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

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Abstract Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, the most common periodic disorder of childhood, presents with the cardinal symptoms of periodic fever, aphthous stomatitis, pharyngitis, and adenitis typically before age 5. This review presents the recent literature on PFAPA and summarizes key findings in the pathogenesis, evaluation, and treatment of the disease. Theories surrounding the pathogenesis of PFAPA include a faulty innate immunologic response in conjunction with dysregulated T-cell activation. A potential genetic link is also under consideration. Mediterranean fever *(MEFV)* gene variants have been implicated and appear to modify disease severity. In individuals with the heterozygous variant, PFAPA episodes are milder and shorter in duration. Diagnostic criteria include the traditional clinical signs, in addition to the following biomarkers: elevated C-reactive protein in the absence of elevated procalcitonin, vitamin D, CD64, mean corpuscular volume, and other nonspecific inflammatory mediators in the absence of an infectious explanation for fever. Treatment of PFAPA includes tonsillectomy, a single dose of corticosteroids, and, most recently, interleukin 1 blockers such as anakinra, rilonacept, and canakinumab. Tonsillectomy remains the only permanent treatment modality.

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome was first recognized in 1987[1] as a recurrent fever disorder resembling cyclic neutropenia. PFAPA is the most common periodic fever disorder in children, with 90% of cases appearing before age 5.[2] A Norwegian study of PFAPA patients reported an incidence of 2.3 per 10,000 children; worldwide epidemiologic patterns have yet to be studied.[3] PFAPA is characterized by periodic fevers higher than 40°C that occur every 3 to 8 weeks, resolve spontaneously within a few days, and are associated with one or more of the cardinal signs of aphthous stomatitis, pharyngitis, and adenitis.

Although historically the age of onset of most PFAPA cases (90%) is before age 5,[2] recent studies have described possible adult-onset cases.[4–10] These remain to be explored, specifically because previous data support the notion that PFAPA syndrome characteristically self-resolves by late childhood or early adolescence.[11]

PFAPA belongs to a group of monogenic periodic fever syndromes, including familial Mediterranean fever (FMF), tumor necrosis factor receptor–associated periodic syndrome (TRAPS), cryopyrin-associated autoinflammatory syndrome (CAPS), and mevalonate kinase deficiency, among others. Their common features include recurrent fevers, elevation of

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acute phase reactants, and multiple clinical manifestations. PFAPA is by far the most common of the periodic fevers. Although they resemble one another to a certain extent, the diseases can be differentiated based on the overall clinical presentation or by genetic testing.[12]

Pathogenesis

Overview

The pathogenesis and exact etiology of PFAPA have remained an enigma despite awareness of the disease for more than 2 decades. Historically, the general theory was a faulty innate immunologic response to an infectious agent[13–15]; however, in a recent small study, analysis of tonsillar tissue microbiome of PFAPA patients and control patients using next-generation sequencing did not reveal a responsible pathogen, rendering infectious etiologies less likely.[16] With bacterial infection, both C-reactive protein (CRP) and procalcitonin are typically elevated. In PFAPA patients, although CRP was elevated,[13,14,17,18] procalcitonin was found to be normal.[19,20] Elevated CRP in the presence of elevated interleukin 1β (IL-1β) and IL-6, but in the absence of elevated procalcitonin, points to an adaptive immunologic etiology for PFAPA and argues against a bacterial or infectious origin.[17]

Faulty immunity

Recent studies have not completely abandoned the notion of an initial infectious insult and a triggered immune response as a potential explanation for the pathogenesis of PFAPA. Research continues to indicate a dichotomous finding involving components of both a dysregulated innate immune response and inappropriate T-cell activation. Studies illustrating abnormal T-cell activation found levels of cytokines consistent with a T helper 1 inflammatory response in blood samples of PFAPA patients, namely oscillations of tumor necrosis factor α (TNF-α), interferon γ, IL-6, and interferon γ–induced protein 10, as well as decreased IL-4 and IL-17 levels.[11,12] Elevation of interferon γ has also been supported by additional research.[21] In another study, positive prophylactic use of cimetidine prevented future flares of PFAPA, which, among other therapeutic mechanisms, inhibits T-cell activation.[14]

Regarding the role of the innate immune system in the pathogenesis of PFAPA, a study[11] found increased levels of monocytes and neutrophils, in addition to elevated IL-1β production, in the study population of PFAPA patients. Genetic analysis of these patients revealed a high frequency of variation in the NOD-like receptor protein 3 *(NLRP3)* gene, which has already been established as the responsible gene in the disease CAPS. The implication of an *NLRP3* variant is a gain-of-function mutation causing dysregulated inflammasome activity.[11] The finding of elevated IL-1β has been supported by two groups[18,22] that have found abnormal IL-1β activation, with the innate immune response playing a key role in the pathogenesis of PFAPA.[22] Elevated C-X-C motif ligand 10 (CXCL10) may be found during febrile and nonfebrile episodes, suggesting persistent innate activation. CXCL10 also serves as a chemoattractant for T cells, reinforcing the hypothesis that PFAPA involves both components of the immune system.

An overall explanation incorporating both components of the immune system has been summarized[18] in which an initial infectious insult may trigger the innate immune response (indicated by elevated IL-1β, complement, and granulocyte colony-stimulating factor), leading to T-cell recruitment and activation. This hypothesis incorporates the results of the aforementioned studies, several of which had data supporting involvement of both innate and adaptive immune systems.

Mediterranean fever gene variants

The potential hereditary nature of PFAPA is still disputed, despite reports of familial occurrences[23–26] and identification of suspect gene mutations.[11,27–29] One group[30] hypothesizes on the genetic etiology of PFAPA, based on its similarity to other hereditary periodic fever syndromes, the numerous familial case reports, and recent studies finding potential genetic mutations resulting in PFAPA.

Interestingly, studies of periodic fever syndromes with known heritability, such as FMF and TRAPS, have identified the responsible gene mutations. The Mediterranean fever *(MEFV)* gene mutation, implicated in FMF, has a possible association with PFAPA syndrome. The research is varied; some studies have found mutations in the *MEFV* gene in a portion of their PFAPA patients to be statistically significant[31–33]; others have reported statistically insignificant[34] results, and yet another group found no relevant gene mutations in their PFAPA patients whatsoever.[35] One study argued strongly against the association of *MEFV* and PFAPA.[36] Of the studies that have found *MEFV* mutations present in PFAPA patients, this finding appears to modify the disease. This modification has been reported in at least three separate studies and revealed that: (1) Only one *MEFV* allele is affected, and (2) the clinical phenotype of PFAPA with the *MEFV* mutation is milder, with shorter febrile periods and less oral involvement.[28,31,33] Overall, the implication of *MEFV* mutation in PFAPA is promising and warrants further study because the genetic makeup of PFAPA remains unclear.[27]

Vitamin D

Two studies have analyzed the link between vitamin D levels and PFAPA syndrome. One study noted a significant correlation between PFAPA and vitamin D deficiency,[37] whereas the other study (albeit small, with 25 participants) reported an inverse correlation between vitamin D levels and PFAPA fever episodes, and direct correlation with CRP values.[38] Another[38] found that vitamin D supplementation