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Review

Treatment in PFAPA Syndrome: A Review

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Abstract

The most common disease with recurrent fever is PFAPA syndrome, which includes fever, aphthous stomatitis, pharyngitis, and cervical adenitis. Medical treatment (attack treatment, prophylactic treatment) and tonsillectomy are recommended treatments for this disease, and there are corticosteroids that are effective in the management of fever attacks, colchicine for the prophylaxis of febrile attacks, and some drugs whose efficacy has not yet been proven. Tonsillectomy may be an option for some patients. PFAPA syndrome of childhood usually resolves during adolescence. There are also adult-onset and childhood-onset PFAPA syndrome cases.

Keywords: Aphthous stomatitis, corticosteroid, recurrent fever, pharyngitis, PFAPA syndrome

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Periodic fever is a childhood condition caused by more than one disease or syndrome. The most common of these diseases is PFAPA syndrome, which includes periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. This syndrome, which was described by Marshall et al. 35 years ago, is the most common cause of non-infectious recurrent fever in children.[1,2]

It is characterized by fever attacks lasting 3-6 days, recurring every 3-8 weeks, associated with at least one of the three main symptoms: aphthous stomatitis, cervical adenitis, and pharyngitis.[3]

The cause of the PFAPA syndrome is unknown, but it is thought to be caused by immune system dysregulation. According to the findings of the studies, there is an irregularity in the immune system components and an inflammatory-mediated pathway in the activation of the symptoms, and thus the PFAPA syndrome was classified as an autoinflammatory disease.[4] Furthermore, a strong familial history suggests that the syndrome is genetic in nature. The presence of variants in inflammatory genes, primarily NLRP3 and MEFV, suggests that these genes may play a role in the pathogenesis of PFAPA.[5]

The disease usually starts before the age of five and ends during adolescence. Between attacks, patients are asymptomatic and grow normally. Infection, abnormal host immune responses, or a combination of both have been proposed to contribute to pathogenesis.

In the diagnosis of PFAPA syndrome, clinical findings are prioritized. Recurrent fever, pharyngitis, aphthous stomatitis, and cervical adenitis are among the findings. Other diagnostic criteria include the absence of cyclic neutropenia, normal growth and development, and the ability to function normally in between attacks. Since these findings can be seen in other diseases with recurrent fever, the patient should be screened clinically and genetically in terms of other syndromes with periodic fever before the diagnosis of PFAPA syndrome.[6]

Methods

The purpose of this article is to conduct a literature review on the treatment of the PFAPA syndrome and to review and present the results. MEDLINE, PubMed Central, and other NCBI databases associated with the PubMed platform were searched for this purpose. The research also presented the

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data obtained by examining the Cochrane Library, Scopus, Web of Science electronic databases.

Medical and surgical options were evaluated in the treatment. In medical treatment, two separate headings were determined as attack treatment and prophylactic treatment. As a surgical treatment, tonsillectomy was prioritized.

In the treatment of attacks, it is aimed to increase the quality of life of the family and the child, and in prophylactic treatment, it is aimed to reduce the frequency of attacks.

Attack Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids are at the forefront in the treatment of attacks.

NSAIDs are used to treat fever and pain, but their effectiveness is limited. It has been discovered that only NSAIDs completely suppress the symptoms in 4% of patients with PFAPA syndrome, and this rate rises to 70-80% when combined with steroids.[7] NSAIDs are drugs that are used primarily for fever control, and they reduce fever to a limited extent. They have no effect, however, on reducing the duration and frequency of fever symptoms.

Steroids are the most used and most effective drug class in the treatment of this disease's attacks. Glucocorticoids inhibit leukocyte migration into inflammatory foci by suppressing the production and effects of various proinflammatory mediators. As a result of its strong anti-inflammatory effect in acute attacks, it provides a rapid improvement in symptoms.[8]

This dramatic response can also be used to diagnose the PFAPA syndrome.[7] A randomized clinical trial[9] found that 0.5 to 2 mg/kg prednisone (or equivalent) in a single dose at the onset of fever was beneficial, and thus glucocorticoids can be recommended as level of evidence 2B in PFAPA patients.[7] However, sometimes additional doses of glucocorticoids may be required. Their use does not prevent subsequent attacks and may even be associated with an increased frequency of attacks in 25-50% of cases.[7]

In the study of Thomas et al., a single dose of prednisone (1-2 mg/kg) or betamethasone (0.1-0.2 mg/kg) at the beginning of the attack can control the fever attacks within a few hours. If one dose is not effective in resolving the exacerbation, a second dose can be given the next day.[3]

Hofer et al. found that steroids were used to treat 147 of 301 patients with PFAPA syndrome in their study. They reported that 93 (63%) of these patients recovered quickly from fever after a single dose of steroids, but 46 (32%) had a partial response and only 8 (5%) did not respond.[10] In another study in which 60 patients were evaluated, it was reported that steroid treatment given to 44 patients during PFAPA attack was effective in 37 (84%) patients.[11]

In a study conducted in 54 patients on low-dose steroid (0.6 mg/kg/day) treatment given at once, it was reported that fever symptoms resolved within 10 hours in 51 patients.[12] In a study on the efficacy of a single low-dose steroid conducted by Yazgan et al., 40 patients with PFAPA syndrome were given 2 mg/kg/day steroids during the attack, and 46 patients were given 0.5 mg/kg/day steroids, and no statistical difference in terms of effectiveness was found.[9]

Steroids are drugs that can occasionally be used with low compliance due to parental concerns about side effects. However, studies have shown that they frequently cause restlessness and have no serious side effects.

As a result, steroid use is the most effective drug group in the treatment of PFAPA syndrome attacks, and it is also data that can be used in the differential diagnosis from other periodic fever syndromes. Except for recurrent fever caused solely by mevalonate kinase deficiency, other recurrent fever diseases do not respond significantly to single-dose steroid therapy.[10]

Prophylactic Therapy

The goal of prophylactic treatment is to improve the patient's and family's quality of life by reducing the number and frequency of attacks. In the literature review, colchicine, cimetidine, IL1 antagonists, and vitamin D supplementation are mentioned.

The study sought to investigate the efficacy of cimetidine and colchicine in prophylactic treatment, even though there is limited evidence for their efficacy in the literature. While other drugs (IL-1 blockers, vitamin D) were considered for prophylaxis, only peer-reviewed publications on the subject were included.

Colchicine is a natural alkaloid derived from two lily plants: Colchicum autunnale and Gloriosa Superba, also known as meadow saffron and glory lily. Colchicine's anti-inflammatory and antimitotic properties have made it popular in the last decade.

Colchicine's anti-inflammatory mechanism of action is not fully understood. One possibility is that colchicine binds to tubulin to form a tubulin-colchicine complex, which inhibits neutrophil and lymphocyte migration and adhesion by altering the structure and function of the cytoskeleton.

Colchicine is an accepted treatment for familial Mediterranean fever that is still in use today. The rationale for using colchicine as a prophylactic treatment for PFAPA is primarily based on clinical and laboratory similarities between FMF and PFAPA, as well as long-term experience with this drug in the treatment of FMF. For these reasons, an alternative diagnosis of FMF should be considered when colchicine is effective in PFAPA patients.

In PFAPA syndrome, colchicine reduces the frequency of attacks by increasing the time between attacks. It does not, however, provide complete remission. Colchicine's prophylactic effect has been linked to the presence of a heterozygous mutation in the MEFV gene in studies.[13,14]

Butbul et al. conducted a controlled randomized study in 2016 on children with PFAPA syndrome and found that colchicine treatment for 3 months with dose adjustments (0.5-1.5 mg/day) reduced the frequency of attacks significantly. Eight patients received colchicine and ten patients received steroid treatment. A decrease in the number of prominent attacks was observed in the colchicine group. Interestingly, 8 of these patients had FMF mutations, and 6 of them were in the colchicine treatment group.[15]

Padeh et al. reported that colchicine had only a partial effect and was discontinued in FMF patients who showed PFAPA clinic and MEFV gene mutation in 6 of them.[16]

In a study investigating the efficacy of colchicine treatment in 9 PFAPA patients with frequent attacks (with an interval of ≤14 days), it was reported that colchicine treatment significantly increased the interval between attacks in 8 patients.[17]

Colchicine treatment is generally well tolerated, has low (10%) gastrointestinal side effects, and may be an effective second-line therapy in PFAPA patients, particularly if prednisone shortens the time between attacks, to prevent frequent recurrent episodes of fever.

Cimetidine, which has H2 receptor antagonist properties, is another medication. It is known that it can play a role in immune system regulation, and that it does so by inhibiting chemotaxis and T cell activation.

Feder was the first to recommend cimetidine as an effective prophylactic treatment for PFAPA.[18] Cimetidine was 43% effective in a study of 28 patients, according to Thomas et al.[3] Wurster et al. found that cimetidine was effective as a symptomatic treatment in 6 of 25 (26%) patients, and the treatment was ineffective in the remaining patients.[11] When recent studies were examined, there were large patient series, and no cimetidine was used in any study.[19,7] This indicates that cimetidine is being used less frequently. Furthermore, no randomized controlled trials have been conducted to date to support the benefits of cimetidine.

Stojanov et al. revealed that IL-1 has a fundamental role in the pathogenesis of PFAPA.[20] Among the IL-1 receptor blockers, the drug that we come across in the literature on this subject is Anakinra. Anakinra is a recombinant, non-glycosylated form of the human IL-1 receptor antagonist (rhIL-1Ra) that binds to the IL-1 receptor type I (IL-1RI) and acts as a competitive inhibitor of IL-1α and IL-1β. A single dose of anakinra on the second day of fever significantly improved both the clinical picture and laboratory parameters in a study with a small group of 5 children with PFAPA syndrome.[21] According to Frediana et al., a 27-year-old male patient who was resistant to conventional therapy (corticosteroids, colchicine, and tonsillectomy) was treated with subcutaneous anakinra injection and his fever attacks were completely resolved. Despite these interesting reports, the use of IL-1 blockers for the treatment of PFAPA is limited to selected cases due to the lack of randomized controlled trials in large groups.

Vitamin D has recently received a lot of attention because it is thought to play a role in inflammatory processes. Two recent studies have investigated the possible role of vitamin D in PFAPA syndrome. Mahamid et al. observed a significant difference in vitamin D levels between 22 PFAPA patients and 20 healthy controls, as well as a link between PFAPA and vitamin D deficiency.[23] Stagi et al. confirmed this finding and showed that after vitamin D supplementation (400 IU of 25-hydroxyvitamin D per day in winter months), there was a significant decrease in the number of febrile attacks and a shortened mean duration of attacks in patients.[24] However, based on these findings, it is not possible to conclude that vitamin D is effective in treating or preventing PFAPA syndrome; further research, including large patient groups and randomized clinical trials, is required.

Surgical Approach

Tonsillectomy/adenotonsillectomy is intended as a surgical treatment for PFAPA syndrome. The role of tonsillectomy in the treatment of PFAPA syndrome is debatable, and the risk of surgical complications stands out as a significant disadvantage of this approach. The first study on this subject included only four patients and was reported to be an effective method.[25]

In a prospective randomized controlled study with 39 PFAPA patients, 19 patients underwent adenotonsillectomy and 20 patients received medical treatment.[26] In the 18-month follow-up, the attacks resolved in 12/19 (63%) cases 6 months after the operation, and the attacks completely resolved within 1 year in the adenotonsillectomy group.

Licameli et al. analyzed the long-term efficacy of adenotonsillectomy in 102 patients with PFAPA who were followed up for more than 6 months (mean 43 months) after surgery: 99 recovered completely immediately after surgery and one recovered 6 months later. Recurrent fever attacks persisted in the remaining two patients.[27]

According to one review, only two randomized controlled trials on small patient groups demonstrated the efficacy of tonsillectomy in the treatment of PFAPA in children. Furthermore, these studies have not demonstrated improved outcomes, which could be attributed to the heterogene-

ity of the study population, the use of different diagnostic criteria, and the use of different types of interventions (for example, combining adenoidectomy with tonsillectomy compared to tonsillectomy alone).

Considering the age-limiting nature of PFAPA and possible post-surgical complications, for example, in cases where the interval between attacks is very short and corticosteroid treatment is not appropriate, adenotonsillectomy may be recommended for selected patients.[28]

Conclusion

PFAPA syndrome is a disease that can occur in childhood and adulthood, has an autoinflammatory process characterized by recurrent fever, and is caused by a genetic mutation.

Spontaneous remission over the years and the self-limiting nature of the disease in childhood PFAPA patients have been identified as the positive aspects of this syndrome.

The drugs in the steroid group are seen to be the most appropriate medical treatment in the treatment. Prophylactic treatment is a treatment that can be applied in patients with a history of frequent attacks, and colchicine is seen as the most effective drug.

Surgical treatment is a contentious issue, and recent studies have emphasized that it can be applied to specific patient groups and that the risks of surgical complications must be considered.

Based on the literature, there is no clear treatment method that provides complete remission and that large patient groups require randomized controlled trials to determine such a treatment method.

Disclosures

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