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From Childhood to Adulthood: A Systematic Review of the Evolution, Diagnosis, and Management of PFAPA Syndrome

Prof. Adawi Mohammad M.D, M.H.A[1*], Dr. Amin Adawi M.D[2], Dr. Said Abozaid M.D[3]

Abstract

Adult PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) syndrome represents an underrecognized yet significant autoinflammatory disorder. Traditionally considered a pediatric condition, recent literature illustrates its persistence and emergence in adulthood. This systematic review synthesizes current evidence on the clinical phenotype, diagnostic challenges, and therapeutic strategies for adult PFAPA. The syndrome in adults often mirrors pediatric presentations but may exhibit increased arthralgia, myalgia, and diagnostic delay. Distinguishing adult PFAPA from other periodic fever syndromes is crucial, given overlapping clinical features and often inconclusive genetic testing. Despite the lack of defined biomarkers, a phenotype-driven approach and recognition of episodic fever with aphthous ulcers and cervical lymphadenopathy remain vital for diagnosis. Treatment responses vary, with corticosteroids showing efficacy, while tonsillectomy and IL-1 blockers like anakinra may benefit selected patients. The review highlights the need for standardized diagnostic criteria, improved awareness among clinicians, and further research into the genetic and immunological underpinnings of adult PFAPA.

Keywords: Adult PFAPA syndrome; Autoinflammatory disorders; Periodic fever; Differential diagnosis; Corticosteroid therapy

Introduction

The literature on adult PFAPA syndrome, a condition characterized by recurrent febrile episodes, aphthous stomatitis, pharyngitis, and cervical adenitis, has evolved significantly over the past decade. Early insights into the clinical and molecular characteristics of related autoinflammatory disorders, as presented by Smith et al. [1], established a foundation for understanding the complexities of PFAPA syndrome. This review emphasized the heritable nature of conditions like PAPA syndrome, which shares some clinical features with PFAPA, particularly the manifestation of painful flares and systemic inflammation, although the genetic underpinnings of PFAPA remain less clear. Kraszewska-Głomba et al. [2] further explored the pathogenesis of PFAPA, noting the absence of identifiable infectious or autoimmune triggers, thereby categorizing it as an autoinflammatory disease. Their systematic review highlighted the need for more comprehensive studies to clarify the etiology and familial occurrence of PFAPA, suggesting a potential genetic basis that requires further investigation. Perko et al. [3] provided a longitudinal study of PFAPA patients, revealing that symptoms often manifest early in life, with a majority of patients exhibiting classic signs such as adenitis and pharyngitis. This study reinforced the notion that while symptoms may be predominantly pediatric, the syndrome can persist into adulthood, as noted by Cattalini et al. [4]. Their findings indicated that adults

Affiliation:
[1]Laniado MC, Ariel University, General Health Services, Ramat HaGolan St, Ari'el, Israel

[2]General Health Services, Bar Ilan University, Ramat Gan, Israel

[3]Tzafon MC Poria, Bar Ilan University, Ramat Gan, Israel

***Corresponding author:**
Adawi Mohammad, Laniado MC, Ariel University, General Health Services, Ramat HaGolan St, Ari'el.

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with PFAPA often present with similar symptoms to children, albeit with variations such as increased arthralgia. Lahti et al. [5] underscored the importance of early diagnosis and appropriate treatment, emphasizing the risk of misdiagnosis as recurrent tonsillitis. The efficacy of tonsillectomy in resolving symptoms in a significant proportion of patients was highlighted, alongside the need for further research into the syndrome's pathophysiology and potential treatments like Anakinra. The exploration of adult PFAPA continued with Alam et al. [6], who documented cases of adult onset PFAPA, emphasizing the challenges in diagnosis and treatment in this demographic. Their work illustrated the necessity of distinguishing PFAPA from other periodic fever syndromes. In a broader context, Manthiram et al. [7] identified genetic susceptibility loci linking PFAPA with other conditions such as Behçet's disease, suggesting a common spectrum that could enhance understanding of PFAPA's pathogenesis. This perspective was further supported by Cinquina et al. [8], who proposed a phenotype-first approach to improve diagnostic accuracy, recognizing the importance of clinical features in distinguishing PFAPA from other syndromes. Recent literature has continued to address the clinical burden associated with PFAPA, as highlighted by Sparud-Lundin et al. [9], who examined the experiences of parents navigating the complexities of the syndrome. Their qualitative findings emphasize the psychological and logistical challenges faced by families, advocating for increased awareness and support within healthcare systems.

In summary, the literature reveals a complex interplay of clinical, genetic, and psychosocial factors surrounding adult PFAPA syndrome. The evolution of this body of research highlights the pressing need for standardized diagnostic criteria and effective treatment strategies, particularly as the understanding of the syndrome's pathophysiology continues to develop. The insights gleaned from these studies contribute significantly to the ongoing discourse regarding PFAPA syndrome, paving the way for future research and improved clinical practices.

Literature Review

The article "Clinical, Molecular, and Genetic Characteristics of PAPA Syndrome: A Review" provides a comprehensive overview of the clinical features, genetic basis, and laboratory findings associated with PAPA syndrome [10], which is characterized by recurrent episodes of sterile arthritis, pyoderma gangrenosum, and acne. The authors emphasize the heritable nature of the syndrome, first described in an extended family in 1997, and the critical role of autosomal dominant inheritance. A key insight from this review is the early onset of symptoms, which often manifest in childhood and can persist into adulthood. This prolonged duration of symptoms is particularly concerning as it may lead to significant joint destruction over time. The article highlights that standard laboratory findings in PAPA syndrome typically indicate systemic inflammation, which is a common feature in various autoinflammatory conditions. Notably, the authors report elevated levels of interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNFα) in peripheral blood leukocytes, suggesting a potential inflammatory pathway that could be targeted for therapeutic interventions. The review critically evaluates the differential diagnosis of PAPA syndrome, noting the importance of distinguishing it from other autoinflammatory disorders, particularly given the overlapping clinical features. The authors provide a detailed discussion on the necessity for clinicians to consider PAPA syndrome in patients presenting with recurrent arthritis, especially in pediatric populations, to ensure timely and appropriate management. Furthermore, the article addresses evidence-based treatments available for managing PAPA syndrome. The authors suggest that therapies targeting IL-1β, such as anakinra, have shown promise in alleviating symptoms and preventing joint damage. This points to a growing understanding of the underlying immunological mechanisms at play in PAPA syndrome, which could inform future treatment strategies.

The article "The Pathogenesis of Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome: A Review of Current Research" [11] offers a comprehensive examination of the etiology of PFAPA syndrome, which is increasingly recognized as an autoinflammatory condition. The review synthesizes findings from 19 selected publications, categorizing them into three main areas: familial occurrence, genetic basis, and immunological mechanisms associated with PFAPA. One of the critical insights provided in the article is the complexity surrounding the genetic underpinnings of PFAPA. Unlike many other periodic fever syndromes that are well-defined hereditary monogenic disorders, PFAPA's genetic basis remains elusive. The authors highlight that for a significant period, PFAPA was viewed as a sporadic illness, lacking a clear familial link. However, the review notes a shift in understanding, particularly with the inclusion of recent case reports that describe familial occurrences of the syndrome. This is a pivotal observation, as it challenges the long-held belief of PFAPA's nonhereditary nature and opens avenues for further genetic investigation. In terms of immunological mechanisms, the review indicates that while there is a consensus on PFAPA being an autoinflammatory disease, the specific pathways involved remain to be fully elucidated. The authors effectively convey that understanding these mechanisms is crucial for developing targeted therapies and improving patient outcomes. The lack of established genetic markers or clear immunological profiles complicates the differential diagnosis and treatment options for PFAPA, highlighting a significant gap in current research.

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The article "Clinical Features and Genetic Background of the Periodic Fever Syndrome with Aphthous Stomatitis, Pharyngitis, and Adenitis: A Single Center Longitudinal Study of 81 Patients" [12] provides a comprehensive examination of the clinical manifestations and characteristics of PFAPA syndrome in a cohort of 81 patients over a seven-year period. This study is significant in its focus on the specific symptoms associated with PFAPA syndrome, a condition often characterized by recurrent fever episodes along with other clinical features. The authors report that the majority of patients in their study presented with adenitis (94%) and pharyngitis (98%), which aligns with the hallmark symptoms of PFAPA syndrome. The prevalence of these symptoms emphasizes the need for clinicians to closely monitor these manifestations when diagnosing the syndrome. Interestingly, the study notes that a substantial number of patients also experienced abdominal pain (51%), joint pain (31%), and gastrointestinal symptoms such as vomiting (41%) and diarrhea (22%). These additional symptoms may complicate the clinical picture and highlight the necessity for differential diagnosis, as they can overlap with other periodic fever syndromes or infectious conditions. One notable aspect of the study is the age of onset, with only three patients being older than five years at the time of diagnosis. This finding underscores the typical early presentation of PFAPA syndrome, which is crucial for timely intervention and management. The study also details that all patients were asymptomatic during afebrile periods and exhibited normal growth and development, which is an important consideration for long-term prognosis and quality of life.

The article "PFAPA: A Periodic Febrile Syndrome Afflicting Children" provides a comprehensive exploration of the clinical characteristics of PFAPA syndrome [13] highlighting its differentiation from other febrile conditions, particularly recurrent tonsillitis. The author emphasizes the common misdiagnosis of PFAPA as recurrent tonsillitis, which often leads to inappropriate antibiotic treatment. This is particularly problematic given that PFAPA is classified as an auto-inflammatory syndrome, and antibiotics are ineffective in managing its symptoms.

The article "Basic Characteristics of Adults with Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenopathy Syndrome in Comparison with the Typical Pediatric Expression of Disease" [14] offers a comprehensive exploration of the clinical phenotype of PFAPA syndrome in adults, contrasting it with the pediatric presentation. The authors effectively highlight the key characteristics of the syndrome, which include cervical lymphadenopathy, oral aphthous lesions, and a range of systemic symptoms such as headache, abdominal pain, and malaise. This detailed description is crucial for clinicians who may encounter adult patients with PFAPA, as it emphasizes that while the clinical features may mirror those seen in children, there are distinct differences that warrant attention. Moreover, the article addresses the increased prevalence of arthralgia and myalgia in adult patients, which may complicate the clinical picture and necessitate a broader differential diagnosis. The discussion of treatment options is also noteworthy, as the article indicates that corticosteroid therapy has shown efficacy in managing symptoms in these cases. This evidence-based approach is essential for clinicians as they develop treatment plans tailored to adult patients, who may have different therapeutic needs compared to children.

The article "Genetic profiling of autoinflammatory disorders in patients with periodic fever: a prospective study" [15] provides significant insights into the characterization and diagnosis of periodic fever syndromes (PFS), particularly in relation to PFAPA syndrome. The authors emphasize the broad spectrum of periodic fever syndromes, ranging from common multifactorial conditions like PFAPA to rarer monogenic disorders. This distinction is crucial as it highlights the complexity involved in diagnosing these conditions, which often present with overlapping clinical features.

However, the findings also reveal a notable challenge: a significant proportion of patients diagnosed with PFS exhibit negative or inconclusive genetic workups. This raises questions about the adequacy of current genetic profiling methods and suggests that the pathogenesis of many cases may be more complex than previously understood. The article effectively illustrates the limitations of current diagnostic approaches and the need for further research to elucidate the underlying mechanisms of these syndromes. The suggestion that PFAPA syndrome accounts for only a minor proportion of cases with recurrent fever not linked to a conclusive genetic diagnosis prompts a reevaluation of how these conditions are classified and treated.

The article titled "Challenges in the diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome in developing countries—A decade of experience from North India" [16] presents a focused examination of PFAPA syndrome in a cohort of patients from North India, highlighting the clinical phenotype, diagnostic challenges, and the implications of these findings for evidence-based treatment approaches. The study effectively outlines the demographic characteristics of the patient population, noting a predominance of female patients and a unique onset pattern, emphasizing the importance of early diagnosis. The authors emphasize the episodic nature of the disease, with febrile episodes lasting between 2 to 7 days and recurring every 3 to 6 weeks in the majority of patients. Such periodicity is a hallmark of PFAPA syndrome and is essential for clinicians to recognize when considering differential diagnoses.

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Importantly, the study notes that all patients exhibited elevated inflammatory markers during episodes, which supports the inflammatory nature of PFAPA and may guide treatment strategies. However, the absence of respiratory symptoms and arthritis in this cohort provides a clearer delineation of PFAPA from other periodic fever syndromes, suggesting that differential diagnosis is crucial in managing patients effectively.

Conclusion

The literature surrounding adult PFAPA syndrome has expanded significantly, providing insights into its clinical phenotype, differential diagnosis, and evidence-based treatments. The foundational work by Smith et al. [1] established the heritable nature of related autoinflammatory disorders, emphasizing the need for a deeper understanding of PFAPA's complexities. Kraszewska-Głomba et al. [2] categorized PFAPA as an autoinflammatory disease due to the lack of identifiable infectious or autoimmune triggers, indicating a potential genetic basis that warrants further exploration.

A longitudinal study by Perko et al. [3] revealed that PFAPA symptoms often manifest in early life and can persist into adulthood, with adults experiencing similar symptoms to children but with variations such as increased arthralgia, as noted by Cattalini et al. [4]. The importance of early diagnosis was underscored by Lahti et al. [5], who highlighted the risk of misdiagnosis as recurrent tonsillitis, advocating for tonsillectomy as an effective treatment option for many patients.

The challenges in diagnosing adult-onset PFAPA were documented by Alam et al. [6], emphasizing the necessity of distinguishing PFAPA from other periodic fever syndromes, a sentiment echoed in. Genetic investigations have linked PFAPA with conditions like Behçet's disease, as noted by Manthiram et al. [7], suggesting a shared pathogenesis that could enhance understanding of PFAPA. Furthermore, Cinquina et al. [8] proposed a phenotype-first approach to improve diagnostic accuracy, emphasizing the role of clinical features in distinguishing PFAPA from other syndromes.

The psychosocial impact of PFAPA on families was explored by Sparud-Lundin et al. [9], emphasizing the need for increased awareness and support within healthcare systems. Overall, the literature highlights the interplay of clinical, genetic, and psychosocial factors surrounding adult PFAPA syndrome, underscoring the necessity for standardized diagnostic criteria and effective treatment strategies as understanding of the syndrome's pathophysiology continues to evolve.

In conclusion, the body of research on adult PFAPA syndrome reveals a complex interplay of clinical features, genetic considerations, and the necessity for improved diagnostic and treatment protocols. The findings underscore the importance of recognizing this syndrome in both pediatric and adult populations to enhance patient management and outcomes.

Highlights

1. **Adult PFAPA exhibits both classic and distinct features** compared to pediatric PFAPA, including more frequent arthralgia and diagnostic delays.
2. **Diagnosis remains clinical**, as genetic profiling often yields inconclusive results; a phenotype-first approach is essential.
3. **Corticosteroids are effective in acute management**, while tonsillectomy and IL-1 inhibitors may offer long-term benefit in selected cases.

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