an infectious role is provided by the reduction in symptom-free periods after immune-suppressive treatment. The overall body of literature, albeit limited, supports the theory of a dysfunction in cytokine regulation, given the self-limiting nature of the condition, the dramatic response to corticosteroids, the absence of symptoms between attacks, and the periodicity of the attacks.3

The exact mechanism responsible for the pathogenesis of PFAPA is yet unknown, and the expansion of case series and reports is limited by the rare incidence of the disease. The similarity with other genetically transmitted periodic fever syndromes raises the question of a possible genetic etiology, because many of them are caused by gene mutations. Nevertheless, once again, the self-limiting nature of the disease challenges a true autosomal or recessive genetic cause.4

2. Clinical description

In 1987, Marshall et al. reported a previously undescribed periodic fever syndrome of unknown cause in 12 children. These patients presented febrile episodes that recurred every 2 to 12 weeks (mean cycle = 4.5 weeks). In all cases, the onset of symptoms started before 5 years of age and the fever reached high temperatures (40 to 41°C) lasting approximately 5 days. Fever was associated with pharyngitis and stomatitis in 9 of the 12 cases (75%), cervical reactive adenopathies in 8 of the 12 (66.6%), and other minor symptoms such as headache, abdominal pain, nausea, vomiting, chills and malaise5. None of these children were immunodeficient. Bacterial, viral, and fungal studies were all negative. Only 2 patients had group A β- hemolytic Streptococcus isolated from the pharynx. Acute episodes were often associated with leukocytosis and mild elevation of the

erythrocyte sedimentation rate, but no patient showed atypical lymphocytosis or neutropenia. During asymptomatic intervals, the children were in good health and growth was normal. On the assumption of streptococcal pharyngitis, all patients underwent unsuccessful therapy with antibiotics and nonsteroid anti-inflammatory drugs. The use of oral prednisone dramatically controlled symptoms, although subsequent relapses were not prevented. Therefore, a patient who complains of periodic fever (during asymptomatic periods growth is normal) associated with aphthous stomatitis, pharyngitis, and cervical adenitis can be considered to be affected by Marshall's/PFAPA syndrome. In these patients, anti-inflammatory and antibiotic therapy is ineffective, whereas one or 2 oral doses (1 to 2 mg/Kg) of corticosteroid (i.e. prednisone) temporarily resolved symptoms within 24-36 hours, although it did not avert the next cycle.6

3. Differential diagnosis

The differential diagnosis of Marshall's/PFAPA syndrome includes several recurrent fever syndromes such as recurrent tonsillitis, a number of infectious diseases, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, familial Mediterranean fever (FMF), familial Hibernian fever (FHF), and, finally hyperglobulinemia D syndrome, (Feder et al 1992; Scimeca et al 1996;Thomas et al 1999; Padeh et al 1999;. Lee et al 1999; Dahn et al 2000; Feder et al 2000; Scholl et al 2000). Recurrent tonsillitis is a very common disease in pediatric age. Such illness is due mainly to viral or bacterial agents. It manifest with fever, tonsillitis, and adenitis.7 The diagnosis may be facilitated by means of bacterial and viral studies and antibiotic therapy is usually effective in bacterial form.8 In this last type of tonsillitis, Group A â-hemolytic Streptococci is generally more isolated pathogen. Several infectious agents (Borrelia recurrentis, Streptobacillus moniliformis, hepatitis B virus, Rickettesia prowazekii, Entamoeba histolytica, Plasmodium malariae, herpes simplex virus, Epstein-Barr virus) can also cause periodic fever.8,9,10 All these diseases have identifying characteristics that allow their diagnosis by means of positive past history, and physical, and/or laboratory features. (Southern et al. 1969; Lekstom-Himes et al. 1996; Whitley et al. 1998; Feder 1992, 2000). Juvenile idiopathic arthritis presents with arthritis, fever, hepatosplenomegaly, and systemic adenopathies. The fever lasts several weeks or months and the onset of the following episode is not predictable. Anemia, morning stiffness, rashes have been observed in some case (Condemi 1987; Feder 2000,).11,12,13 Behçet's disease manifests with aphthous ulcers of various sizes (from 1 to 3 cm) in the oral cavity, associated with genital ulcerated lesions, iridocyclitis, and synovitis. Furthermore, erythema nodosum, thrombophlebitis, and meningoencephalitis are also observed. The fever usually lasts more than 1 week, but it does not show the characteristic periodicity of PFAPA syndrome (Rakover et al. 1999; Ghate et al. 1999; Dahn et al. 2000).13,14,15

Cyclic neutropenia generally begins within the first year of life and is characterized by a reduction of the neutrophil count every 3 weeks. Febrile attacks are due to infections and an absolute monocytosis is often present during the febrile period. In PFAPA, febrile episodes do not have a regular frequency and neutropenia has never been reported. (Wright et al 1981; Arav-Boger et al 1997; Yang et al 1991; Feder 2000). FMF is an autosomal recessive disease that can be easily differentiated from PFAPmA by family history. It is characterized by periodic acute febrile episodes lasting a short time (usually 2 days), associated with arthritis, peritonitis, pleuritis, and rash. Most patients are of Arab, Armenian, Jewish, and Turkish descent and the onset of illness is generally in childhood. These children do not respond to steroid treatment (Raimann 1949; Meyerhoff et al. 1980; Wolff 1991; Gedalia et al. 1992; Arav-Boger et al. 1997; Padeh et al. 1999; Dahn et al. 2000) .Reported the first time in a northern European family (Scholl 2000), FHF, that is indicated also with the acronym TRAPS (Tumor necrosis factor receptor superfamily 1A-Associated Periodic Syndrome) (Dode et al. 2003), is an autosomal dominant disease. Likewise, this disorder may also be excluded by a negative family history. It is not periodic and manifests with arthritis, muscular pain, and rash (Williamson et al.1982; Lee et al. 1999)14,15,16

The hyperglobulinemia D syndrome, which is characterized by self-limiting febrile episodes (Range 3 to 7 days) of variable frequency (weeks or months), was described first time in 1980s. (Prieur and Griscelli 1983; van der Meer et al. 1984). Periodic fevers usually begin in infancy and may be associated with arthritis, cervical adenitis, chills, headache, macular rash, and splenomegaly. High serum Ig-D levels are present and are often associated with elevated serum Ig-A.16,17,18

4. Treatment

Treatment of PFAPA syndrome is controversial owing to the lack of epidemiologic information about the prevalence of the disease and the absence of controlled studies. Nonsteroidal anti-inflammatory agents and antibiotics have been used with disappointing results, and the existent literature supports the use of steroid therapy (prednisone 1-2 mg/kg) given as a single dose. Variations to this approach include increasing the dosage to up to 7 days and using alternate-potency steroid preparations, such as prednisolone (2 mg/kg/day)

for multiple doses, and betamethasone (0.3 mg/kg). Immune suppressants have had some effect for a brief period of time. The severe side effects of steroid therapy warrant caution in children, as frequent exposure to steroids has been associated with growth abnormalities. The risks might outweigh the benefits, as steroid therapy has been linked to shorter symptom-free intervals. Cimetidine, a common H2 antagonist, has immune modulating properties, inhibiting chemotaxis and T-cell activation. Cimetidine has been used with some success in dosages of 150 mg once or twice a day and 20-40 mg/kg/day.17,18,19 Thomas et al. reported a 43% efficacy of cimetidine in a group of 28 patients on data based on telephone recall. Eight of the 28 patients taking cimetidine had been symptom free for at least 6 months and were taking a dosage of 150 mg twice a day. Several reports underscore tonsillectomy and/or adenoidectomy.18,19

Owing to the observed slow healing of the oral ulcers, even in the presence of systemic steroid treatment, the authors suggest that management of the oral stomatitis in PFAPA syndrome include the short-term application of topical high-potency steroids on the affected mucosa.20,21,22 The aphthous ulcers should be exposed to the steroid for at least 20 min 2-3 times a day, for 3-4 days, depending on the number of ulcers that are present. Because most of the lesions in these patients are consistent with minor aphthous stomatitis, this approach is probably adequate for symptom management. When the stomatitis is severe, local steroid rinses (i.e. dexamethasone elixir) can be used to decrease inflammation and hasten healing in children older than 5, owing to the inability of younger patients to expectorate. Adjuvant therapy can be considered to alleviate oral symptoms, including a mixture of dyphenhydramine, lidocaine, and kaopectate, which serves as a mucosal protector and topical anesthetic during mastication.

Colchicine is used for therapy of FMF but has shown no efficacy in patients with PFAPA syndrome.11 Although colchicine has been moderately efficacious in the treatment of recalcitrant aphthous ulceration, current evidence does not support the use of this medication as an initial approach to treatment of oral aphthae. Furthermore, the effectiveness of colchicine in controlled oral aphthae trials has not been shown, in contrast to FMF.16,17,18,19

5. Clinical Significance in Dentistry

The role of the dentist, either as a consultant in a hospital practice or as a private practitioner, is to recognize the signs or symptoms that could be suggestive of periodic fever syndromes. Diagnosis of PFAPA syndrome is reached by exclusion of other periodic fever conditions, by means of a thorough serologic and immunologic workup. Although the major concern for pediatricians is the management of the acute febrile episodes, dental professionals can provide valuable expertise in managing the intraoral component of this syndrome. Effective control of the oral discomfort is of utmost importance in young patients, in light of the obvious nutritional compromise of reduced oral intake, and the rapid onset of dehydration in children which might require hospitalization. Often these patients can be initially misdiagnosed, especially because of the brief duration of the attacks and the prolonged periods of health in between them. The astute clinician should perform a thorough medical history of the patient who presents with the chief complaint of oral ulcers and fever, and consider PFAPA syndrome among the differential diagnoses. Many advances have been done in the diagnosis and pathophysiology of periodic fever syndromes which could prove useful in understanding the etiologic process of PFAPA syndrome and shed light into novel treatment approaches for this condition.

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