Evolving Frontiers in the Treatment of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis (PFAPA) Syndrome

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ABSTRACT: Fevers recurring at a nearly predictable rate every 3–8 weeks are the signature symptom of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome, an acquired autoinflammatory disorder, which recurs in association with at least one sign among aphthous stomatitis, pharyngitis, and cervical lymph node enlargement without clinical signs related to upper respiratory airway or other localized infections. The disease usually has a rather benign course, although it might relapse during adulthood after a spontaneous or treatment-induced resolution in childhood. The number of treatment choices currently available for PFAPA syndrome has grown in recent years, but data from clinical trials dedicated to this disorder are limited to small cohorts of patients or single case reports. The response of PFAPA patients to a single dose of corticosteroids is usually striking, while little data exist for treatment with cimetidine and colchicine. Preliminary interesting results have been published with regard to vitamin D supplementation in PFAPA syndrome, while inhibition of interleukin-1 might represent an intriguing treatment for PFAPA patients who have not responded to standard therapies. Tonsillectomy has been proven curative in many studies related to PFAPA syndrome, although the evidence of its efficacy is not widely shared by different specialists, including pediatricians, rheumatologists and otorhynolaryngologists.

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Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome was first described 40 years ago and is probably the most frequent and least recognized cause of non-infectious recurrent fevers in children [1]. Because recent findings have proven a dysregulation in different components of innate immunity and a significant inflammasome-mediated activation, PFAPA syndrome has been included in the family of autoinflammatory disorders [2]. Critical PFAPA features are regularly recurring episodes of fever with clockwork regularity, separated by intervals of complete wellness and normal child development in the absence of upper respiratory tract symptoms or known foci of other infections [3]. PFAPA syndrome is mainly diagnosed in children under the age of 5; nonetheless, there are also examples of the disease occurring in older children and adolescents as well as in young adults. The self-limiting nature and impressive response to corticosteroids support the non-infectious nature of the disorder, but a hypothetic genetic origin of the syndrome has never been definitely proven [4]. Diagnosis of PFAPA syndrome is currently based on the clinical criteria proposed by Marshall and co-authors [5] in 1987, then modified by Thomas and colleagues [6] in 1999, for children younger than 5 years of age, in whom cyclic neutropenia has been excluded. Table 1 outlines the diagnostic criteria for PFAPA syndrome.

Patients with a later onset of PFAPA-like manifestations have also been considered as having the syndrome, mostly if other hereditary causes of autoinflammatory disorders have been ruled out [7-9].

Treatment of PFAPA syndrome is primarily targeted to the resolution of acute inflammatory episodes. Non-steroidal anti-inflammatory drugs and antipyretics are usually ineffective in managing PFAPA symptoms, while corticosteroids have long been considered the cornerstone of treatment for this condition.

Acute flare-ups of PFAPA syndrome may be successfully controlled by administering a corticosteroid on the day of fever

Table 1. Diagnostic criteria for PFAPA syndrome

1) Regularly recurring fevers with an early age of onset (< 5 years of age)
2) Symptoms in the absence of upper respiratory infection with at least one of the following clinical signs: a) Aphthous stomatitis b) Pharyngitis c) Cervical lymphadenitis
3) Exclusion of cyclic neutropenia
4) Completely asymptomatic intervals between episodes
5) Normal growth and development

onset, although it does not prevent the recurrence of febrile episodes [10]. A single dose of prednisone (1–2 mg/kg of body weight) or betamethasone (0.1–0.2 mg/kg) is usually effective in relieving symptoms in patients with PFAPA syndrome within a few hours if it is administered close to fever onset. A complete response to single corticosteroid administration has been detected in 85 to 95% of treated subjects [11,12]. Low doses of prednisone (0.5 mg/kg of body weight) can also be effective in the management of attacks: 19/21 PFAPA patients treated with 0.5 mg/kg of prednisolone became afebrile within 8–12 hours; the two remaining patients received a second dose of prednisolone 24 hours after the first administration, obtaining fever resolution within 12 hours [13]. Experiencing side effects after a single corticosteroid administration is infrequent; however, the administration of corticosteroids can shorten intervals between fever flare-ups in most PFAPA patients [14].

Periodic fevers with an abrupt onset recurring at a nearly predictable rhythm every 3 to 8 weeks, are the hallmark of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome

The use of the histamine H_2-receptor antagonist cimetidine, a potent inhibitor of gastric acid secretion, which is largely known for treating peptic ulcers, has been reported to be a potential prophylactic strategy in PFAPA syndrome [15]. However, at the dosage of 150 mg given once or twice a day (or 20 to 40 mg/kg/day), cimetidine induces disease remission in only 27–44% of PFAPA patients [12,16].

The affinity of PFAPA syndrome with different hereditary autoinflammatory disorders, a group of systemic syndromes characterized by sterile inflammatory attacks with fever and organ-specific inflammation [17], and the increased prevalence of *MEVF* mutations among PFAPA patients [4] were the main reasons for choosing colchicine as a prophylactic agent for the febrile attacks in PFAPA syndrome, similar to most known hereditary autoinflammatory disorders such as familial Mediterranean fever [18]. Dusser and co-authors [19] performed a retrospective study on 20 children diagnosed with PFAPA syndrome treated with colchicine (at a daily mean dose of 0.85 mg). They reported that nine of them responded to treatment. A higher percentage of colchicine-responders was identified in an observational study performed on nine patients by Tasher et al. [20], who also showed a longer interval between fever episodes. In addition, Butbul Aviel and colleagues [21] conducted a randomized controlled study on 18 PFAPA patients divided into two groups. The first 10 were left untreated, the other 8 patients were observed for 3 months and later treated with colchicine (0.5–1 mg/day) for an additional 3 months. The number of PFAPA episodes during the first 3 months was similar in both groups, but in the second period the 8 colchicine-treated patients showed significantly fewer attacks (1.6 ± 1.2 vs. 4.9 ± 2.3 flare-ups). Although further studies are still needed on larger cohorts of patients, data currently available suggest a possible beneficial role of colchicine as a prophylactic agent for PFAPA syndrome.

Acute flares of Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome may be controlled by administering a single dose of corticosteroid in the day of fever onset

Despite clinical studies linking vitamin D deficiency and different infectious disorders or immune-mediated diseases, molecular mechanisms behind these observations are unclear. Mahamid and colleagues [22] evaluated levels of vitamin D in 22 patients with PFAPA syndrome and 20 healthy controls, highlighting that vitamin D was significantly decreased in the PFAPA group. Accordingly, Stagi et al. [23] found that vitamin D levels were inversely correlated with the number of febrile PFAPA episodes and that vitamin D supplementation (given at a dose of 400 IU/day) led to a consistent decrease in both number and duration of attacks.

Based on the evidence of inflammasome-mediated activation and interleukin-1β overproduction during acute febrile phases, five PFAPA patients were treated with the recombinant interleukin-1 receptor antagonist anakinra, and all showed a relevant clinical response, suggesting that interleukin-1 blockade might become an interesting new tool for treatment of PFAPA syndrome [24]. In several small cohorts of patients and case reports, the administration of anakinra was effective in suppressing disease flare-ups and escaping PFAPA recurrence in long-term follow-up studies [25,26]. Similarly, one case of adult-onset PFAPA syndrome was treated with canakinumab, the fully human monoclonal antibody targeting interleukin-1β, and administered at a standard dose of 150 mg every 8 weeks after having shown that anakinra had lost its efficacy [27].

Immunostimulant drugs have been largely used to prevent or attenuate infections. Pidotimod (3-L-pyroglutamyl-L-thiazolidine-4carboxylic acid) is a synthetic dipeptide with immunomodulatory properties, which are shown to enhance immunity cells on adaptive and innate immunity and to increase the concentration of salivary immunoglobulin A (IgA) [28]. Moreover, pidotimod induces dendritic cell maturation, upregulates the expression of human leukocyte antigen-antigen D related (HLA-DR) and of co-stimulatory molecules, drives differentiation toward a Th1 phenotype, and promotes phagocytosis [29]. A recent Italian study on 37 children diagnosed with PFAPA syndrome proposed the use of pidotimod in combination with a bacterial lysate for the prevention of PFAPA flare-ups: 25/37 subjects (67.5%) were partial responders, and 4/37 (10.8%) complete responders [30].

The probiotic bacterium *Streptococcus salivarius* K12 produces two bacteriocins, named salivaricin A2 and B, which can

interfere with the growth of different oral bacteria commonly involved in the pathogenesis of pharyngotonsillitis and/or otitis media [31]. Recent clinical trials have shown that treatment with the probiotic K12 reduces the occurrence of episodes of pharyngotonsillitis and otitis, and suggested that its anti-inflammatory properties might counteract PFAPA syndrome [32]. Di Pierro et al. [33] administered the probiotic K12 formulated as slowly-dissolving oral tablets (containing no less than 1 billion colony-forming units/tablet of *Streptococcus salivarius* K12) in four children diagnosed with PFAPA syndrome. The tablet was given every night before sleep and was allowed to slowly dissolve in the oral cavity, without biting or swallowing. Three out of four patients had no episodes of fever nor any PFAPA sign during the 3 months of treatment with the probiotic. This very preliminary result confirms that PFAPA syndrome is characterized by the involvement of tonsillar lymphoid tissue, probably stimulated by bacterial infections.

Interleukin-1 blockade might be considered as a new potential tool for treatment of refractory Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome

In closing, tonsillectomy has been a widely used option for the management of PFAPA syndrome when disease symptoms severely interfere with a child's quality of life, especially when other strategies, such as treatment with corticosteroids, have failed. Evidence related to the efficacy of tonsillectomy are not widely or fully shared by different specialists, including pediatricians, rheumatologists and otorhynolaryngologists. According to a meta-analysis by Peridis et al. [12], tonsillectomy is more effective than cimetidine in preventing the occurrence of PFAPA flare-ups and is equivalent to corticosteroids. Similarly, Garavello and co-authors [34] showed that the rate of complete remission of PFAPA syndrome after tonsillectomy is more than 80% of patients, while Licameli and colleagues [35] reported a complete resolution of symptoms in 97% of PFAPA patients. A recent comparative trial of medical therapy vs. tonsillectomy in PFAPA syndrome reported a notable rate of complete remission after surgery at 2 years of follow-up, while 13/30 patients treated with corticosteroids continued to have fevers despite a decrease in the frequency and number of flare-ups [36]. Conversely, Vigo and co-authors [37] reported a complete remission rate in 27/41 patients treated with tonsillectomy (65.9%) without statistically significant differences when compared to the medical therapy. Lantto and colleagues [38] reviewed the medical records of 3852 children who underwent tonsillectomy (with or without adenoidectomy) from 1990 to 2007, and found 108 children who had a tonsillectomy because of recurring fevers. They invited these patients to an outpatient visit 9 years after the procedure, and, strikingly, tonsillectomy was curative in 56 of 58 children who presumably had PFAPA syndrome.

For patients diagnosed with PFAPA syndrome, the overall short- and long-term prognosis is excellent, with spontaneous resolution of the disease occurring in over 80% of children; however, the reoccurrence of PFAPA syndrome has been reported after tonsillectomy [39].

CONCLUSIONS

PFAPA syndrome is largely under-diagnosed among the non-hereditary causes of autoinflammatory disorders, and is sometimes confused with other causes of recurrent fevers, recurrent bacterial infections favored by recent viral infections, primary or acquired immunodeficiencies, and transient IgA deficiency. Criteria drafted by Marshall et al. [5] were applied to a large cohort of PFAPA children recruited in an international web-based registry, and their accuracy was evaluated by Hofer and colleagues [40]. The findings revealed some relevant limitations in those criteria and suggested a consensus-based stricter definition of the syndrome. Unfortunately, even though 40 years have passed since its first description, the options for managing PFAPA syndrome and stopping the recurrence of fevers are rather non-specific, and no consensus exists about the best treatment choice to use in children who receive a new diagnosis and in adults and refractory patients, for whom interleukin-1 blockage might be indicated.

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Capsule

Thymosin α1 represents a potential potent single-molecule-based therapy for cystic fibrosis

Cystic fibrosis (CF) is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) that compromise its chloride channel activity. The most common mutation, p.Phe508del, results in the production of a misfolded CFTR protein, which has residual channel activity but is prematurely degraded. Because of the inherent complexity of the pathogenetic mechanisms involved in CF, which include impaired chloride permeability and persistent lung inflammation, a multi-drug approach is required for efficacious CF therapy. To date, no individual drug with pleiotropic beneficial effects is available for CF. Romani co-authors reported on the ability of thymosin alpha 1 (Tα1)–a naturally occurring polypeptide with an excellent safety profile in the clinic when used as an adjuvant or an immunotherapeutic agent–to rectify the multiple tissue defects in mice with CF as well as in cells from subjects with the p.Phe508del mutation. Tα1 displayed two combined properties that favorably opposed CF symptomatology: it reduced inflammation and increased CFTR maturation, stability, and activity. By virtue of this two-pronged action, Tα1 has strong potential to be an efficacious single-molecule-based therapeutic agent for CF.

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