# *PFAPA Syndrome (Periodic Fever, Adenitis, Pharyngitis, Aphtous Stomatitis) Understanding an Autoinflamatory Disease*

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Most physicians have already seen children with recurrent infections of the oral cavity, especially pharyngitis, stomatitis and high fever, in episodes that last for 3 to 5 days. The most significant aspect in these patients is that whatever the adopted therapy (antibiotics, steroids, NSAIDS), two things invariably occur: the first one is that the patients improve, and the second is that the disease reappears approximately one month later.

Periodic fevers have been a concern among physicians for a long time. In a pioneering study published in JAMA, in 1948, Reinmann described 50 children with periodic fever, recurrent abdominal pain, lesions particularly in the oropharynx region, some of them presenting arthralgia and others neutropenia as well. Reinmann was, in fact, describing two types of children: those with PFAPA and those with cyclic neutropenia.

In 1984, Van der Meer described another entity causing periodic fever in children, the Hyper IgD, which is found among Dutchs and more rarely among those of French or German origin. These children have significant abdominal prodromes such as diarrhea, nausea, vomit, abdominal pain, skin rash, periodic fever and splenomegaly.

In 1987, the University of Connecticut Pediatrics group described children possibly presenting Marshall's Syndrome or PFAPA. These children had periodic fever with recurrent cervical adenitis, stomatitis and pharyngitis.

In a study that included 28 Israeli children, Padeh, Brezniak & Zemer suggested that PFAPA could be considered as a superinfection: with onset occurring always before 5 years of age. The authors also noted the ethnic diversity of the patients, the reduced severity of episodes with the use of steroids and the cure of some patients after tonsillectomy. On the other hand, the presence of aphtous stomatitis, the duration of the Syndrome, and the clinical response to steroids together with an asymptomatic period before the episodes, would lead us to think of an immune system disorder.

**The immunlogic explanation – autoinflammatory disease**

The PFAPA syndrome belongs to the group of the autoinflammatory diseases. The etiology occurs due the immune system activation and it is antigens-antibodies independent.

The protein secreted and synthesized by T-B and NK lymphocytes are know as

cytokine, which some of them receive the classification of interleukin (IL). These proteins act on local modal or systemic to promote and facility the immune cells differentiation and proliferation.
Stojanov, Hoffmann, Kery coworker (2006) observed an increased of the serum level in proinflammatory cytokine (IL-1 beta, IL-2, IL-12, INF-gamma) and a decreased of the serum level in anti-inflammatory cytokine in fever episodes in 40 children with PFAPA.
The children with PFAPA in intercritical periods presented high levels of proinflammatory cytokine and regulation of migration lymphocytes such as (IL-1, IL-2, IL-8, TNF-alfa and gamma).
These findings suggest the immunologic explanation for this syndrome with the immune system dysregulation, with an activation of the proinflammatory cytokine and a decrease of the anti-inflammatory cytokine.
The next years, we expected to identify the molecular mechanism, genetics process in PFAPA syndrome and others periodic fever in childhood.

**Criteria for diagnostic inclusion**

In 100% of the cases, children (<5 years of age) start presenting recurrent fever episodes. The fever lasts for approximately 5 days, never less than 3 and rarely more than 7, with the presence of aphtous stomatitis in 80% of the cases. Stomatitis affects mainly the anterior region of the mouth, allowing a differential diagnosis from herpangina, and as a rule does not involve the gums, allowing us to exclude herpetic gingivostomatitis. In general lesions are small, measuring less than 3 mm, which allows us to exclude Behcet's disease.
In 75% percent of the cases, during recurrent fever episodes, these children present cervical adenitis, small lymphonodes in the upper cervical area, which are mobile, painless, and also the last ones to disappear. Pharyngitis is found in 90% of these children with diffuse hyperemia of the tonsils and the whole palate.
Important for the diagnosis of PFAPA is the exclusion of other periodic syndromes, such as Familial Mediterranean Fever, Hyper IgD and Juvenile Rheumatoid Arthritis, as well as Behcet's Disease among others. Perhaps the most important differential diagnosis is cyclic neutropenia, in which children present with recurrent fever that lasts for a period of time similar to PFAPA, but with a very significant difference. First, the child looks really sick during the episodes and the fever recurrences lead to a delay in weight and growth gain.
Children with PFAPA go through an asymptomatic period between episodes, in which they are very well and have normal growth and development.

**Laboratory tests**

Serial blood tests are required for the exclusion of clinical neutropenia, though mothers hesitate in submitting their child to repeated CBC and this may well be the greatest diagnostic difficulty.
Serum immunoglobulins, VHS, FAN and C-reactive protein must be evaluated. Results of the acute phase tests are usually normal: VHS is low and C-reactive protein is invariably lower than 10. It should be remembered that FAN is positive in only 20% of cases of systemic juvenile rheumatoid arthritis, but even when it is negative, VHS and C-reactive protein are elevated.

Serology for cytomegalovirus, herpes and Epstein-Baar should be requested in at least one episode. A tonsillar secretion culture should be conducted in at least 2 different, non-sequential episodes.

**Differential diagnosis**

The three main affections to be excluded are cyclic neutropenia, Familial Mediterranean Fever and Hyper IgD.

Fever episodes also start before 5 years of age in cyclic neutropenia, and their duration is reasonably similar to those caused by PFAPA, though, in general, there is no cervical adenomegaly, whereas splenomegaly is a quite common finding. Children with cyclic neutropenia present very painful lesions that also involve the gum. Recurrent cyclic neutropenia episodes generally lead to tooth losses as well as to severe periostitis and periodontitis.

One of the causes of periodic fever in childhood to be always excluded is Familial Mediterranean Fever. Its onset may not always occur before 5 years of age. It may start in childhood, during adolescence or even in young adulthood. It is generally found among Jews, Turks, Armenians and Arabs and includes recurrent fever and polyserositis, especially peritonitis and pleuritis. As a rule, children with Familial Mediterranean Fever improve with colchicine.

In the Hyper IgD Syndrome, fever starts invariably before one year of age. The child presents with recurrent fever but has also significant systemic signs. Besides pharyngitis, adenitis and stomatitis the child may present macular petechial rash as well as generalized serositis.

**Therapy**

Once the child presents with recurrent fevers and has been included in Marshall's Diagnostic criteria, therapy should be started. The proposed regimen includes prednisone, 1 to 2 mg per kilo/day during 3 to 5 days. In general, when the child responds to prednisone there is an improvement after the second dose. The sole negative aspect of steroid-based treatment is that it seems to reduce the interval between episodes. In their study of 94 Syndrome-bearing children in the US, Thomas, Feder & Marshall found only one Cushing's Syndrome case, due to an obviously wrong use of the corticoid and an intestinal perforation in one of the children.

For those children that do not respond to steroids, the second option is cimetidine. Cimetidine seems to be an immune system regulator that increases the production of interferon and modulates the release of cytokines and of the chemotactic factor of neutrophils, and should be given at 20-40 mg/day as a single dose or divided into two, for 6 up to 8 months.

Tonsillectomy has also been proposed, especially in cases of hypertrophy.

Thus, every child presenting with periodic fevers and stomatitis, cervical adenitis or pharyngitis could be a PFAPA patient. Once other causes of periodic fever in childhood are excluded and the diagnosis is established, therapy should start with the purpose of reducing the recurrence rate, improving the child's quality of life and decreasing the family anxiety levels.

## Recommended readings

1. Reinmann HA. Periodic disease: periodic fever, periodic abdominalgia, cyclic neutropenia, intermittent arthralgia, angioneurotic edema, anaphylactoid purpura and periodic paralysis. JAMA 1949;141:175-83.
2. Ver der Meer JWM, Vossen JM, Radl J, van Nieuwkoop JA, Meijer CLMJ, Lobbato S, Van Furth R.Hiperimmunoglobulinaemia D and periodic fever: a new syndrome. Lancet 1984;1:1087-90.
3. Padeh S, Brezniak N, Zemer D, Pras E, Livnrh A, Langarevitz P, Migdal A, Pras M, Passwell JH. Periodic fever, aphtous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. J Pediatr 1999 Jul;135(1):1-5.
4. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 1987;110:43-6.
5. Drenth JPH, van der Meer JWM. Hereditary Periodic Fever. The New England Journal of Medicine 2001; 345:1748-57
6. Stojanov S, Hoffmann F, Kery A, Renner ED. Cytokine profile in PFAPA syndrome suggests continuous inflammation and reduced anti-inflammatory response. Eur Cytokyne Netw 2006 Jun;17 (2):90-7