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Periodic Fever, Aphthous Stomatitis, Pharyngitis (Pfapa) Syndrome, and Nlrp3 Gene Association

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Review Article

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ABSTRACT

PFAPA syndrome, which includes aphthous stomatitis, pharyngitis, and adenitis, is the most common type of recurrent fever in children. Usually happens before the age of five. This syndrome is characterized by attacks lasting 3-7 days, recurring every 2-8 weeks with high fever (39 C and above) accompanied by at least one of the signs of aphthous stomatitis, pharyngitis, and/or cervical adenitis. Between attacks, the child is completely healthy. PFAPA is a benign disease that regresses with age. Steroids are used in the treatment of attacks. Colchicine is often preferred in prophylactic treatment. However, if there is no response to medical treatment, surgery (tonsillectomy) can be performed. Genetic and environmental factors are considered in the etiology. Genetic susceptibility concentrated on the genes for Familiar Mediterranean Fever (FMF, MEFV), TNF-Receptor-Associated Periodic Syndrome (TRAPS, gene TNFRF1A), HyperIgDSyndrome (HIDS, gene MVK), and Cryopyrin-Associated Periodic Syndrome (CAPS, gene NLRP3). But its etiology is still unknown.

Periyodik Ateş, Aftöz Stomatit, Farenjit (PFAPA) Sendromu ve NLRP3 Geni İlişkisi

Süreç

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ÖZ

PFAPA sendromu, aftöz stomatit, farenjit ve adenit içeren tekrarlayan ateşin en yaygın görülen türüdür. Genellikle beş yaşından önce ortaya çıkar. Bu sendrom, yüksek ateş (39°C ve üzeri) ile birlikte aftöz stomatit, farenjit ve/veya servikal adenit belirtilerinden en az biri eşlik eden 3-7 gün süren ve 2-8 haftada bir tekrarlayan ataklarla karakterizedir. Ataklar arasında çocuk tamamen sağlıklıdır. PFAPA, yaşla birlikte gerileyen, zararsız bir hastalıktır. Atakların tedavisinde steroidler kullanılır. Profilaktik tedavide genellikle kolşisin tercih edilir. Ancak tıbbi tedaviye yanıt alınamıyorsa cerrahi (tonsillektomi) uygulanabilir. Etyolojide genetik ve çevresel faktörler göz önünde bulundurulmaktadır. Genetik yatkınlık, Ailevi Akdeniz Ateşi (FMF, MEFV geni), TNF-Reseptörle İlişkili Periyodik Sendrom (TRAPS, TNFRF1A geni), HiperIgD Sendromu (HIDS, MVK geni) ve Cryopyrin-İlişkili Periyodik Sendrom (CAPS, NLRP3 geni) için odaklanır. Ancak etiyolojisi hala bilinmemektedir.

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Introduction

PFAPA syndrome was first described by Marshall et al.in 1987 as Marshall Syndrome [1]. Later, this disease was named PFAPA syndrome in 1989 [2]. PFAPA syndrome is the most common periodic fever condition in childhood [3]. The incidence in children under 5 years of age is 2.3/10000 in a recent Norwegian study [4]. In the majority of cases (90%), symptoms begin under 5 years of age [5]. This syndrome is characterized by attacks lasting 3-7 days, recurring every 2-8 weeks with high fever (39 C and above) accompanied by at least one of the signs of aphthous stomatitis, pharyngitis, and/or cervical adenitis. Between attacks, the child is completely healthy. Patients show normal growth and development [5,6]. Although it is a common disease in childhood, symptoms regress before adolescence. However, there are cases that continue until adulthood [7]. The diagnosis is based on clinical findings, and the absence of a specific laboratory and genetic test complicates the diagnosis. For diagnosis, other causes of periodic fever should be excluded [5]. Modified Marshall's criteria are used for diagnosis [8]. Although infectious agents, immunological mechanisms, and genetic predisposition are considered in the etiology, the true cause is still unknown [8].

Etiopathogenesis

Immunological processes and infectious organisms are believed to contribute to the etiology of PFAPA [9]. However, it is thought that infectious causes do not play a role in the etiology due to the fact that inflammatory causes should be excluded in the diagnosis, it responds dramatically to a single dose of steroid, and it has a self-limiting nature [10]. Serum levels of proinflammatory cytokines are high in patients with a diagnosis of PFAPA [11]. Mucosal interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) levels are higher in these patients compared to healthy individuals [12]. It was determined that the IL-1β, IL-6, and IL-18 levels of the patients were higher than the healthy individuals [13]. In the literature, IL-1β and IL-6 levels were compared during the attack of patients with PFAPA and serum levels of patients with pneumonia, and it was observed that they were higher in patients with PFAPA [14]. In addition, when the tonsils of patients with PFAPA were examined, it was observed that T cell early developmental stages and T cell chemoattractant proteins increased [15]. On the other hand, it was determined that the serum level of the anti-inflammatory cytokine IL-4 and the levels in the patients' tonsillar tissue were lower than in the healthy individuals [16,17]. All these findings suggested that there is an immune system disorder associated with cytokine dysfunction in PFAPA syndrome [8].

25[OH] vitamin D levels have also been the subject of research in patients with PFAPA. The role of vitamin D in immune regulation suggested that it may be effective in this regard [18]. Patients with PFAPA were shown to have significantly lower serum 25[OH] vitamin D levels than healthy people [19]. Additionally, a lack of vitamin D has been linked to an increased likelihood of relapsing symptoms and difficulty controlling attacks [19]. Another study determined that the duration and frequency of attacks decreased after vitamin D replacement was given to patients diagnosed with PFAPA with vitamin D deficiency [20].

The pathogenesis of PFAPA syndrome is thought to be caused by a number of different variables in addition to vitamin D deficiency [18]. For example, Kettunen et al. found that the rates of breastfeeding in patients with PFAPA were lower than in healthy individuals. In the same study, they found that the rate of smoking in mothers of patients with PFAPA was higher than in healthy individuals [21]. These findings suggest that environmental factors may be effective in the pathogenesis of PFAPA [18].

Genetic Background

PFAPA was classically known as a sporadic disease [22]. However, studies have shown that there are individuals with a similar history in the families of these patients [18]. A study showed that 38 of 84 patients with PFAPA had a positive family history of recurrent fever, and 10 of these patients had a family history of PFAPA [23]. This percentage was discovered to be 45% and 78% in various investigations [24]. An increase in the rate of positive family history suggests that PFAPA syndrome is not a sporadic disease but also has a genetic potential [25]. However, Yıldız et al. found the rate of positive family history to be 29.9% in their study. As a result of this study, it has been suggested that familial predisposition may not be definitive proof of genetic predisposition but may be due to exposure of family members to the same environmental factors [26].

Genetic predisposition specifically focused on the genes of Familiar Mediterranean Fever (FMF, MEFV), TNF-Receptor-Associated Periodic Syndrome (TRAPS, gene TNFRF1A), HyperIgDSyndrome (HIDS, gene MVK), and Cryopyrin-associated periodic syndrome (CAPS, gene NLRP3) [18].

Kaynak et al. discovered MEFV mutation in 32.5% of patients diagnosed with PFAPA [27]. Yıldız et al. found that clinical symptoms were milder in patients with PFAPA diagnosis and those with MEFV gene mutations [28]. The same results were also found by Dagan et al. [29]. Ünsal et al. also found MEFV gene mutations in 41.66% of patients with PFAPA who were examined for MEFV gene mutation [30].

Relationship of NLRP3 Gene and PFAPA

The multiprotein complex known as NLRP3 is crucial for the secretion of IL-1. Together with its activation, the sensor protein NLRP3 combines the adapter protein ASC (A caspase accumulator domain containing a dot-like protein associated with apoptosis) and procaspase-1. This combination results in the formation of caspase-1. As a result of this formation, IL-1β and IL-18 release occur [31].

The mutations of the NLRP 3 gene in exon 3 lead to hyperactivation of caspase-1, which leads to an increase in IL-1β secretion [11,31,32].

High serum levels of IL-1β and IL-18 in PFAPA-diagnosed patients suggested that there could be a defect in the NLRP3 gene in the etiology [8,11].

When the NLRP3 gene is considered, research by Perko et al. that included 81 individuals with PFAPA revealed 13 of the patients to have NLRP3 gene mutations [24]. In another study, Kolly et al. found that 12 out of 57 patients diagnosed with PFAPA had mutations in the NLRP3 gene [11]. Kubota et al. found that only 1 of 9 patients diagnosed with PFAPA had a mutation in the NLRP3 gene [33]. However, Dagan et al. did not find NLRP3 gene mutation in a study group of 57 patients [34]. DiGioia et al. did not obtain significant results in the NLRP3 gene mutation in a study on 68 individuals from 14 families [35]. In Turkey, when Ekinci et al. performed a genetic analysis in 104 patients with PFAPA, they found NLRP3 gene mutation in only 1 patient. But this mutation was insignificant [36]. In a study, Kaynak et al. looked at the NLRP3 polymorphism and serum levels of individuals with PFAPA and discovered no significant difference between the PFAPA patients and the control group [27]. Ünsal et al. also studied NLRP3 gene analysis in 14 patients with PFAPA and did not detect any mutations [30].

As a result of these studies, it was thought that the pathogenesis was not monogenic and different genes might have a synergistic effect [8,27].

TREATMENT OPTIONS

Medical Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, colchicine, and cimetidine are medical agents used in the treatment of PFAPA [25]. NSAIDs may be given during an attack, especially acetaminophen as a febrile suppressant. However, acetaminophen has not been shown to reduce the fever exactly. Also, NSAIDs do not reduce the frequency and duration of attacks [37].

Daily intake of cimetidine has been to reduce the frequency and severity of attacks [22,25]. However, meta-analysis studies have shown that the effect is not as successful as surgery [38]. In cases of mild form and in patients who do not respond to surgical treatment, cimetidine treatment may be indicated [37].

Colchicine has been considered as an alternative treatment option in patients with PFAPA due to its blocking effect on microtubule polymerization [39]. When used, it is shown to prolong the time between attacks [40]. Additionally, it has been demonstrated that patients with MEFV gene mutations benefit more from colchicine prevention [41,42].

Corticosteroids are the most preferred medicines in the treatment of fever attacks. Generally, prednisone 1-2 mg/kg/dose (max:60 mg) reduced fever in 95% of patients 43. Instead of prednisone, 0.1-0.2 mg/kg/dose of betamethasone can also be used [44]. Steroids do not prevent the next attack [26]. It has also been shown to shorten the time between attacks [6].

Considering the effect of vitamin D deficiency in patients with PFAPA, the use of vitamin D was considered [20]. However, there are not sufficient studies on the routine use of vitamin D in these patients [18].

Streptococcus salivarius K12, a probiotic, has also been studied in the literature. It has been demonstrated to reduce symptoms and enhance the quality of life in individuals with PFAPA, but additional research is required to verify its efficacy [44].

Surgical Treatment

A treatment option is a tonsillectomy. A significant rate of remission in symptoms following tonsillectomy has been documented in the literature [45]. However, some studies have also shown that there is no difference between tonsillectomy and other treatment options [46,47]. Therefore, the choice of surgical method should be decided by considering the self-limiting nature of this syndrome and the risks to the surgeon. All of these issues should be thoroughly discussed with the family before choosing a course of treatment [28].

In conclusion, PFAPA syndrome is a common recurrent fever in children. Patients who present to pediatric clinics with recurrent fever should have it on their list of possible diagnoses. Its etiology has not been fully explained yet. In light of current literature, it is thought that it develops in a genetic predisposition with the effect of environmental factors.

Table1 : Modified Marshall's criteria for the diagnosis of PFAPA syndrome [22]

I-Recurrentfeverepisodesonsetbeforetheage of five
II-Having at least one of the following symptoms without upper respiratory tract infection a) aphthous stomatitis, b) cervical lymphadenitis, c) pharyngitis
III-Completly asymptomatic interval between episodes
IV-Normal growth and development
V- Exclusion of cyclic neutropenia

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