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PFAPA syndrome: A practical review

Abstract

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is rare, benign recurrent/periodic fever syndrome of unknown etiology that normally affects children under the age of 5. The diagnosis is made based on clinical assumption, after excluding other pathology. In this report to provide a practical assessment of PFAPA syndrome regarding epidemiology, pathogenesis, natural history, clinical manifestations, diagnosis criteria, differential diagnosis, and available medical and surgical treatments.

Keywords: periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis, syndrome, pfapa, autoinflammatory diseases

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Abbreviations : ESR, erythrocyte sedimentation rates; CRP, C-reactive protein; FMF, familial mediterranean fever

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a benign recurrent/periodic fever syndrome of unknown etiology. Periodic fever syndromes are autoinflammatory diseases characterized by attacks of unprovoked inflammation. They differ from autoimmune conditions by the lack of pathologic adaptive immune responses (autoreactive antibody or T cell responses). Most periodic fever syndromes are rare, and some have monogenic inheritance. PFAPA, however, does not, and is the most common diagnosis among these patients, despite being an exclusion diagnosis. It was first described by Marshall et al[1] and therefore also known as Marshall's syndrome. In 1989, the acronym FAPA has been proposed and later changed to PFAPA to highlight the importance of the main symptom, periodic fever.[2,3] The aim of this review is to provide a practical assessment of PFAPA syndrome regarding epidemiology, pathogenesis, natural history, clinical manifestations, diagnosis criteria, differential diagnosis, and available medical and surgical treatments.

Material and methods

The Cochrane Library and MEDLINE/PubMed databases were searched (with results until July 2021) according to the published guidance on narrative reviews4. The following keywords were used: "periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome", "PFAPA", "FAPA", "Marshall's syndrome" and "autoinflammatory diseases". Articles in English and Portuguese were analyzed as well as relevant studies from the references.

Literature review

Epidemiology

PFAPA syndrome (together with familial Mediterranean fever) is the most common periodic fever syndrome, and it normally begins in the pediatric setting, between 1-4 years of age.[5-7] There seems to be no predilection for a particular ethnic or racial group.[8-12] According to the described natural history, the periodic attacks tend to cease by 10 years old,[13] but they can continue into adulthood. In a small subset of patients, the periodic fever episodes only start in adulthood,[14,15] although its incidence in this age group remains to be elucidated.[16]

Pathogenesis

The pathogenesis of PFAPA, to this day, remains unknown.

Two main etiopathogenesis theories can be identified: infectious etiology and autoinflammatory etiology. The former is highly unlikely, given that there is no response to antibiotics, lack of affected close contacts during exacerbations and no seasonal predominance.[16] In addition, no consistent differences in the presence of virus or bacteria in the flora of the patients with PFAPA and controls have been found.[17-19]

The autoinflammatory etiology is favored by the periodic fever, presence of aphthous ulcers, quick cessation of attack with corticosteroids[20] and increased incidence in early childhood (since it is a period characterized with immunologic immaturity).[14] It seems to be a complex interaction between polygenetic factors that predispose an individual to respond to a trigger (probably environmental factors) in an exaggerated way.[21] High rates of response to tonsillectomy suggest that this trigger may accumulate/originate in tonsils.[16]

Clinical Manifestations

The most important feature of PFAPA syndrome is periodic fever. The child has normal growth and development and usually there are no symptoms or abnormal laboratory values between episodes.

Fever – PFAPA flares usually last for 3-7 days and recur every 2-8 weeks.[16] Fever begins abruptly and may have a prodrome of symptoms such as malaise, irritability, mood change, sore throat, or aphthous ulcers.[22] Temperatures are high and normally range from 39-40.5ºC[23] and rarely last for more than seven days.[22] The average duration is 4-4.5 days.[24-25] The fever is more prominent at early stages of the disease and the attacks get less severe and with longer intervals as the child grows.[26] As noted, before, there is no seasonal predominance.

Pharyngitis – present in 65-100% of cases.[3,16,22] It can be unilateral or bilateral[22] and can be erythematous or exudative.[16] Aphthous stomatitis – occur during episodes in approximately 40 to 80% of patients.[22] Normally, ulcerations occur in the inner lips or buccal mucosa (non-masticatory surfaces).[6,22] They may go unnoticed, especially in small children, therefore a careful physical exam is recommended.

Cervical Adenitis – accompanies the flares in 72-88% of cases13 and normally are bilateral, moderately tender and < 5cm in diameter.[27] Other symptoms – headaches, nausea/vomiting, abdominal pain, joint pain, skin rash may occur but are less frequent.[24,25,28,29] Prominence of symptoms outside the oropharynx and atypical symptoms should alert for the possibility of an alternative diagnosis.[22]

Laboratory findings

There are no specific laboratory findings. The diagnosis is based on clinical history and physical examination.

Normally, during the acute phase, lymphopenia, neutrophilia and monocytosis can be observed, as well as elevation of erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP). These findings are typically absent between attacks. Procalcitonin elevates during bacterial infections, but not during PFAPA flares,[30,31,32] a finding that can be unique and helpful in the differential diagnosis. However, more studies are needed.[22]

There are several more biomarkers studied to differentiate PFAPA from bacterial infections, monogenic autoinflammatory diseases and other conditions, but none of them are used in real day-to-day practice.

The reader is referred to the article from[16] for more information about this topic.

Diagnosis criteria

Several diagnosis criteria have been proposed, however no universally accepted criteria have been developed.[22]

The original Marshall criteria were defined in 1989[2] and have been later modified by Thomas et al in 1995[8] – Modified Marshall's criteria – and include the following features:

- Age of onset < 5 years of age
- Recurrent occurring fevers
- At least one of the three following features: Pharyngitis, Cervical Adenitis and/or Aphthous Stomatitis
- Completely asymptomatic between flares, with normal growth and development
- Exclusion of Upper Respiratory Tract Infections (URTI) and Cyclic Neutropenia

More recently, Vanoni et al., defined new criteria for the diagnosis of PFAPA,[33] as described below. Its utility remains to be seen.

- Age of onset < 6 years of age
- Periodic fever ≥ 6 months

Daily fever of ≥ 38.5 °C (axillar) for 2-7 days

≥ 5 regularly recurring fever attacks with ≤ 2-month intervals

- At least one of the three following features in every episode: Pharyngitis, Cervical Adenitis and/or Aphthous Stomatitis; with at least two in most of the episodes
- Full recovery between flares with normal linear growth
- Exclusion of Infections, Immunodeficiencies, Cyclic Neutropenia and other causes of recurrent fever

Differential diagnosis

As stated before, PFAPA syndrome is an exclusion diagnosis since there are no pathognomonic features. Therefore, some conditions need to be excluded before making the final diagnosis.

The key aspects for the diagnosis are:

- Periodic Fevers/flares (that are similar between them and occur at regular intervals)
- Absence of symptoms (and inflammatory biomarkers) between episodes
- Normal growth and development
- Quick cessation of each attack after 1 or 2 doses of corticosteroids

The latter aspect may be useful to distinguish from hereditary autoinflammatory periodic fever syndromes, including Familial Mediterranean Fever (FMF) and hyperimmunoglobulin D (hyper-IgD) syndrome (HIDS).[9,14,22] Also, these syndromes are not truly periodic, because they do not have a consistent interval between episodes[22] and normally have other symptoms outside the cervical area. The diagnosis needs to be reconsidered if the fever recurs after 2mg/kg prednisone per episode.[22] However, since the differential diagnosis can be quite difficult, a low threshold for genetic testing (MVK, MEFV, and TNFRSF1A) should be kept. The Gaslini diagnostic score can be helpful to determining who needs a genetic analysis.[34] According to this score, genetic testing should be done only in patients who do not fulfill the criteria for PFAPA.[22] The presence of abdominal pain, chest pain and diarrhea, as well as the absence of oral aphthosis and young age at onset correlates with a positive test result.[34]

We recommend a quick bloodwork (to exclude neutropenia) in at least one of the episodes, so that Cyclic Neutropenia can be excluded because the clinical manifestation closely resembles PFAPA. Based on clinical history and physical examination, viral/bacterial URTI and alternative diagnosis (i.e other infectious diseases, malignancy, etc.) can normally be excluded. As stated before, procalcitonin may be helpful distinguishing from a bacterial infection and throat swabs are important to exclude streptococcal tonsilitis.[16]

Management and treatment

PFAPA is a benign disease with resolution in most patients by 10 years of age and the episodes tend to be less severe, less frequent, and shorter in duration with time.[15] There is no consensus on the treatment. Since children grow and develop normally with no long-term sequelae,[15] treatment of any kind is optional. It depends upon response to treatment and how disruptive the flares are to the child (i.e missing several days of school per month) and family (i.e missing days of work or family stress).[22]

Therapy options can be divided in 3 groups:

- Crisis (acute) therapy
- Prophylactic therapy
- Possibly Curative therapy

As stated above, before discussing the advantages and disadvantages of each therapy, we emphasize that observation is acceptable, since no long-term sequalae have been described, although it is not our practice to do so.

Crisis therapy

Antibiotics are not effective.[20,35,36,37]

Antipyretics may be used, although the efficacy in reducing the symptoms is not high. Acetaminophen is only effective in one quarter of patients and nonsteroidal anti-inflammatory drugs (NSAID) are effective in more than half, as reported by Wurster et al., One dose of corticosteroid (for example prednisolone 1 mg/kg orally) results in abrupt cessation of attacks in 85-95% of patients.[16] The fever normally subsides in few hours,[5,9,14] although the other classic symptoms take longer to resolve.[22] A second dose (1mg/kg orally) may be given 12-24 hours later,[7] especially if the fever recurs.

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Two disadvantages of corticosteroid therapy when used during acute attacks in PFAPA syndrome are potential systemic side effects (a feature that worries some parents) increase in the frequency of acute episodes in PFAPA syndrome

The toxicity related to the low dose of glucocorticoids used in PFAPA (normally < 2mg/kg per month) is theoretically very low and has not been reported, except with the description of possible restlessness and change in moods in the day of administration,[22] although no studies have specifically examined what dose of glucocorticoids can be used in this syndrome.[22] An increase in attack frequency could be observed in the long-term use of corticosteroids as reported in several different studies.[38,39] This occurs in 19-50% of patients.[40-41]

Patients requiring more than 2mg/kg of glucocorticoid per episode should be evaluated for other periodic fever syndrome, as stated above. Therefore, apart from the therapeutic aspect described, glucocorticoid administration also plays a role in the diagnosis,[22] and that is why we recommend its administration at least once.

There are also several reports describing a cessation of attacks with IL-1 inhibitors, but its usage is not widely spread yet.[42,43]

Prophylactic therapy

There have been several drugs reported, but only cimetidine or colchicine have been used consistently with some efficacy so far. Cimetidine is a histamine H2-receptor antagonist with immunomodulator capacities. There are no randomized controlled trials with cimetidine prophylaxis, but its beneficial effect has been noted in some case series and case reports.[22] In cohort studies, a quarter of patients had complete resolution of the episodes, a third had partial efficacy with reduction of severity or frequency and the remainder had no effect.[22] The dose described is 20 to 40 mg/kg/day every 12 hours (maximum 1200mg/day).[22] An attempt to discontinue is appropriate after 6 to 12 months. Normally is well tolerated with few side effects.

Colchicine, the main treatment for Familial Mediterranean Fever, has been used for prophylactic treatment in patients with PFAPA syndrome. The mechanism of action in PFAPA syndrome remains to be elucidated.[16] The majority (few) of the randomized trials and/or retrospective studies were conducted in Israel, where a large proportion carries pathogenic MEFV variants[22] which could compromise the interpretation of the results. Most of the patients in these studies had fewer episodes with longer interval between them. The recommend dosage is 0.6 to 1.2 mg/day in children 4-6 years and 1.2-1.8 mg/day in children > 6 years).[22] The major side effects are abdominal pain, diarrhea and lactose intolerance. These side effects can be minimized by slowing increasing dosage over several weeks (0.3mg/day).[22]

IL-1 inhibitors (anakinra) have also been reported to be effective, although its cost-effectiveness is probably not favorable, since PFAPA is a benign disease with no major complications.[16] Because patients with PFAPA syndrome have been reported to have lower levels of 25 (OH) vitamin D compared with healthy controls,[44,45] vitamin D, has been proposed as an effective alternative in reducing the number of episodes and CRP levels, especially during winter months. However, controlled trials are needed to prove its efficacy.

Possibly curative therapy

Total Tonsillectomy is an effective surgical treatment for patients with PFAPA. In a recent review of several studies, with a total number of 555 children, tonsillectomy was curative in 92% of cases.[46] Adenoidectomy alone seems to have no benefit,[20,35,36] and the efficacy of the addition of adenoidectomy to tonsillectomy is uncertain, according to a Cochrane systematic review.[47] A recurrence of aphthous stomatitis has been reported after tonsillectomy.[22] The risks of the surgery and the benign course of the disease need to be considered when deciding the appropriate management. It can be especially useful in patients who fail to respond to medical therapy or have considerable disruption of theirs lives.[22] In our opinion, since it has excellent response rates and there are few alternatives, it can be used as a second line therapy.

Conclusion

PFAPA syndrome is one of the most (if not the most) common periodic fever in children. It remains, however, a rare and difficult condition to diagnose, being an exclusion diagnosis. It has a benign course, with no long term sequalae, with spontaneous resolution by 10 years old in most cases. Single dose corticosteroid therapy is the most effective therapy for acute attacks, but it has the disadvantage of increasing the frequency of the flares with repeated use. The only possibly curative therapy is total tonsillectomy, recommended by some at the diagnosis, while others never recommend it. Treatment guidelines for PFAPA syndrome based on controlled studies are needed, as well as a better understanding of the disease itself.

Conflicts of interest

No conflicts of interest.

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