

Marshall's syndrome or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

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Summary

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.

Key words

Marshall's syndrome, PFAPA syndrome, periodic fever, tonsillitis, tonsillectomy, children's diseases, rare disease

Disease name and synonyms

Marshall's syndrome

Periodic fever, Aphthous stomatitis, Pharyngitis, cervical Adenitis (PFAPA)

Excluded disease

Other periodic febrile illnesses such as:

- Recurrent tonsillitis
- [Mediterranean fever \(FMF\)](#),
- [Familial Hibernian fever \(FHF\)](#),
- [Hyperglobulinemia D syndrome](#),
- [Behçet's disease](#),
- [Cyclic neutropenia](#),
- [Juvenile rheumatoid arthritis](#),

and number of infectious diseases should be excluded

Diagnosis criteria / Definition

In 1948, Raimann coined the term "periodic disease" to identify a heterogeneous group of disorders of unknown cause, characterized by short episodes of illness that regularly recur for several years alternated with healthy periods. Many periodic diseases have been subsequently described with well-defined clinical and laboratory characteristics. (Raimann *et al.*, 1949; Ehrenfeld *et al.* 1961; Sohar *et al.* 1967; Chajek *et al.* 1975; Wright *et al.* 1981; Reeves *et al.* 1984; van der Meer *et al.* 1984)

In 1987, Marshall *et al.* described a new periodic fever that was initially indicated as *Marshall's syndrome* and subsequently given the acronym *FAPA* (fever, aphthous stomatitis, pharyngitis, cervical adenitis) (Feder 1989). This was later changed to *PFAPA* (periodic fever, aphthous

stomatitis, pharyngitis, cervical adenitis) syndrome in order to emphasize the presence of periodic fever, which is considered a main characteristic of the illness (Marshall *et al.* 1989).

The Marshall's/PFAPA syndrome is defined clinically and diagnosis is made by exclusion. The dramatic resolution of febrile attacks by single oral administration of corticosteroids can also be used as diagnostic criterion (Padeh 1999).

Nevertheless, in order to facilitate recognition of the disease, in 1989 diagnostic criteria were proposed (Marshall *et al.* 1989), which were modified 10 years later (Thomas *et al.* 1999) (see table 1).

Table I. Diagnostic criteria for Marshall's/PFAPA syndrome (Thomas *et al.* 1999)

Regularly recurring fevers with an early age of onset (<5 years of age)
Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs: a) aphthous stomatitis b) cervical lymphadenitis c) pharyngitis
Exclusion of cyclic neutropenia
Completely asymptomatic interval between episodes
Normal growth and development

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. The diagnosis may be facilitated by means of bacterial and viral studies and antibiotic-therapy is usually effective in bacterial form. In this last type of tonsillitis, *Group A β-hemolytic Streptococci* is generally more isolated pathogen.

Several infectious agents (*Borrelia recurrentis*, *Streptobacillus moniliformis*, hepatitis B virus, *Rickettsia prowazekii*, *Entamoeba histolytica*, *Plasmodium malariae*, herpes simplex virus, Epstein-Barr virus) can also cause periodic fever. 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,).

[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; Ghatte *et al.* 1999; Dahn *et al.* 2000).

[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)

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. (Priour 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. During febrile

attacks, high levels of [mevalonic acid](#) are found in urine, a finding which has never been reported in patients with PFAPA syndrome (Grose *et al.* 1996; Feder 2000; Scholl 2000)

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 malaise. 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. In 1999, Thomas *et al.* and Padeh *et al.* reported respectively 94 and 28 patients affected by Marshall's/PFAPA syndrome. Both authors confirm the clinical picture observed by Marshall in 1980s. 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.

Management including treatment

The treatment of PFAPA syndrome is still a matter of debate. Administration of antibiotics (penicillins, cephalosporins, macrolides, and sulfonamides), nonsteroidal anti-inflammatory drugs (acetaminophen, ibuprofen), acyclovir, acetylsalicylic acid and colchicine has been shown to be ineffective, apart from the reduction of fever induced by anti-inflammatory agents. On the contrary, the use of oral steroids (prednisone or prednisolone) causes a dramatic resolution of

febrile episodes, although it does not prevent their recurrence. (Marshall *et al.* 1987; Scimeca *et al.* 1996; Thomas *et al.* 1999; Padeh *et al.* 1999).

Other authors have described successful results with cimetidine (Feder 1989, 1992; Lee 1999) a H₂-antagonist that inhibits suppressor T cells by blocking histamine H₂ receptors. Moreover, this drug increases interferon production, eosinophil and neutrophil chemotaxis, neutrophil lysosomal enzymatic release, and migratory inhibitory factor production. (Jorizzo *et al.* 1980; Melman *et al.* 1981; Talpaz *et al.* 1982)

In 1989, Abramson *et al.* reported for the first time the efficacy of tonsillectomy with adenoidectomy in 4 children with PFAPA. Resolution of symptoms was observed in all patients; however, other authors expressed some criticism on this therapeutic strategy because of the limited number of patients. (Thomas *et al.* 1999).

Thomas *et al.* in 1999 presented an interesting report in which they described a large series of patients with Marshall's/PFAPA syndrome, most with long-term follow-up. By follow-up telephone interviews with parents, 34 of 83 (41%) children had not had fever for one or more years after a mean duration of 4.5 years before resolution. The remaining patients (59%) had presented febrile episodes within the past year, with a mean interval of 40.2 days and, in particular, 2 patients continued to have attacks after more than 17 years. Analysis of the different therapeutic strategies (antibiotics, anti-inflammatory drugs, colchicine, steroids, cimetidine, tonsillectomy with or without adenoidectomy) used in these children confirmed the positive effect of steroids and considered cimetidine and surgical procedure as effective treatments. H₂-antagonists were given to 28 patients, but resolution of illness was observed in only 8 cases (28.5%). Moreover, reversal of cimetidine-induced remission was reported upon discontinuation of the drug in several children. On the contrary, tonsillectomy was successful in 7 of 11 (64%) patients and improved symptoms in another 2 of 11 (18%). These authors recommended the use of steroids (prednisone or prednisolone) for treatment of Marshall's/PFAPA syndrome, since it may persist for many years without long-term health consequences.

To date, data regarding the long-term efficacy and possible rebound phenomena associated with steroids are not available (Padeh *et al.* 1999). Furthermore, an increased frequency of the febrile cycles and persistence of fever and other symptoms have been observed in some children after steroid therapy (Thomas *et al.* 1999; Padeh *et al.* 1999). Finally, Marshall's/PFAPA syndrome resolves spontaneously after several years in about 40% of patients (Thomas *et al.* 1999), and, in some cases, neurobehavioral and social effects such as

difficulties with peer relations and absenteeism from school have been observed.

In 2000 Dahn *et al* emphasized the role of tonsillectomy with or without adenoidectomy in the management of PFAPA, reporting successful results in 5 children. More recently, (Galanakis *et al* 2002) observed similar results in a cohort of 15 patients. Thus to our knowledge, a total of 43 patients with PFAPA have undergone surgical procedures, including our series (5 children) (Abramson *et al.*1989; Thomas *et al.* 1999; Padeh *et al.* 1999; Dahn *et al.* 2000; Galanakis *et al.* 2002; Berlucchi *et al.* 2003). Overall, tonsillectomy was successful in 90.6% of children and improved symptoms in 4.6% of cases.

In conclusion, we believe that tonsillectomy (with or without adenoidectomy) can be currently considered the ideal treatment for patients with Marshall's/PFAPA syndrome.

Etiology

At present, the cause of Marshall's or PFAPA syndrome remains unknown. The ability of steroids to resolve febrile episodes in PFAPA-patients seems to suggest that the origin of illness may be inflammatory. Elevated levels of cytokines observed during attacks could support this hypothesis (Thomas *et al.* 1999). Finally, since Marshall's/PFAPA syndrome does not recur in most children after tonsillectomy, it is postulated that the disease can be elicited by an immunologic process beginning at the level of the tonsillar parenchyma. Studies on the tonsillar immunologic profile could provide additional information on the pathogenesis of this rare disease.

Diagnostic methods

In order to rule out other periodic febrile illnesses, the following tests are recommended: cultures from the oropharynx for bacterial, fungal, and viral pathogens, chest radiography, and laboratory studies (complete blood counts made biweekly for 6 weeks, total hemolytic complement, quantitative immunoglobulins, IgG subsets, IgD, antinuclear antibody, C3, lymphocyte T4/T8 ratio, Epstein-Barr virus and adenovirus serology). These specific laboratory and culture analysis are usually negative except for leukocytosis and an elevated erythrocyte sedimentation rate during febrile attacks.

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