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RESEARCH ARTICLE

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome at a Single Children's Hospital

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Abstract

Background: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (PFAPA) is characterized by periodic cyclical fever, cervical adenopathy, pharyngitis, and aphthous stomatitis. Administration of oral corticosteroids at the onset of fever is the current initial treatment. Tonsillectomy resolves PFAPA symptoms in 50-100% of patients.

Objective: The goal of this retrospective observational study was to characterize aspects of PFAPA patients seen at a medium size children's hospital between 2008 and 2016 and evaluate treatment outcomes.

Methods: Medical records were reviewed of patients with "periodic fever" in their problem list or encounter diagnoses. Charts were included if there was a physician diagnosis of PFAPA or periodic fever syndrome with symptoms typical of PFAPA. Demographic/growth characteristics and details of symptoms, diagnosis, and treatment were recorded in a de-identified manner and analyzed.

Results: Analysis of 87 subjects correlated well with demographics and symptom distribution described in previous studies and showed an average 1.7-year delay between onset of symptoms and diagnosis. PFAPA episodes resolved for 73.1% of tonsillectomy subjects. Genetic testing revealed MEFV heterozygous gene in 3 subjects. Incidence of Transient Hypogammaglobulinemia of Infancy was found in 4.6%, Mannose-Binding Lectin Deficiency in 1.1%, and Specific Antibody Deficiency in 4.6%.

Conclusions: Significant delay existed between symptom onset and diagnosis of PFAPA, despite a typical demographic and symptom profile. In addition, several primary immunodeficiencies were observed as comorbidities in this population. Greater awareness is needed among primary care providers in the diagnosis of this disorder, thereby initiating earlier appropriate referrals.

Abbreviations

ESR: Erythrocyte Sedimentation Rate; FMF: Familial Mediterranean Fever; G-CSF: Granulocyte Colony-Stimulating Factor; IFN-γ: Interferon Gamma; IL: Interleukin; MBL: Mannose-Binding Lectin; MIG: Monokine Induced By Gamma Interferon; OSA: Obstructive Sleep Apnea; PFAPA: Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis; SAD: Specific Antibody Deficiency; *S. pneumoniae: Streptococcus Pneumoniae*; THI: Transient Hypogammaglobinemia of Infancy; TNF-α: Tumor Necrosis Factor Alpha

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome was first described in 1987 by Marshall, et al. [1]. It was characterized as a constellation of symptoms primarily affecting children of European descent at approximately 2 to 3 years of age with a slight male predominance (1.8:1) [2-11]. The fever is usually abrupt in onset, lasts 3 to 5 days, re-

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curs every 3 to 6 weeks, and ranges from 101° to 103° F but could be as high as 105° F. Associated symptoms include aphthous stomatitis, pharyngitis, and cervical lymphadenopathy [11]. Prodromal symptoms may include headache, abdominal pain, nausea and diarrhea 20 hours before the onset of fever. PFAPA syndrome typically resolves by adolescence without sequelae [2-11]; however, a rare adult-onset variant has also been described [12-20].

Autoimmune dysregulation and activation of the inflammasome are thought to cause the symptoms of PFAPA, via upregulation of interleukin-2 (IL-2), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) with over-expression of complement, interleukin-1 (IL-1) and products of interferon-induced genes, such as IL-6 and IL-18 [20-24]. Laboratory evaluation is not required for diagnosis, but if examined, the erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and total white blood cell count are elevated during febrile episodes and return to normal values during asymptomatic periods. This response has been postulated to originate from the tonsils, with tonsillar biopsy showing upregulation of genes related to innate immune activation without manifesting a unique bacterial or viral profile when compared to those of obstructive sleep apnea or hypertrophied tonsils [25]. Histologically, tonsils from patients with PFAPA syndrome show larger germinal centers compared to patients who underwent tonsillectomy for obstructive sleep apnea (OSA) [26]. Many patients also demonstrated lower rates of upper respiratory infections, which later normalized following resolution of PFAPA [24]. Thus, PFAPA has been postulated to represent a syndrome of increased immune reactivity to infectious triggers [23,25].

PFAPA is generally regarded as a sporadic disease; however, PFAPA has been reported with hereditary links [27]. Although no single gene mutation has been identified to correlate with disease occurrence, patients with PFAPA demonstrate a higher than normal population rate of heterozygous *MEFV* gene mutations. *MEFV* encodes the innate immunity regulator pyrin and is typically related to Familial Mediterranean Fever (FMF) [28]. PFAPA is diagnosed clinically in a patient with a typical history where no other source of fever is identified. In a patient with an atypical clinical picture, hematologic or genetic testing may be beneficial to rule out other diagnoses since FMF and PFAPA can be easily confused. A 1999 study of 10 patients with PFAPA who had previously been diagnosed as FMF, found 6 to have a heterozygous mutation in the *MEFV* gene [6]. In a study of 359 patients diagnosed with PFAPA by Pehlivan, et al. patients with symptoms resembling FMF, who were unresponsive to tonsillectomy, or who had a family history of FMF were investigated further for *MEFV* gene mutation; 33.8% of these patients were positive for *MEFV* gene mutation [29]. Other studies have shown a prevalence of 24.7% to 55.4% of *MEFV* variants in patients diagnosed with PFAPA, especially in FMF-endemic regions [30-32]. Patients with coexistent FMF and PFAPA may have a poorer response to surgical treatment and a better response to colchicine [29,30].

The initial management of febrile episodes is oral corticosteroids, which can resolve symptoms within 6 hours, but do not prevent future episodes and can shorten the interval between episodes [2,4-7,9,33-35]. The histamine type 2 receptor antagonist cimetidine has also been used preventively but has recently been shown to have inconsistent febrile episode resolution rates [3,15,24]. For those patients in whom corticosteroid therapy is unsuccessful, an IL-1 receptor inhibitor, such as anakinra, has been shown to reduce episode length in small patient populations [23,29,36]. However, cost/benefit ratio must be carefully considered, and currently there are no published cost-benefit analyses of anakinra use in patients with PFAPA. Tonsillectomy has been shown to be helpful. In a recent Cochrane review, there was a relative risk reduction of 4.38 in PFAPA symptoms and an overall reduction in both severity and frequency of episodes post-tonsillectomy [37]. Demonstrating a possible link between FMF and PFAPA, colchicine, an anti-inflammatory medication commonly used in the treatment of FMF, has been shown to increase the interval between episodes but does not reduce the severity and has been reserved for patients whose symptoms do not resolve following tonsillectomy [35].

Improved awareness of PFAPA, especially for primary care providers, is essential for diagnosis and referral to specialists in the management of PFAPA. In this study, we aimed to garner a more complete picture of the epidemiology and present the symptoms and resolution rates of PFAPA in response to tonsillectomy.

Methods and Materials

This study was approved by the Saint Louis University Institutional Review Board. A retrospective chart review was performed, selecting patients seen by Pediatric Allergy & Immunology, Pediatric Rheumatology, or Pediatric Infectious Diseases between 2008 and 2016 for diagnosis code of recurrent fever or periodic fever and subsequently diagnosed with PFAPA. From 180 charts, 120 were found to have confirmed diagnosis of PFAPA syndrome. The research team recorded de-identified patient information including age, gender, ethnicity, age at presentation, age at which diagnosis was made, symptoms reported by caregivers and documented by physicians, and treatments. A follow-up written survey was mailed to 33 patients whose records were incomplete. Of that group, 5 patients who completed and returned their surveys; the remaining 28 participants who did not respond were removed from the study.

Statistics: Data presented as mean ± SD and as percentage.

Table 1: Demographic data is presented for the study participants, along with frequency of immunodeficiency comorbidities, average immunoglobulin D (IgD) and frequency of elevated IgD.

Characteristics	Result N = 87
Age onset of symptoms, years (range)	2.2 ± 1.7 (0.2-8)
Age at diagnosis, years (range)	3.9 ± 2.5 (1-9)
Female, n, %	43, 49%
Race, n, %	
White	79, 90.8%
Black	6, 6.9%
Hispanic	1, 1.1%
Asian	1, 1.1%
Associated conditions, n, %	
THI	4, 4.6%
SAD	4, 4.6%
MBL deficiency	1, 1.1%
MEFV heterozygous mutation	3, 3.4%
IgD, mg/dl, (range)	6.8 ± 9.7, (0.69 to 44.43)
Elevated IgD, %	10.80%
***S. pneumoniae* antibody, % protective**	
Pre	45.7% ± 17.0%
Post Prevnar® immunization	69.3% ± 26.1%
Post Pneumovax® immunization	80.0% ± 18.5%

Table 2: Frequency of PFAPA Syndrome episode symptoms are presented, showing typical fever severity and duration.

Symptom	Result N = 87
Fever, n, %	87, 100%
Tmax, °F (range)	103.8 ± 1.1 (101-107)
Fever duration, days (range)	3.7 ± 2.0 (1.5-14)
Fever frequency, weeks (range)	3.7 ± 1.1 (2-12)
Cervical adenopathy, n, %	43, 49.4%
Pharyngitis, n, %	53, 60.9%
Aphthous stomatitis, n, %	26, 29.9%
Headache, n, %	17, 19.5%
Abdominal pain, n, %	21, 24.1%

Table 3: Treatment methods are presented, with 100% of participants treated during episodes with NSAIDs, 84.0% treated episodically with oral corticosteroids, and 49.3% having undergone tonsillectomy. This population showed a mean response rate to tonsillectomy of 73.1%.

Treatment	Patients, n, %
Oral corticosteroids, n, %	73, 84.0%
Response to OCS, n, %	72, 82.9%
NSAIDs, n, %	87, 100.0%
Tonsillectomy ± adenoidectomy, n, %	43, 49.3%
Response to tonsillectomy ± adenoidectomy, n, %	63, 73.1%

Results

The average age of onset of PFAPA symptoms was 2.2 ± 1.7 years (Table 1). However, the average age of diagnosis of PFAPA was 3.9 ± 2.5 with a range of 1 to 9-years-old. There was an average of 1.55 ± 1.6 years from the onset of symptoms to diagnosis, with a maximum of 8 years. There was an equal female to male ratio. Overall, most PFAPA-diagnosed patients were of European descent (82.8%). Additional comorbid conditions found in study participants included: Transient hypogammaglobulinemia of infancy (THI) in 4.6% (n = 4), specific antibody deficiency (SAD) in 4.6% (n = 4), mannose-binding lectin deficiency (MBL) in 1.1% (n = 1), and *MEFV* heterozygous mutations in 3.4% (n = 3) (Table 1). Immunoglobulin D (IgD) levels were 6.8 ± 9.7 mg/dl, with elevated IgD greater than 10 mg/dL in 10.8% of patients. Patients had decreased antibody titers to *Streptococcus pneumoniae* (*S. pneumoniae*) at initial evaluation, with protection to only 45.7% ± 17.0% of the serotypes. However, *S. pneumoniae* protective antibody titers improved to 69.3% ± 26.1% and 80.0% ± 18.5% following immunization with Prevnar® or Pneumovax®, respectively, which are considered normal levels of response to the vaccines.

Symptoms in patients with PFAPA syndrome are presented in Table 2. Fever occurred in 100% of the 87 participants, with an average maximum temperature of 103.8 °F ± 1.1 °F, which lasted an average of 4 days and cycled every 3.7 ± 1.1 weeks (Table 2). The next most prevalent symptoms were pharyngitis (60.9%), cervical adenopathy (49.4%), aphthous stomatitis (29.9%), abdominal pain (24.1%), and headache (19.5%).

Prior to diagnosis of PFAPA, 100% of patients were initially treated with acetaminophen and/or ibuprofen, with only transient relief of symptoms (Table 3). After diagnosis of PFAPA, 84.0% of patients were treated with oral corticosteroids, typically methylprednisolone 1 to 2 mg/kg. 82.9% of corticosteroid recipients experiencing shortened duration of fever and related symptoms. Tonsillectomy with or without adenoidectomy was performed in 49.3% of patients and completely resolved PFAPA symptoms in 73.1% of those patients. Many patients were lost to follow-up after tonsillectomy, thereby their response could not be assessed, and this number may be an underestimate.

Discussion

PFAPA can be under-recognized by primary care providers. Diagnostic criteria include regularly recurring fevers in patients less than 5-years-old, who also demonstrate at least 1 of the following: Aphthous stomatitis, cervical lymphadenopathy or pharyngitis, and exclusion of other sources of fever [4]. This study aimed to present the clinical characteristics of PFAPA to raise awareness among primary care providers regarding its diagnosis. Our participants' symptoms are similar to those previously reported, but, not all symptoms were present in all patients in our study population. Only 29.9% of subjects in our study reported aphthous stomatitis, for example. Increased awareness among primary care providers of periodic fever syndromes helps to identify patients appropriate for referral to specialists trained in periodic fever diagnosis and management. This would limit unnecessary treatment for infectious causes while speeding initiation of prodromal steroid or referral for tonsillectomy [38,39].

PFAPA is an autoinflammatory disorder with positive modulating effects on patients' immune response to infections. In our patients, antibody titers against *S. pneumoniae* were frequently decreased, but responded appropriately to booster vaccination. Further study is needed to analyze *S. pneumoniae* antibody responses in larger populations of patients with PFAPA. Many of the patients studied here had undergone multiple investigations for Group A *Streptococcus*, Epstein Barr virus, and influenza virus and received repeated courses of antibiotics. Their clinical courses did not qualitatively differ from patients who did not receive antibiotics. Use of antibiotics is especially common in the early episodes of PFAPA syndrome, when a clinical pattern has yet to appear. However, the use of antibiotics has been shown neither to benefit patients nor to correlate with earlier PFAPA resolution rates [39]. Earlier recognition of PFAPA can lead to fewer treatment courses for perceived infections. Although no comorbidities have been explicitly linked to PFAPA syndrome, subjects in this study were also evaluated for immune deficiencies and some for other periodic fever syndromes. No genetic anomaly has been linked to PFAPA syndrome, although it does seem to occur more frequently in northern Europeans [27]. In some cases, genetic testing for other autoinflammatory disorders may aid in eliminating other causes of periodic fever. In the present study, genetic testing was performed in 9 of the 87 patients, 3 of whom had heterozygous mutations of *MEFV*. *MEFV* mutation is associated with FMF, which is characterized by recurrent fever and episodes of serosal inflammation affecting the joints, lungs, peritoneum, and heart [28]. While some studies have not found a significant difference in clinical features among PFAPA patients with and without coexistent FMF [29], others have found that patients with PFAPA syndrome and *MEFV* gene mutations have a shorter duration of febrile episodes [40,41]. While the sample population studied here is too small to propose a correlation, heterozygous *MEFV* carriers present an area of ongoing study of the implications for periodic fever syndromes.

Comorbid primary immune deficiency was identified in 4 patients with transient hypogammaglobulinemia of infancy (THI), 4 patients with specific antibody deficiency (SAD) and 1 patient with mannose-binding lectin deficiency (MBL). In these subjects, prophylactic antibiotics were used but the patients continued to express the clinical manifestations of PFAPA, further supporting the inefficacy of antibiotics in PFAPA therapy. THI has been described with an incidence of 0.061 to 1.1 per 1000 live births [42,43] versus the incidence of 4.6% in this study. MBL deficiency affects approximately 5 to 15.6% of the world's population, with increased incidence in certain ethnicities such as sub-Saharan Africans [44,45]. Finally, SAD's prevalence has not been well-defined; in a patient population being evaluated for recurrent infections, among 6-24% were found to have SAD [46]. Of the patients evaluated in this study who were found to have an immunodeficiency, all were primarily evaluated for recurrent infections and then found to have PFAPA syndrome. It should also be noted that booster immunizations with *S. pneumoniae* vaccines did not alter the symptoms of PFAPA. Thus, the correlation of decreased *S. pneumoniae* antibody titers and PFAPA is uncertain.

Although tonsillectomy has been found to be the most effective treatment for long-term resolution of PFAPA, studies have rarely shown complete efficacy [39]. Oral corticosteroids and tonsillectomy have been shown to perform better than cimetidine, colchicine or no treatment in reducing overall episode burden. Of note, patients report shorter but more frequent febrile episodes on oral corticosteroids [9]. There is no consensus regarding the best treatment when comparing oral steroids and tonsillectomy [39,47]. Vigo, et al. reported in a review of 15 studies that tonsillectomy effectively resulted in complete resolution of symptoms in 130 of 159 patients (81.8%) with a range of 50% to 100% [10]. A smaller scale study of 12 patients found a 75% resolution rate following tonsillectomy [9]. In a 2010 meta-analysis of 374 patients examining treatment resolution rates, no immediate advantage could be found when directly comparing tonsillectomy and steroids, but tonsillectomies in general led to better long-term resolution rates [34]. In a recent study of 23 patients, 91% of patients had complete resolution of PFAPA symptoms immediately after surgery, with 100% of patients achieving resolution within 3 months [48]. Finally, a Cochrane review of randomized controlled trials (n = 65) comparing surgery versus corticosteroids or expectant management found complete resolution in all tonsillectomy patients by the end of 6 months [37]. In this study of 87 patients, there was a 73.1% success rate of tonsillectomies resolving episodes, which correlates well with previous literature results. However, follow-up data was limited by patients' lack of consistent return to clinic.

This study found a troubling delay between onset of symptoms and referral for diagnosis of PFAPA. The one-and-a-half-year delay illuminates the need to increase primary care providers' awareness of PFAPA. However, one must consider the diagnostic time it takes to rule out infectious causes, document a pattern of monthly periodic fever and refer to a pediatric specialist in Infectious Disease, Rheumatology or Allergy and Immunology. In a 2013 European study, patients experienced a median delay of 20 months (1.67 years) between onset and diagnosis with an average age at diagnosis of 27 months (2.25 years) [4]. Future studies additionally could expand the care of PFAPA syndrome by screening patients with THI for periodic fever symptoms [49].

Limitations

Follow-up data and information on the progression of patients' symptoms after tonsillectomy represented a significant limiting factor. Of the 32 participants

to whom surveys were mailed, phone contact was attempted with all participants and only 5 returned the packets. Over the eight years which the study examined, many patients and their parents were not actively continuing to track their PFAPA-related symptoms. It is possible that once patients began to have symptomatic improvement, they discontinued follow-up appointments.

Conclusion

Increased awareness among primary care providers of periodic fever syndromes and their wide variety of presenting symptoms will aid in identifying patients appropriate for referral to specialists trained in periodic fever diagnosis, limit their exposure to unnecessary treatment for infectious causes and speed the initiation of prodromal steroid or referral for tonsillectomy.

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