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Towards better diagnostic criteria for PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome

Short running title: Diagnosis and treatment of PFAPA

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Abstract

Aim: Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is the most common cause of a periodic fever in childhood. The exact pathogenesis and the aetiology of PFAPA are still unknown.

Methods: We conducted a non-systematic review of published articles about PFAPA syndrome and summarized the evidence for diagnostic criteria and treatment options for PFAPA.

Results: The first proposed diagnostic criteria for PFAPA, in addition to periodic fever, included aphthous stomatitis, pharyngitis or cervical lymphadenitis in children younger than five years at the beginning of the symptoms. C-reactive protein (CRP) levels and leukocyte counts increase in most patients during episodes. Recent research reveals that tonsillectomy provides an immediate and long-lasting cure for PFAPA, even in the absence of classic criteria of aphthous stomatitis, pharyngitis or cervical adenitis and in children older than 5 years.

Conclusion:

We suggest that PFAPA can be diagnosed in children with at least five regularly occurring fever episodes without any other explanation, even in the absence of aphthous stomatitis, pharyngitis or cervical lymphadenitis and also in children older than five years.

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Key notes

- After the introduction of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) in 1987, cumulating research evidence has clarified clinical features of the syndrome.
- Tonsillectomy provides an immediate and long-lasting cure for PFAPA, even in the absence of classic criteria of stomatitis, pharyngitis or cervical adenitis and in children older than 5 years.
- It is time to reconsider the diagnostic criteria for PFAPA in future research and in clinical practice.

Introduction

In 1987, Marshall et al. published the first series of 12 patients with an earlier unknown periodic fever syndrome (1). The term 'periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome' (PFAPA) was introduced two years later (2) since most of the patients in the original series presented with local findings in the mouth and throat. Based on the main clinical characteristics of the first 12 patients, Thomas et al. suggested the first proposed diagnostic criteria for PFAPA (3) (Table 1). The syndrome has become better recognised and research has increased. The purpose of this review is to evaluate whether we have enough evidence to clarify the diagnostic criteria for PFAPA.

Methods

We performed a literature search at PubMed from 1987 to 31.12.2018 with the term PFAPA and collected relevant articles for nonsystematic review. The focus of this review is in the diagnostic

criteria and treatment of PFAPA syndrome in children and the most important results from the articles concerning the pathogenesis are also covered.

Results

Epidemiology and clinical picture

The only published population-based estimate of the incidence of PFAPA, from a study in Norway, is 2.3/10,000 per year in children up to five years of age, making PFAPA the most common paediatric periodic fever syndrome (4). In Finland, using our earlier population-based cohort of 133 PFAPA patients that had undergone tonsillectomy between 1990-2007, the annual incidence would have been 2/10,000 children up to five years of age (5). PFAPA occurs in both sexes with a slight male predominance of 55-65% (3,6-8). The syndrome has been reported in patients of different ethnicities (3,6,7).

Age

The first symptoms of PFAPA syndrome begin most often between the ages of 11 months and four years (4,6,8,9). However, febrile episodes have been reported to begin at an older age, and even among adults (7,10-12). In the first cohort of 12 PFAPA cases (1), not all patients had their first symptoms before the age of 5 years. In large cohorts, 10-20% of PFAPA patients experience their first symptoms after five years of age (5-7). Data on adult cases of PFAPA is limited and the results from paediatric studies may not be applicable to adults (10-11,60).

Fever

The most distinctive feature of PFAPA is a clockwork periodicity of fevers (13-15). In most cases the episodes can be forecasted within a margin of 7 days (5). During the fever flares, the average highest temperature is 39.3–40.5 °C for a mean of four days (Table 2)

(3,4,6,7,16). As inflammatory markers rise during the fever flare, the first episodes are often empirically treated with antibiotics after sepsis workout. In patient series, the mean or median maximum C reactive protein (CRP) values during the flares range between 120–179 mg/l (17,18). The patients are asymptomatic on average for 24 days between the febrile episodes (3,4,6,7,16). However, due to the regularly occurring symptomatic days, the health-related quality of life of children with PFAPA is markedly lower than that of healthy children (19).

Other symptoms

In large PFAPA patient series, 60-90% of the patients have pharyngitis, 40% tonsillitis, 53-93% cervical lymphadenitis and 27–57% aphthous stomatitis at least sometimes during the fever flares (Table 2) (3-7). In these studies the children had clinical examination only once during the fever episodes and we do not know if the results would change with repeated examinations on consecutive symptomatic days. The literature shows that 30-76% of PFAPA patients have additional symptoms, such as abdominal pain, nausea, diarrhoea and arthralgia (7,20).

Differential diagnostics

Recurrent viral infections, common in small children, constitute the most important differential diagnostic option for the diagnosis of PFAPA. Increased inflammatory markers during recurrent fever episodes are an important clue for differentiating PFAPA from recurrent viral infections. Even though adenovirus infections in small children may mimic a single PFAPA episode with an elevated CRP value and tonsillitis, recurrent febrile episodes with a high CRP value are typical for PFAPA. At the time of PFAPA fever flares, family members and other close contacts of the patient remain healthy (6).

During the first episodes, when the patients present with high fever without an explanation and inflammatory markers rise, exclusion of bacterial infections using blood, throat and urine cultures are often necessary. Malaria and other tropical infections may cause recurrent fevers, but the episodes seldom appear as regularly as in PFAPA (21).

Cyclic neutropenia affects one per million people in the general population. The patients have periodic fevers about every 21 days, and blood neutrophil levels oscillate, being near zero for several days during the cycle. Painful mouth ulcers, cellulitis and other invasive infections may be associated with the disease. Cyclic neutropenia can be diagnosed with genetic tests, repeated neutrophil counts and bone marrow samples (22).

Monogenic autoinflammatory fever syndromes, such as Familial Mediterranean Fever (FMF), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS) and hyperimmunoglobulinemia Dare important entities in differential diagnostics of PFAPA, but their role in practical diagnostics depends on the ancestry of a population (21,23). For example, the prevalence of FMF is very high - more than one in 256 in some parts of the Middle East - but the disease is extremely rare in patients with Northern European ethnicity (24-26). In the recent proposal of a new nomenclature for autoinflammatory diseases, the word ‘periodic’ remained in the names of three conditions: CAPS, TRAPS and PFAPA (27).

Monogenic autoinflammatory syndromes are often chronic and progressive diseases with significant morbidity (28,29). The incidences of all monogenic periodic fever syndromes are markedly lower than those of PFAPA in children with Northern European ethnicity (Table 3). In PFAPA, most patients have regular clockwork episodes of fever with healthy periods between, whereas in monogenic fever syndromes the symptoms occur more irregularly. A symptom diary is the main tool to determine the pattern of periodicity and symptom profile of

the disease and to separate PFAPA from other recurrent fever diseases (21). Genetic analysis of a large cohort comprising both PFAPA patients and monogenic autoinflammatory syndromes showed that genetically positive patients had more abdominal pain, diarrhoea, vomiting, cutaneous rashes and arthralgia than PFAPA patients (13). The prominence of these symptoms, at least in patients nonresponsive to tonsillectomy, should lead to genetic testing even in populations where monogenic autoinflammatory syndromes are rare. In the era of feasible genetic panels and whole exome sequencing, rare genetic causes for recurrent fevers have become easier to exclude.

Risk factors and associations to other diseases

In a cohort of 119 PFAPA patients, PFAPA was associated with risk factors similar to common childhood infectious diseases (30). Lack of breastfeeding, maternal smoking, the history of respiratory infections and use of antibiotics was more common in PFAPA patients than in healthy controls (16,30). Vitamin D deficiency has been found to be more common in PFAPA patients compared to that of matched controls (31), and a diminishing of symptoms has been found to occur with vitamin D supplementation (32). The growth of PFAPA patients is similar to those of age- and sex-matched controls (16). In a long-term follow-up, the occurrence of subsequent autoimmune diseases after treatment for PFAPA has not been different from that of matched controls (16). Interestingly, oral thrush was reported more commonly in the history of PFAPA patients compared to the controls (16).

Aetiology and pathogenesis

During febrile episodes, erythrocyte sedimentation rate, CRP levels and leukocyte counts, due to elevated neutrophil and monocyte counts, increase in PFAPA patients but normalise after the flare (18,33-35). However, the serum procalcitonin level remains low throughout the febrile period (36-39). Serum amyloid A levels are high at the time of PFAPA fevers but decrease between the flares, unlike in many autoinflammatory fever syndromes (34,36). Quantitative immunoglobulin levels are normal in PFAPA patients (6,17,40).

The inflammatory process that causes the symptoms of PFAPA includes increased production of interleukin 1β (IL -1β) and IL-18 in inflammasomes (36,41,42). Even during healthy periods, the serum levels of proinflammatory cytokines IL-1b, IL-6, TNF-a, CXCL-10 and IL-12 remain elevated while anti-inflammatory IL-4 is lower in patients compared to healthy controls (40,42,43).

Since the signs of inflammation in PFAPA often localise in the pharyngotonsillar region, and tonsillectomy has been shown to be an effective treatment for the syndrome (17,44), the palatine tonsils have been a logical focus of research. The histology of palatine tonsils in PFAPA has not shown significant differences when compared to tonsil tissues removed for other reasons (45,46), but the distribution of both B- and T-lymphocytes and the production of pro- and anti-inflammatory cytokines seems to be different (35,42,47,48). Tonsils removed from PFAPA patients have revealed smaller amounts of B- lymphocytes and more naive polyclonal T-lymphocytes when compared to tonsils removed for other reasons (48). The number of cytotoxic T cells has been higher and production of anti-inflammatory IL-4 lower in both tonsils and blood in PFAPA patients than in controls (43).

The trigger of the febrile response and cytokine production in PFAPA is not known, but host-microbe interaction has been considered to be the most likely possibility (42,48,49). With routine clinical microbiology, the throat or tonsillar samples of PFAPA patients have revealed no evident viruses or bacteria responsible for the symptoms (4,46,48,50). However, unspecific biofilms and *Candida albicans* were found more often and *Staphylococcus aureus* less often in tonsil samples removed from PFAPA patients compared to controls (46).

With next-generation sequencing of the bacterial 16S gene, differences in bacterial microbiota between PFAPA patients and hypertrophic tonsils have been shown (51). At the phylum level, PFAPA tonsils were more likely to contain *Cyanobacteria* and *Synergistetes* than controls. At the genus level, the mean relative abundance of *Streptococci* was lower and that of *Prevotella* higher in the cases than in controls (51).

Genetics

Family members of PFAPA patients have PFAPA, other recurrent fevers or recurrent tonsillitis in 17-78% of cases (4,7,52-54). Published pedigrees of families with PFAPA syndrome have features of an autosomal dominant inheritance pattern (53,55). Patients with monogenic autoinflammatory diseases, such as familial FMF and TRAPS, have mutations in inflammasome-related proteins, which results in an abnormal innate immune response. Any mutations or variants in the genes causing monogenic autoinflammatory syndrome have not been found to be associated with PFAPA (54,56-58). Whole-genome sequencing has not yet indicated any mutated gene that causes the syndrome (55).

Follow-up without treatment

The spontaneous recovery rate of PFAPA without any treatment varies markedly between study populations. According to Feder and Salazar (6), 20% of 105 PFAPA patients healed spontaneously in a 10-year follow up. In a randomised controlled trial, spontaneous recovery occurred in 50% of diagnosed PFAPA patients within six months (17). Without any treatment, PFAPA patients may occasionally skip an episode of fever and then return to periodic symptoms (6). The febrile episodes of PFAPA are reported to appear less frequently and appear milder before spontaneous healing (12,59-61). Antibiotics and non-steroidal anti-inflammatory agents are ineffective in treating PFAPA (3,7,62).

Corticosteroids

Glucocorticoids are effective in reducing the duration of febrile episodes in 95% of PFAPA patients (3,7,9,62-65). Some centres use the response to single dose of glucocorticoids as a part of the diagnostic process. Glucocorticoids do not prevent upcoming episodes and may shorten the interval between fevers (3,6). The usage of short-course corticosteroids is associated with adverse reactions, mainly vomiting, behavioural changes and sleep disturbances in children. Altogether, 15–35% of PFAPA patients report side effects, most commonly restlessness, due to corticosteroid treatment (8,66).

Surgery

The first case report of four PFAPA patients successfully treated by tonsillectomy or adenotonsillectomy was published in 1989 (67). After that, two randomised controlled trials (RCT) regarding tonsillectomy/adenotonsillectomy as a treatment for PFAPA were published

(17,44). In the first RCT, a total of 14 patients (100%) randomly allocated to tonsillecyomy were promptly cured, whereas 50% of controls were spontaneously cured without any treatment within six months (17). In the second RCT, 12 of 19 patients (63%) were cured after tonsillectomy and one from 20 controls (5%) in an 18-month follow-up (44). In observational studies, the efficacy of tonsillectomy has been high, ranging between 97-100% (4-6). In the meta-analysis by Peridis et al (62), surgical treatment of PFAPA was superior to medical treatment.

The additional effectiveness of adenoidectomy combined with tonsillectomy in treating PFAPA is unclear. In the RCT by Garavello et al, all patients underwent adenotonsillectomy, but the patients in the study by Renko et al either had tonsillectomy or adenotonsillectomy (17,44). Adenoidectomy without tonsillectomy was ineffective in three patients in a cohort of Thomas et al (3), and no other studies solely focused on adenoidectomy have been published.

The most common risk of tonsillectomy is perioperative haemorrhage. On average, 0.8–2.7% of children under the age of 11 experience postoperative bleeding after tonsil surgery (68,69). The risk of postoperative bleeding is lowest in younger children, and serious postoperative bleedings are rare. The prospective audit of 33,921 TEs in Great Britain revealed only one lethal complication (70).

Preliminary and experimental treatment options

Colchicine, used as a prophylactic treatment of FMA and therefore studied in PFAPA, seems to increase the interval between fever attacks in some PFAPA patients (63,71). Cimetidine, a common H2 antagonist with immune-modulating properties, may reduce symptoms in some PFAPA patients (6). Stojanov et al tested anakinra, an IL-1R antagonist, in five PFAPA patients at the time of fever flares with good results. The efficacy of anakinra further

confirms the role of IL-1 in the pathogenesis of PFAPA, which has been suspected earlier based on the cytokine profile of the disease (42,43). Vitamin D and pidotimod, an immunomodulatory agent with activity on both innate and adaptive immune responses, have shown promising preventive effects for PFAPA patients by relieving the symptoms and frequency of flares (32,72). Preliminary observations of the administration of the oral probiotic strain *Streptococcus salivarius* (strain K12) to four PFAPA patients reduced signs and symptoms, resulting in full remission for three of them (73).

Long-term health of PFAPA patients

The long-term prognosis of PFAPA after tonsillectomy is good. A prospective Turkish series of 23 PFAPA patients reported sustained remission after tonsillectomy in 91% of cases in a one-year follow-up (14). Licameli et al (74) reported that 97% of 102 PFAPA patients went into complete remission immediately after the operation, and outcomes were sustained after a mean 3.6 years of follow-up. In the longest follow-up study by Lantto et al (5), 96% of patients were free of symptoms after the mean follow-up period of nine years. The participants regarded their health to be as good as matched controls, and no differences in growth and risk for other chronic diseases were found between PFAPA patients and matched controls (16).

Proposed novel diagnostic criteria for PFAPA

Since the first publications regarding this syndrome, the practice of PFAPA diagnostics has varied between clinical centres (7,75). The need for new diagnostic criteria has been recognised (15). In some centres the presence of aphthous stomatitis, pharyngitis, and

adenitis are not required for the diagnosis (17,74-76). The effectiveness of tonsillectomy appears to be excellent, both in patients fulfilling the classic Thomas criteria and those with fever as the only symptom during flares (5). In the 106 patients responding favourably to tonsillectomy, fever was the only symptom during flares in 32% of patients (5). In the same cohort, the clinical picture of PFAPA, the efficacy of tonsillectomy and long-term prognosis did not differ in patients with onset before or after the age of five years (5). In most published cohorts the patients have gone through a minimum of 4-6 fever flares, or the symptoms have lasted for at least six months (5, 6). Based on these findings, we suggest novel diagnostic criteria for PFAPA (Table 1). In our population of mainly Finnish ethnicity, we perform genetic testing only if the fevers are not regular or if tonsillectomy fails to stop the fevers. The need for genetic testing is, however, dependent on the likelihood of other febrile syndromes in the population, and requires clinical judgement.

Conclusion

Since tonsillectomy offers an effective treatment for PFAPA even in the absence of classic criteria, we suggest that the diagnosis can be made and tonsillectomy offered also in cases where aphthous stomatitis, pharyngitis, and adenitis have not been documented during the fevers and when the symptoms begin after the age of five years.

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Conflicts of interest

No conflicts of interest.

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Table 1. The classic and new suggested diagnostic criteria of PFAPA.

Thomas et al diagnostic criteria of PFAPA syndrome (3)	**Suggested new diagnostic criteria for PFAPA syndrome (5)**
Regularly recurring fevers with an early age of onset (< 5 years of age)	Regular, periodic fever episodes History of ≥ 5 regular periods
Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs: Aphthas, adenitis, pharyngitis	No other explanation (e.g. respiratory or urinary tract infection) for fever episodes
Exclusion of cyclic neutropenia	Evaluation of the risk for cyclic neutropenia as well as for genetic periodic fevers, depending on their background rate
Completely asymptomatic interval between episodes	Asymptomatic interval between episodes
Normal growth and development	Normal growth and development

Table 2. Clinical symptoms of PFAPA patients in the largest patient series.

	Age at onset (median, y)	Duration of a fever flare	Duration of period (start to start)	Highe.st measured fever (mean, ºC)	Pharyngitis at least sometimes, %	Adenitis at least sometimes, %	Aphthas at least sometimes, %
Thomas et al, 1999 (3) (n=96)	2.8	3.8 (3.5-4.1)	32	40.5	72	88	70
Feder & Salazar, 2010 (6) (n=105)	3.3 (80% <5y)	4.1 (2-7)	29.8 (14-50)		85	62	38
Førsvoll et al, 2013 (4) (=46)	0.9	4	25		83	93	45
Hofer et al, 2014 (7) (n=301)	1.7	4 (1-10)			90 (tonsillitis 38%)	78	57
Lantto et al, 2016 (5) (n=108)	2.7 (81%<5y)	4.1	27.6	39.3	60	53	27

Table 3. Features of the most important differential diagnostic autoinflammatory diseases (20,21,23,64).

Disease	**Pathogenic features**	**Inheritance pattern**	**Gene**	**Ethnicity**	**Incidence in Northern Europe**	**Age of onset (y)**	**Period**	**Duration of attacks (days)**	**Clinical findings**	**Amyloidosis**
PFAPA	Not known	Autosomal dominant?	Not known	Any	2.3/10 000 children up to 5 years	80% <5	Starting every 28 days	2-7	Regularly reoccurring episodes of fever, with or without pharyngitis, adenitis, aphthas	No
Cyclic neutropenia	Severe neutropenic phases	Autosomal dominant	ELANE	Any	<1/1 000 000		Usually about 21 days	3-6	Fever, pharyngitis, gingivitis, stomatitis, severe infections	
FMF	Inflammasomopathia	Autosomal recessive	MEFV	Mediterranean	<2.5/100 000	< 20	Once a week – a few times per year	1-3	Fever, serositis, erysipeloid erythema, abdominal or chest pain	Yes
TRAPS	Protein folding disorder	Autosomal dominant	TNFRSF1A	European	<1/500 000	< 20	Irregular	> 7	Periodic fever, abdominal pain and periorbital oedema, rash, splenomegaly	Yes
CAPS	Inflammasomopathia	Autosomal dominant/sporadic	NLRP3	European/any	1/360 000 (France)	< 1–20	Irregular	1–3 / continuous	Periods of low fever episodes, conjunctivitis, deafness, headache, nausea, rash, arthropathy	Yes/No
HIDS	Inflammasomopathia	Autosomal recessive	MVK	European	<1/1 000 000	< 1	Every 2-8 weeks	3–7	Fever, rash, adenopathy, serositis, vomiting, diarrhoea, headache, pharyngitis, aphthas	No

PFAPA= Periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome, FMF= Familial Mediterranean fever, TRAPS= Tumour necrosis factor receptor-associated periodic syndrome,CAPS= cryopyrin-associated periodic syndrome, HIDS= Hyper immunoglobulin D syndrom