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Review Article

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: A review

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Abstract Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is the most common periodic fever condition in children, with most cases appearing by the age of 5. Although PFAPA is generally a self-limited condition, it can have a major impact on a child's quality of life, as well as that of their family. Recent research has continued to shed light on the genetic and immunologic factors that play a role in the pathogenesis of PFAPA. There also exists significant heterogeneity in treatment strategies, and progress has been made to develop evidence-based management strategies and establish a standard of care. This review will outline current knowledge regarding the pathogenesis of PFAPA, as well as treatment strategies and our clinical experience.
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Introduction

Since its initial description by Marshall et al in 1987 as an unknown periodic fever syndrome later termed PFAPA syndrome — periodic fever,[1] aphthous stomatitis, pharyngitis, and adenitis — this condition has become better understood. PFAPA is the most common periodic fever condition in children, and the vast majority of cases (90%) appear by the age of 5 years.[2] It is characterized by episodes of high fevers lasting 3—7 days that recur every 2—8 weeks, along with the associated eponymous features of aphthous stomatitis, pharyngitis, and/or cervical adenitis.[2—9] Patients experience resolution between episodes, with normal growth and development. Although this condition has a favorable outcome and generally resolves as the child ages,[6,8—10] it can have a significant impact on the child's quality of life, as well as that of the child's caretakers.[11]

The recognition of PFAPA by clinicians is largely based on clinical features, as currently there is no specific confirmatory laboratory or genetic tests. However, research on PFAPA has accelerated significantly over the last decade. For example, recently conducted work has aimed to refine classification criteria, with the goal of more clearly differentiating between PFAPA and other periodic fever syndromes.[12—14] Additionally, consensus treatment plans have been developed, which will aid in developing evidence-based therapeutic guidelines and establishing a standard of care.[15] Significant progress has been made particularly in the genetic realm, and a number of studies have been conducted to shed light on the potential hereditary factors involved in PFAPA.[16—19]

This review will outline current knowledge regarding the pathogenesis of PFAPA, as well as treatment strategies.

Epidemiology and pathogenesis

Outside of regions with a high prevalence of familial Mediterranean fever (FMF), PFAPA is considered to be the most common periodic fever syndrome in children. The exact incidence is somewhat unclear, although one Norwegian study reported an incidence of 2.3 per 10 000 children up to 5 years of age.[10] The true rate may be higher, as it can be easily confounded with recurrent upper respiratory tract infections, autoinflammatory diseases, or cyclic neutropenia. We agree with the observation by Hofer that over time, with the education of pediatric otolaryngologists and other healthcare providers, the number of cases identified in the pediatric population has increased.[20] Anecdotally, we have also observed an increased number of cases of recurrent fever since the COVID-19 pandemic.

The typical age of onset is in children less than 5 years of age, and studies in the pediatric population show a slight male predominance of around 55%~65%.[2,9,10,21,22] It is generally a self-limited disease, and many patients will experience spontaneous resolution within 3—6 years after onset and before adolescent years.[6,8—10] However, persistent cases with onset in childhood and continuing well into adolescence have also been reported.[8,23] Additionally, relapses after resolution have been observed.[24—26] PFAPA has been shown to present in adulthood, and these cases may be either *de novo* occurrences or relapses after remission in childhood.[26—29]

Familial clustering observed in PFAPA has prompted searches for genetic mutations or variants that may increase an individual's risk for PFAPA. Initially, PFAPA was hypothesized to be a monogenic disorder — caused by mutations in a single gene — similar to other periodic fever syndromes like FMF and mevalonate kinase deficiency (MKD), former known as hyper-IgD syndrome (HIDS). However, whole exome sequencing failed to identify rare, high penetrance mutations in a single gene in multiple families.[30] Therefore, PFAPA is now considered to be a complex genetic disorder. In complex genetic disorders, multiple mutations or variants each contribute some fraction of an individual's risk for the disorder. These risk mutations are often found in non-coding regions of the genome and affect gene expression. The cumulative effect of these mutations, in addition to environmental factors, determines whether an individual develops a particular disease.

In order to identify risk mutations for PFAPA, researchers screened a cohort of 231 European-ancestry individuals with PFAPA for seven risk mutations previously associated with two other inflammatory disorders characterized by oral ulcers, namely Behçet's disease and recurrent aphthous ulcers (RAU).[31] As patients with PFAPA also have aphthous ulcers, these researchers hypothesized that PFAPA may also share the same risk mutations. They found that genetic variants near the *IL12A, IL10, STAT4,* and *CCR1-3* genes were also strongly associated with PFAPA, with the variant near *IL12A* having the strongest association (odds ratio 2.13).[31] The overlap in genetic risk loci among PFAPA, Behçet's disease, and RAU connects these disorders as a family called Behçet's spectrum disorders. Along this spectrum, symptoms experienced in Behçet's disease tend to be most severe, with milder expression in RAU, and with moderate symptomatology in PFAPA patients. In clinical practice, patients with features of more than one of these disorders have been reported; for example, patients with PFAPA who have vaginal ulcers have been noted (features of both PFAPA and Behçet's) and individuals with recurrent, regular outbreaks of aphthous ulcers without fever have also been seen by our group (features of both RAU and PFAPA).[32,33]

HLA type, which is a strong risk factor for Behçet's disease and other rheumatologic diseases, also appears to be a risk factor for PFAPA. Several class I and class II HLA alleles are significantly associated with PFAPA; most of these HLA associations are unique to PFAPA and have not previously been associated with Behçet's disease or RAU.[31] Therefore, HLA type may be one factor that affects where on the Behçet's spectrum disorders an individual's phenotype lies.

The identified risk variants suggest that individuals with PFAPA have heightened activation of CD4+ Th1 and Th17 lymphocytes, particularly during flares. The *IL12A* risk variant is associated with elevated IL-12 production from monocytes, and IL-12 is an important stimulator of IFNγ production from CD4+ and CD8+ T cells.[31] *STAT4* encodes a protein that signals downstream of the IL-12 receptor, and the risk variant that was found is associated with elevated STAT4 expression.[34] IL-10 is an anti-inflammatory cytokine; the risk variant for PFAPA is associated with decreased *IL10* gene expression.[35] The variant near the *CCR1-3* locus has

been associated with decreased *CCR1* expression and decreased monocyte migration to sites of inflammation.[34] It is hypothesized that this contributes to diminished integrity of the mucosal barrier to microorganisms which may lead to ulcer development. Analysis of peripheral blood during PFAPA flares also indicates heighted activation of CD4+ T cells with elevated expression of IFN-related genes and Th1 chemokines.[36] In addition, tonsils from children with PFAPA have elevated expression of Th1 chemokines.[37]

As tonsillectomy leads to episode resolution in most patients with PFAPA, a few studies have assessed the immunologic profile of the tonsils. Tonsils of children with PFAPA, when removed during the asymptomatic period, have been found to have smaller germinal centers on histologic sections compared to tonsils from children with obstructive sleep apnea.[38] In addition, greater time from the last fever flare was associated with larger germinal center size.[38] Flow cytometric studies of lymphocyte populations show fewer B lymphocytes and more CD8+ T cells in the tonsils of children with PFAPA compared to controls.[37] Clonal expansion of T or B cells was not noted in PFAPA tonsils, suggesting that a polyclonal T-cell infiltration may occur during flares.[37] The role of HLA as a risk allele suggests that the microbiome may also play a role modulating the disease. Differences in the tonsillar bacterial microbiome have been noted, but the role of particular organisms in triggering disease have not been elucidated.[39]

Clinical presentation

Since the original description of PFAPA by Marshall, revised classification criteria have been proposed by several authors[3,7,13,40,41]; however, the key features remain. The hallmark of this condition is clockwork periodicity of the fevers. Fevers typically last 3—7 days with a range of 39 °C—40 °C (102.2 °F—104 °F), and recur every 2~8 weeks.[2,4—6,10,42,43] There may be some variation in the frequency of fever attacks, but not significantly. To ensure periodicity, Amarilyo et al propose allowing 1 week of variability for fevers occurring every 2—4 weeks and 2 weeks of variability for fevers occurring every 5~8 weeks.[15] As a general rule, the majority of fevers seem to occur within a 4—6 week pattern with a 3—5 day duration. Documentation of at least 6 consecutive episodes is important as it aids in excluding recurrent infections or malignancy. The revised criteria proposed by Vanoni et al considers the presence of ≥5 regularly recurring fever attacks to be an important factor in classifying PFAPA.[12] Therefore, it is important for parents to keep a fever diary, noting any prodromal symptoms or infectious contacts, as well as treatments given and their outcomes.

Apart from fever, the most common cardinal symptom is pharyngitis, which has been variably described as either erythematous or exudative, and present in over 90% of patients.[2,6,9,10,21,22] Tonsils have been described as either normal and enlarged in size, likely owing to the diversity of practitioners that have reported on this condition and the timing of the exams. This physical finding is important in establishing PFAPA but may be overlooked. Oftentimes caretakers may not bring the child for medical care with each febrile episode. Additionally, in very young children who are unable to express throat discomfort, pharyngitis may manifest only as excessive drooling and/or reduced oral intake.

The next most common finding is cervical adenitis, occurring in 53%—94% of patients in large patient series.[2,9,21,22] The nodes are typically enlarged in the anterior cervical chains bilaterally, are 2—3 cm in size and moderately tender with no overlying skin changes. Finally, aphthous ulcers are present in up to 50% of patients.[2,9,21,22] These lesions are generally around 1 cm in size and are found on the non-masticatory surfaces of the mouth.[9,44,45] Small ulcers could be locate in the pharyngeal area, which may be overlooked by clinicians if a tongue depressor is not used. In addition to these classic signs and symptoms, patients may also experience mild abdominal discomfort, muscle aches, headache, and nausea.[2,9,21,22] In our clinical experience, parents will often state that their child seems listless, has a particular 'fever look', or has glassy or droopy eyes hours before the onset of the fever episode. A prodrome to fever attacks, including fatigue, headache, abdominal pain, or irritability, has been reported in the literature in approximately 60% of patients.[9,46] Signs and symptoms may vary between adult and pediatric patients — in particular, joint pain, muscle aches, and headache may be more common in adults.[29,43,45]

Critical to making the diagnosis of PFAPA is the history of apparent normal growth and development between episodes, the absence of any sick contacts in the family around the time of onset of an episode, and a thorough investigation for any other common cause for fever, such as otitis media, streptococcal tonsillitis or upper respiratory tract infection. It is also important to recognize that over time (usually years), the fevers may become less regular and intervals between episodes may become longer.[9] Some patients may experience a hiatus of several months in the fever cycle, particularly in the summer months.[9,47] This may signify the cessation of their condition or just a temporary reprieve.

Multiple studies have indicated that patients with PFAPA often have family members with the disease.[30,48] Sibling pairs with PFAPA have also been documented.[49—51] Furthermore, it has been shown that first-degree relatives of children with PFAPA are more likely to not only have PFAPA, but also recurrent tonsillitis and recurrent aphthous ulcers.[48] This indicates that a broader spectrum of diseases may be linked to PFAPA. Because of this family history, we find it helpful for clinicians to query patients about family history of not only PFAPA (which may be unrecognized), but also for recurrent tonsillitis (which may have been misdiagnosed as recurrent strep throat), and recurrent aphthous ulcers. The presence of a strong family history of these oropharyngeal disorders may support the diagnosis of PFAPA. In most familial cases of PFAPA, autosomal dominant inheritance is noted.[48]

Treatment options

Medical treatment

As no randomized clinical trials have been conducted in the medical treatment of PFAPA, a standardized therapy is not

available. In the early years of its description, the majority of patients received antibiotics with poor efficacy.[52] Among the medical options, both abortive and preventive treatment modalities have been widely utilized. These current options for symptomatic treatment of PFAPA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine and cimetidine. NSAIDs are given at the onset of fever and during the fever flare. They may be beneficial to many patients, though not completely effective.[8,53] The usual effect is to lessen the fever but often not to a normal temperature. NSAIDS will also not shorten the episode or the duration of the fever cycle.

Cimetidine, when taken daily, has been shown to decrease the severity and frequency of fever episodes in patients, and reports indicate that around 25% of patients may experience complete remission using cimetidine prophylaxis.[6,8,9,54,55] However, evidence supporting the efficacy of cimetidine for PFAPA is limited. Meta-analysis suggests that it is not as effective as surgical treatment,[56] and it has not been studied in large patient cohorts.[45] In our experience, we have found it effective in certain patient populations, particularly those with milder disease or who do not respond to tonsillectomy. It is therefore of interest to conduct further research to better characterize the patient groups most likely to respond to cimetidine treatment.

Colchicine has been proven effective in the treatment of FMF, and remains the principal treatment for that condition.[57,58] Recent work has also investigated its effectiveness in treating PFAPA. Prophylactic colchicine may increase the time interval between fever episodes, though it may not necessarily induce a complete remission.[46,47,59–63] Studies have also demonstrated a greater likelihood for response to colchicine prophylaxis in patients with a heterozygous mutation in the *MEFV* gene.[46,59,61] Further research is necessary to better characterize the effectiveness of colchicine in PFAPA patients, with or without variants in *MEFV*, as well as develop consensus on the duration of prophylactic treatment.

Corticosteroids are a mainstay of abortive treatment for fever attacks. They are typically given as a single dose of prednisone at 1—2 mg/kg at the onset of the fever episode and have been shown to be effective in about 80—95% of patients.[4,9,53,64] A lower dose of prednisone at 0.5 mg/kg has been demonstrated to be effective,[65] as well as betamethasone at 0.1—0.2 mg/kg.[43] Amarilyo et al found that the majority of physicians use 1 mg/kg of prednisone to treat attacks, and recommend increasing to 2 mg/kg in the case of frequent fever flares or incomplete response to the lower dose.[15] The fever episode is usually aborted within hours, with a minority of patients requiring a second dose 8—12 h later. Other symptoms, such as aphthous ulcers, may subside more slowly.[4,66] The rapid response to steroids is felt to be important in confirming the diagnosis of PFAPA, and aids in differentiating between PFAPA and recurrent infection. However, corticosteroid treatment does not prevent subsequent PFAPA episodes. It may also have the untoward effect of causing the fever cycles to occur more frequently over time in some patients.[4,9,29,53,64,67] It is not well-known what the effect is of repeated monthly doses over multiple years. Given the potential side effects of long-term use of steroids, we recommended usage for short-term symptomatic relief and as a diagnostic tool, in particular to rule out an infectious cause.

None of these treatment options have been compared head-to-head. The majority of cohorts reported are retrospective case series; therefore, there is variability in patient characteristics, dose, timing and duration of treatments. This makes comparison among these studies very difficult. In recent years, Consensus Treatment Plans (CTP), a new research methodology, has been introduced with the goal of reducing variations in treatment approaches and prospectively collecting homogenous comparable data. CTPs are generally used to study rare diseases. Several commonly used treatment regimens are defined and treating providers choose one of these regimens to treat their patients in their daily practice. Data are collected prospectively per defined outcome measures, thereby decreasing variability and enabling comparison between regimens in a less costly way than double blind, randomized trials. Recently PFAPA CTPs were published by an international group of researchers from the CARRA (Childhood Arthritis and Rheumatology Research Alliance) PFAPA work group.[15]

Surgical treatment

Removal of the tonsils with or without adenoidectomy has been shown to have a beneficial effect on the disease course and was first described by Abramson et al in 1989.[68] A number of case series have reported a high rate of remission of PFAPA symptoms after tonsillectomy, and a recently conducted review of these series found that surgery was curative in 509 out of 555 (92%) patients.[69]

However, to date, there have only been two randomized controlled trials investigating the efficacy of tonsillectomy in treating PFAPA, by Renko et al[70] in 2007 and Garavello et al[71] in 2009. A recent Cochrane review of these two studies found that children with PFAPA are likely to benefit from tonsillectomy and experience a significant reduction (or resolution) of symptoms, but that the level of evidence to support surgical intervention was only moderate.[72] This is due in part to the small sample size in the controlled trials that have been conducted, as well as the variability of inclusion criteria in these studies. For example, the number of patients randomized to the surgical group was not sufficient to detect potentially important surgical complications such as hemorrhage.[72] Further research is necessary to determine whether tonsillectomy alone is a sufficient treatment or whether it is necessary to remove the adenoids as well.[72] Finally, there is currently no evidence on the efficacy of tonsillotomy in patients with PFAPA.[15]

There is some evidence supporting the efficacy of surgical over medical treatment[73,74]; however, other cohorts of patients have found a similar time to remission in the two approaches.[64,75] Additionally, some patients may not respond fully to tonsillectomy, which in some cases has been linked to mutations in the *MEFV* gene. Pehlivan et al[62] found a significant difference in response to surgical treatment between patients with PFAPA who were heterozygous for *MEFV* mutations and those who were not: among patients who did not respond or responded only incompletely to tonsillectomy, around 50% carried variants in

MEFV. A small number of studies have suggested that adult patients with PFAPA may have a lower response rate than children, although it has also been suggested that tonsillectomy remain a treatment option for adults, given that the disease course is less likely to be self-limited.[29,43,74] Recurrence after surgical treatment has been observed, even years after tonsillectomy.[24,76] This may present as recurrence of aphthous ulcers or cervical adenitis after tonsillectomy without febrile episodes, a so-called 'fever-less flare'.[8,75]

It is important for the clinician, patients, and their families to thoroughly assess the benefits and risks of undergoing surgical versus medical treatment. Our group has had a very good long-term success rate with surgery, in part due to a close association with our rheumatology colleagues who evaluate each child before surgery is entertained.

Differential diagnosis

The diagnosis of PFAPA is one of exclusion, as the clinical features are common to other fever syndromes. Importantly, a source of infection should be investigated with each fever episode, particularly in the first 6—12 months of onset. Viral or bacterial throat infections, otitis media, and bronchiolitis are common in young children. However, it would not be expected that these types of illnesses would occur with distinct regularity, and they would be more likely confined to the winter months. The diagnosis of PFAPA rather than recurrent infection is supported by a number of factors, including: (1) negative cultures, (2) absence of sick contacts in the family, (3) absence of symptoms common to upper respiratory tract infections such as cough or rhinorrhea, (4) failure to respond to antibiotics, and (5) response to single dose corticosteroids.[45] This again highlights the importance of carefully tracking fever episodes and documenting treatment outcomes.

Other less common causes for cyclical fevers include cyclical neutropenia, a rare disorder with autosomal dominant inheritance.[77] Fevers usually occur every 21 days with this condition, which does resemble the clockwork regularity of fevers in PFAPA. Repeated neutrophil counts over time can help solidify this diagnosis. During fever in cyclic neutropenia, neutrophil count is less than 500/mm^3 and aphthous ulcers manifest more severely than they do in PFAPA.[9,77] Many patients also have gingivitis. Additionally, there is no response to single-dose corticosteroid. Mutations in the *ELANE* gene can be screened for to confirm a diagnosis of cyclic neutropenia.

A PFAPA-like phenotype has been described in monogenic autoinflammatory diseases, which include FMF, MKD, and tumor necrosis factor-receptor associated periodic syndrome (TRAPS). FMF should be considered based on the hereditary background of the patient and the presence of additional symptoms of abdominal pain, joint pain/swelling, and occasional skin rashes. Greater irregularity of the fever cycles, as well as the absence of aphthous ulcers and cervical adenitis should also point to the possibility of FMF.[78] Recent studies suggest a strong association between PFAPA and FMF, and that in regions where FMF is endemic, the two may co-occur.[59,79] Patients with MKD may also present with a phenotype similar to PFAPA. MKD is also associated with abdominal pain, diarrhea and splenomegaly in addition to maculopapular or purpuric rashes.[3,80] Febrile flares often occur in response to physical or emotional stress, including birthday parties, travel, vaccination, and infections. Screening for increased excretion of mevalonic acid in the urine can be a helpful biochemical test if done with a sensitive assay, although genetic testing is preferable. Mutations in the *MVK* gene should be screened for in patients for whom MKD is suspected. Finally, patients with TRAPS will present with additional ocular findings such as conjunctivitis or periorbital edema as well as headaches, abdominal pain, splenomegaly, and painful, migratory skin rashes.[3] Episodes are also longer than typical PFAPA episodes, often lasting over one week up to 3 weeks. However, a case of TRAPS with PFAPA-like phenotype has been reported in a patient heterozygous for the R92Q variant in *TNFRSF1A*.[81]

Conclusions

PFAPA syndrome is the most common cause for periodic fever in childhood and can have a significant impact on a child's quality of life, as well as that of their family. The pathogenesis of PFAPA syndrome remains unclear, and research into the immunology and genetic makeup suggests that this is a multifactorial disease process. Therapeutic treatments options include nonsteroidal anti-inflammatory drugs, colchicine, corticosteroids, and adenotonsillectomy. Future studies should reflect validated classification criteria with treatment options evaluated through either randomized clinical trials or pragmatic trials using recently-described CTP methodology.

Declaration of competing interest

None.

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