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REVIEW

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome: main features and an algorithm for clinical practice

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Abstract

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a recurrent fever syndrome of early childhood with increasing number of adult-onset cases. Although it is a self-limited disease, it may negatively affect the quality of life. The aim of this review is to present a detailed analysis of PFAPA syndrome and an algorithm for diagnosis, therapeutic options, and evaluation of outcome. A comprehensive literature search was conducted through the Cochrane Library, Scopus, and MEDLINE/PubMed databases. The main topics covered are the epidemiology, clinical manifestations, diagnosis, differential diagnosis, etiopathogenesis, genetics, management, disease course and prognosis, disease in adults, unsolved issues, and unmet needs in PFAPA. The diagnosis of PFAPA is mainly based on clinical classification criteria. The most relevant hypothesis for pathogenesis is that dysregulated immune system in a genetically predisposed individual responds to a yet unidentified trigger in an exaggerated way. The pedigree analyses suggest a genetic background for the disease with an autosomal dominant pattern of inheritance. For management, single-dose corticosteroids during attacks and tonsillectomy remain the most effective therapies, while colchicine is a promising option to decrease attack frequency. There remain unsolved issues in PFAPA such as the exact etiopathogenesis and genetic background, the reason why the inflammation is restricted to the oropharyngeal lymphoid tissue, reasons for clock-work regularity of attacks, and self-limited disease course. There is need for a valid diagnostic criteria set with a high performance for both children and adults and consensus on management of PFAPA.

Keywords PFAPA · Periodic fever · Aphthous stomatitis · Pharyngitis · Adenitis

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is a recurrent fever syndrome of unknown etiology characterized by clock-work regular episodes of fever, pharyngitis, oral aphthosis, and cervical lymphadenopathy [1]. It was first described in 1987 by Marshall et al. in 12 children [1]. It had been designated as Marshall's syndrome until the acronym of PFAPA was proposed in 1989 [2]. Since the syndrome was first described, we have learned a lot about the clinical manifestations, while the etiology and disease mechanisms remain largely unknown. It is mainly a disease of early childhood (especially below 5 years of age), while the reports of adult-onset disease have considerably increased recently [3–5]. There are several unsolved issues and unmet needs in PFAPA. The unsolved issues are the unknown exact etiopathogenesis, reasons for inflammation being mainly restricted to the oropharyngeal tissues, clock-work regularity of attacks in some patients, self-limited disease course, and the absence of inflammation-related major sequela such as amyloidosis. The unmet needs are lack of high-performance diagnostic criteria which serve for both pediatric and adult patients and the absence of consensus in treatment.

The aim of this review is to analyze the PFAPA syndrome in detail with regard to epidemiology, clinical manifestations, etiopathogenesis, genetics, diagnosis, differential diagnosis, management, disease outcome, unsolved issues, and unmet needs. It also provides an algorithm for diagnosis, therapeutic options, and evaluation of outcome in PFAPA (Fig. 1).

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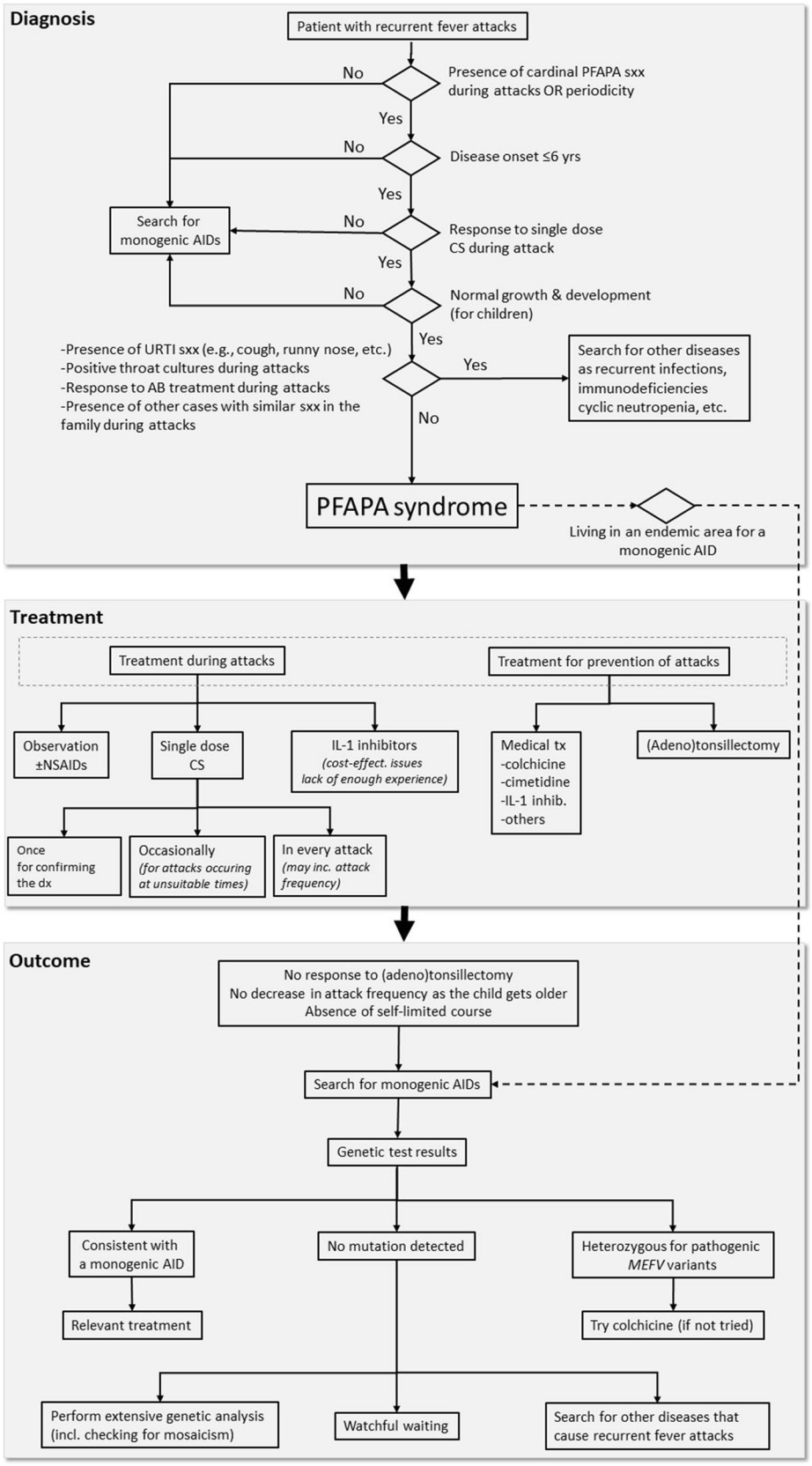

Fig. 1 Algorithm for diagnosis, therapeutic options, and outcome evaluation in periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome (AB, antibiotic; AID, autoinflammatory disease; CS, corticosteroid; dx, diagnosis; IL-1, interleukin 1; NSAID, nonsteroidal anti-inflammatory drug; sxx, symptoms; tx, treatment; URTI, upper respiratory tract infection)

Search strategy

The Cochrane Library, Scopus, and MEDLINE/PubMed databases were searched (from database inception to 1 December 2018) according to the published guidance on narrative reviews [6] by entering the following keywords; "periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome", "PFAPA", and "Marshall's syndrome". Case reports, original research articles, and review articles with a focus on PFAPA syndrome were analyzed. Relevant studies discovered from references of the analyzed articles were also included. The search was restricted to English articles.

Epidemiology

PFAPA syndrome is considered as the most common periodic fever syndrome especially in non-Mediterranean children without predilection for particular ethnic groups [7]. However, there are scarce epidemiologic data for PFAPA. Its cumulative incidence is reported as 2.3 per 10,000 children (up to 5 years of age) in a Nordic study [8]. Its incidence in adults remains to be elucidated. A slight male predominance was observed in most pediatric studies [8, 9, 10–14].

Etiopathogenesis

The exact etiopathogenesis of PFAPA syndrome remains unknown. The initial hypothesis was an infectious origin causing recurrent disease flares [15]. However, several features of PFAPA such as lack of response to antibiotics, abrupt cessation of attacks with corticosteroids, and lack of affected family members during the flares of the patient make this explanation unlikely. The more relevant explanation is that dysregulated immune system of a genetically predisposed individual responds to a trigger in an exaggerated way [16]. This trigger could be environmental. However, high response rate to tonsillectomy suggests that it may be located in tonsils. Having said these, today, we are not far from the point elegantly described by Sarah S. Long in 1999: "PFAPA syndrome walks like dysregulation of cytokines and sounds like an infection" [15].

Immune system

Increase in acute phase reactants as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) points at an acute inflammatory response during PFAPA attacks, while lymphopenia, neutrophilia, and monocytosis along with elevated levels of S100 proteins (S100A8/9 and S100A12) suggest the involvement of both innate and adaptive immunity cells in disease pathogenesis [12, 17–19]. Lymphopenia is probably due to homing of lymphocytes to tonsils [17]. Confirming the role of neutrophils, Sundqvist et al. demonstrated neutrophil dysfunction in PFAPA especially affecting neutrophil apoptosis, priming, and generation of intracellular oxidative burst [19].

Both innate and adaptive immunity seem to take role in PFAPA pathogenesis [20]. The results of different studies suggest that the initial step is innate immune system activation probably mediated by inflammasomes followed by a mainly T-cell-mediated adaptive immune response [20–24].

Inflammasomes control the activation of caspase 1 which cleaves pro-interleukin 1 (pro-IL-1) and pro-IL-18 into the biologically active forms [25–27]. Increase in serum or plasma levels of IL-1β, IL-6, and IL-18 has been demonstrated during PFAPA flares in several studies which suggest a role for inflammasomes in disease pathogenesis [28–30].

IL-1β is a co-stimulator of T-cell function [31]. Activated T cells secrete interferon gamma (IFN-γ) counteracting the anti-inflammatory cytokines as IL-4 and IL-10 while inducing the synthesis of T-cell chemokines such as CXCL9 and CXCL10 [24, 32, 33]. Increased gene expressions and serum levels of these chemokines for activated T cells and proinflammatory cytokines (as IL-6 and IL-18) confirm a Th1-mediated inflammatory response during PFAPA attacks [21, 22, 24]. In addition, a fluctuation of cytokines in the afebrile phase of the disease has been demonstrated, which indicates that the disease is still active at cellular level in inter-attack periods [21, 23].

Tonsils

Activated T cells migrate to tonsils. The cessation of febrile episodes after tonsillectomy in most patients puts tonsils in the center of disease pathogenesis. Probably, either the immune dysregulation itself or the trigger of the immune dysregulation resides in the tonsils.

Dytrych et al. have demonstrated increased expression of T-cell chemokine genes resulting in a lymphoid hyperplasia with higher percentages of CD8+ and naïve CD4+ and CD8+ T cells in PFAPA tonsils compared to tonsils of obstructive sleep apnea patients [22]. Tonsillectomy is performed in inter-attack periods which makes it impossible to see tonsillar changes during attacks. However, Manthiram et al. have shown that longer time from the last PFAPA episode is associated with larger germinal center area and decreased IL-1 receptor antagonist (IL-1RA) staining in tonsils [16].

These results point at homing of early developmental stages of T lymphocytes to tonsils, and an inflammatory milieu in tonsils with increase in T-cell chemokines. In

addition, PFAPA tonsils probably show dynamic histologic changes over time such as shrinking in germinal centers during a febrile attack [16].

Microorganisms

The microbial flora of PFAPA tonsils have been investigated for a possible trigger of disease. Studies have not highlighted a certain microorganism as the trigger of PFAPA attacks. However, certain changes in the relative abundance of microorganisms were detected which could have played a role in disease pathogenesis [34, 35].

Genetics

High frequency of positive family history suggests a genetic background for PFAPA syndrome [36]. It seems to have an autosomal dominant with incomplete penetrance pattern of inheritance based on pedigree analysis [36, 37]. Most frequently, genes of monogenic autoinflammatory diseases (AIDs) [*MEFV* gene for familial Mediterranean fever (FMF), *NLRP3* gene for cryopyrin-associated periodic syndrome (CAPS), *MVK* gene for mevalonate kinase deficiency/hyper-immunoglobulin D syndrome (MKD/HIDS), *TNFRSF1A* gene for TNF-receptor associated periodic syndrome (TRAPS), *CARD15*/*NOD2* for Blau syndrome] have been analyzed in PFAPA patients [11–14, 17, 38–44]. Although PFAPA is probably not a monogenic disease, the variants in genes associated with inflammation could be modifying the disease phenotype. Another hypothesis is that synergic effect of different mutations on different genes could cause the disease [13, 20, 37]. However, it is not clear how different combinations of multiple variants produce this specific phenotype.

Patients who have pathogenic variants in the genes of monogenic AIDs seem to have symptoms other than the three cardinal symptoms of PFAPA (as pharyngitis, adenitis, and oral aphthosis) more frequently during the disease attacks [45]. Thus, it is important to perform genetic tests in PFAPA patients with atypical features.

There are increasing number of studies reporting a strong association between PFAPA and FMF [12, 14]. The frequency of *MEFV* variants among PFAPA patients ranges from 8 to 66% in different studies [11–14, 17, 38–43]. The frequency of *MEFV* variants was often higher than that of normal reference population [11, 14, 38–40, 42]. No difference between PFAPA patients with and without *MEFV* variants was observed in some studies [11, 12], while some others report favorable effect of *MEFV* variants on PFAPA phenotype with shorter febrile episodes, longer attack-free intervals, and need for lower dose of corticosteroids for aborting attacks [13, 38, 42]. A "dose effect" of *MEFV* mutations was also reported in children with periodic fever [46]. An increase in FMF-like symptoms and a decrease in PFAPA-like symptoms were observed from patients carrying a single low-penetrance *MEFV* mutation towards ones with two high-penetrance mutations [46].

There is only one whole exome sequencing study in PFAPA patients [37]. Di Gioia et al. could not identify a monogenic etiology for PFAPA in this study [37]. Cheung et al. investigated the variants in a panel of 32 genes (genes of monogenic AIDs and genes associated with inflammasome) and identified a frameshift variant in *CARD8* gene in PFAPA patients more frequently than controls (14% vs. 3.2%) [47]. This variant also seemed to influence the disease phenotype with a higher prevalence of symptoms in inter-attack periods and oral aphthosis. Normal protein product of *CARD8* gene interacts with the NLRP3 inflammasome inhibiting its ability to activate caspase 1. Caspase 1 activation is necessary for active IL-1β formation. The mentioned variant causes a loss-of-function in CARD8 which leads to increased NLRP3 function [47]. This study suggests a role for NLRP3 inflammasome in PFAPA pathogenesis. Similarly, Kolly et al. previously reported higher frequency of *NLRP3* variants in PFAPA patients than normal healthy population [17]. However, these results should be reproduced in adequate independent cohorts to confirm the role of NLRP3 inflammasome in PFAPA.

Clinical manifestations

The PFAPA flares usually last for 3–7 days (mostly around 4–5 days) and recur every 2–8 weeks (mostly 3–6 weeks) [5, 8, 48, 49]. In around 60% of patients, a prodromal symptom (usually fatigue) preceded the fever [9]. A substantial amount of patients reports periodicity meaning clock-work regularity of attacks [50]. This feature is more prominent at early stages of disease and the attacks usually get less severe and recur with longer intervals as the child grows older [7]. There is no seasonal occurrence of PFAPA attacks unlike upper respiratory tract infections (URTIs) which are more common during the winter. However, some PFAPA patients may skip episodes of fever during the summer [9].

The patients are usually asymptomatic between attacks and growth and development are not affected [5]. However, recently, occurrence of certain symptoms such as oral aphthosis and malaise has been reported in inter-attack periods [10].

The symptoms in a typical PFAPA flare include pharyngitis, oral aphthous lesions, and cervical lymphadenitis along with fever [5]. These are the cardinal features of PFAPA. The body temperature often rises up to 39-40.5 °C [3]. Fever is generally resistant to antibiotics and antipyretics and patients present in good general conditions despite

the high temperature [3]. The most frequent cardinal sign is erythematous or exudative pharyngitis (present in > 90% of patients) followed by cervical adenitis (up to 75% of patients) and oral aphthosis (up to 50% of patients) [3, 9–14]. PFAPA aphthous lesions are typically < 1 cm, painful, shallow, round ulcers with well-defined erythematous margins localized on non-masticatory surfaces of the mouth [9, 51, 52]. Sometimes, a cluster of very small aphthae may be observed [9]. The cervical lymph nodes are usually bilaterally enlarged, moderately tender, and < 5 cm in diameter [15].

PFAPA patients could also have other symptoms such as abdominal pain, arthralgia, arthritis, headache, rash, diarrhea, and nausea/vomiting during attacks [5, 49]. The most frequently associated symptom other than the three cardinal features is abdominal pain [10, 53]. The symptoms of URTIs such as rhinorrhea and cough are usually absent in PFAPA attacks [5, 15].

Diagnosis

Diagnostic/classification criteria

The diagnosis of PFAPA syndrome is usually based on modified Marshall's criteria proposed in 1999 [5]. When applied to clinical practice, they showed a good sensitivity but a lack in specificity [45]. Very recently, a new set of classification criteria has been developed for PFAPA [53]. In 2017, Cantarini et al. defined diagnostic criteria for late-onset PFAPA [54]. These criteria sets are summarized in Table 1.

The three core symptoms of the disease are present in all criteria sets except for the exclusion of oral aphthosis in criteria for late-onset PFAPA [54]. The fever attacks and the diseases to be excluded for PFAPA diagnosis are defined in more detail in the new criteria set by Vanoni et al. than modified Marshall's criteria [5, 53]. Moreover, the threshold age for disease onset has been changed to 6 from 5 years. Because of the detailed definitions for attacks, it will be difficult to use the new set retrospectively while including patients into studies. Due to same reason, the new criteria set by Vanoni et al. seems too restrictive. However, it will be helpful for defining more homogeneous patient groups for studies.

Both modified Marshall's criteria [5] and new criteria set by Vanoni et al. [53] exclude patients with disease onset in late childhood, adolescence, or adulthood. However, the diagnostic criteria set by Cantarini et al. was developed for late-onset PFAPA (≥ 16 years of age) [54]. This is also the first PFAPA criteria developed based on statistical procedures [54]. In this criteria set, the age threshold, oral aphthosis, and normal growth/development are not mentioned. It has a high performance (sensitivity of 93.4% and specificity of 91.7%) in the original patient cohort [54]. Negative result

Table 1 Diagnostic/classification criteria for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome

Criteria set	Modified Marshall's criteria	Criteria set by Vanoni et al.	Criteria set for adult PFAPA by Cantarini et al.
Reference number	[5]	[53]	[54]
Age at onset	< 5 years of age	< 6 years of age	No threshold mentioned[a]
Definition of "recurrent fever"	Regularly occurring fevers	Periodic fever for ≥ 6 months a. Daily fever of ≥ 38.5 °C (axillar) for 2–7 days b. ≥ 5 regularly recurring fever attacks with ≤ 2-month intervals	Recurrent fever
Symptoms	**≥ 1/3** Aphthous stomatitis Cervical lymphadenitis Pharyngitis	**≥ 1 in every episode; ≥ 2/3 in the majority of episodes** Aphthae Cervical adenitis Pharyngitis	Erythematous pharyngitis **and/or** cervical lymphadenitis
Inter-attack periods	Completely asymptomatic Normal growth and development	Full recovery Normal linear growth	Symptom-free
Exclusion	Cyclic neutropenia Upper respiratory tract infection	Infections Immunodeficiencies Cyclic neutropenia Other causes of recurrent fever	Infections (throat swab negative and antibiotic therapy ineffective) Autoimmune diseases Neoplastic diseases Monogenic AIDs Febrile polygenic AIDs

AIDs autoinflammatory diseases

[a]This criteria set should be applied to patients ≥ 16 years

of throat swab and ineffectiveness of antibiotic treatment during attacks were also mentioned, which specify the exclusion of URTIs.

In addition to the features included in the criteria sets, there are a few additional clues we use in clinical practice while diagnosing PFAPA patients:

- Abrupt cessation of the attack in response to 1–2 dose of corticosteroids.
- Family history of recurrent pharyngitis and tonsillectomy.
- Lack of infections among family members during disease attacks of the patient.

In a study by Manthiram et al., more than 80% of physicians agreed that the patients should have stereotypical fever attacks, be asymptomatic between attacks, and have normal growth and development to be diagnosed with PFAPA [55]. Only 17% (44% if the age criterion was excluded) required all aspects of modified Marshall's criteria to make a diagnosis of PFAPA.

Biomarkers

There are no specific biomarkers for PFAPA diagnosis. An ideal diagnostic biomarker for PFAPA should be specific to be used for differential from infections and other AIDs, preferably both during disease attacks and inter-attack periods.

Lymphopenia, neutrophilia, and monocytosis could be observed in PFAPA patients during attacks [12, 17]. In addition, several markers such as CRP, ESR, SAA, S100A8/A9, and S100A12 increase during PFAPA flares [17–19, 56]. However, these are mainly nonspecific inflammatory markers. Procalcitonin remarkably elevates during bacterial infections but not during PFAPA flares [12, 21, 57, 58].

Stojanov et al. showed that the levels of several cytokines and chemokines as IP10/CXCL10, MIG/CXCL9, MIP-1β, IL-1RA, and granulocyte colony stimulating factor were significantly higher during PFAPA flares than flares of monogenic AIDs [24]. In addition, the levels of IP-10/CXCL10 diminished after IL-1 inhibitor therapy. Of note, only 12 patients with monogenic AIDs were included in this study and the levels of the cytokines and chemokines were not compared during inter-attack periods. Førsvoll et al. demonstrated that CXCL10 remained elevated during asymptomatic periods of PFAPA [28].

Yamazaki et al. showed that CD64 expression on neutrophils and monocytes was higher in PFAPA patients during disease flares compared to healthy controls and patients with monogenic AID flares [29]. However, CD64 expression was similar among healthy controls, PFAPA patients, and monogenic AID patients in inter-attack periods [29].

Tekin et al. showed that the mean platelet volume (MPV) values were lower in PFAPA patients both during attacks and attack-free periods compared to healthy controls [59]. However, decrease in MPV was also reported in other AIDs including FMF [60].

Galectin-3, a proinflammatory mediator with regulatory functions in inflammation could be a promising biomarker. Sundqvist et al. demonstrated similar and homeostatic plasma levels of galectin-3 in PFAPA patients and healthy controls [19]. Yılmaz et al. showed that serum galectin-3 levels were higher in FMF patients compared to controls [61]. Further controlled studies could verify the role of galectin-3 in discriminating PFAPA from monogenic AIDs including FMF.

Differential diagnosis

Cyclic neutropenia cause recurrent attacks of fever and oral aphthous ulcers as well as bacterial infections [62]. Periods of severe neutropenia occurs with 21 day intervals, which bears resemblance to clock-work regularity of attacks in PFAPA. Certain features of cyclic neutropenia help for the differential diagnosis. In cyclic neutropenia, neutrophil count is less than 500/mm^3 during fever, there is no response to single dose corticosteroid, and stomatitis and multiple aphthous ulcers are more severe than the oral manifestations of PFAPA [9, 62]. The diagnosis of cyclic neutropenia could be confirmed by checking for mutations in *ELANE*, the gene for neutrophil elastase [62].

Exclusion of recurrent URTIs is also required for PFAPA diagnosis. Moreover, successfully differentiating a PFAPA attack from bacterial URTI is critical to decrease the unnecessary use of antibiotics. There are several features that make the differential diagnosis easier: (1) there are affected family members in recurrent URTIs; (2) URTIs occur more frequently during winter months; (3) there is no periodicity in recurrent URTIs; (4) patients with URTI do not respond to single dose corticosteroids; (5) patients with bacterial URTI respond to antibiotic treatment (in contrast to those with PFAPA); and (6) there are other symptoms such as rhinorrhea and cough during URTIs [7, 9, 54]. Throat swabs are important for excluding streptococcal tonsillitis. Nucleic acid amplification tests and antigen detection assays could help while testing for respiratory pathogens [63]. Procalcitonin increases during bacterial URTIs, while it remains within normal range during PFAPA attacks [12, 21].

Differentiating PFAPA from monogenic AIDs remains the real challenge especially in areas that are endemic for certain AIDs [64]. It is critical to select appropriate patients for genetic testing to exclude monogenic AIDs. Gaslini score is helpful for determining patients for whom genetic analysis should be ordered [65]. According to this score, young

age at disease onset, the absence of oral aphthosis, and the presence of abdominal pain, chest pain, and diarrhea are correlated with a positive genetic test result [65].

Some patients with monogenic AIDs could also present with a PFAPA-like phenotype which makes the differential diagnosis more challenging [14, 17, 43, 66]. This type of presentation is not rare for FMF in endemic populations [14]. In addition, it is a common practice to check for *MEFV* mutations in most PFAPA patients in such populations [11, 14]. Patients with MKD/HIDS could also present with a PFAPA-like phenotype. Moreover, elevated serum immunoglobulin D could be observed in PFAPA patients [8, 67]. In addition, high-dose corticosteroids could induce rapid resolution of disease attacks in MKD/HIDS, as well [68, 69]. That is, it could be difficult to differentiate MKD/HIDS from PFAPA clinically. PFAPA-like phenotype could also be observed in TRAPS patients with R92Q variant in *TNFRSF1A* gene [66, 70].

In 2015, The Pediatric Rheumatology International Trials Organization (PRINTO) developed the Eurofever classification criteria for monogenic AIDs as FMF, CAPS, MKD/HIDS, and TRAPS [71]. The disease controls were PFAPA patients in this study. In these criteria, the absence of aphthous stomatitis and enlarged cervical lymph nodes is scored in favor of FMF, while the absence of exudative pharyngitis is positively scored for TRAPS. The absence of oral aphthosis is also rated in favor of CAPS diagnosis, while the presence of aphthous stomatitis during disease flares is in favor of MKD/HIDS diagnosis [71]. These criteria could help for differentiating PFAPA from monogenic AIDs along with Gaslini score.

There are increasing number of studies reporting a strong association between PFAPA and FMF [12, 14]. In the study by Butbul-Aviel et al., 51 out of 270 PFAPA patients were also diagnosed with FMF [14]. 50 of these patients were fulfilling both modified Marshall's criteria for PFAPA [5] and Yalcinkaya-Ozen criteria for FMF [72]. In around 70% of them, the genetic test results were supporting the diagnosis of FMF [14]. In addition, most of these children had symptoms suggesting PFAPA and FMF at the same time. As expected, abdominal pain, arthralgia, and myalgia were more frequently observed in PFAPA/FMF group than only-PFAPA group. In 16% of PFAPA/FMF patients, PFAPA symptoms proceeded those of FMF. Thus, one should keep in mind that FMF could co-occur with PFAPA especially in endemic regions [14, 73].

Management

There is no consensus on treatment of PFAPA syndrome. Goals of therapy are mainly to control the acute attacks and to decrease the attack frequency. In a study investigating the physicians' perspectives in PFAPA, Manthiram et al. reported that antipyretics, cimetidine, tonsillectomy, and corticosteroids were the most commonly prescribed therapies, whereas corticosteroids and tonsillectomy were the most effective ones [55]. In a meta-analysis, Peridis et al. showed that tonsillectomy was the most effective therapeutic intervention, while corticosteroids were the most effective medical treatment option [74]. In 2013, the Eurofever registry results on treatment of AIDs were presented with a literature review [68]. In this report, 92 PFAPA patients from Eurofever registry and 404 PFAPA patients from the literature were evaluated. The level of evidence was presented as 1a for (adeno)tonsillectomy, 2b for corticosteroids, and 4 for anakinra [68]. Cimetidine, thalidomide, and IL-1 inhibiting agents were not used in the Eurofever PFAPA patients, although they were mentioned to be beneficial in a few reports [68]. The current level of evidence is 1a [systematic review of randomized controlled trials (RCT)] for (adeno)tonsillectomy, 1b (at least one RCT) for colchicine, and 2b (individual cohort studies) for corticosteroids. For other therapeutic options, the level of evidence is 4–5 (case series or expert opinion).

Treatment of acute attacks

Antipyretics could be used during attacks with partial efficacy in reducing fever. Nonsteroidal anti-inflammatory drugs (NSAID) are slightly more effective than acetaminophen [68]. Wurster et al. reported that only one-fourth of PFAPA patients rated acetaminophen as effective, while more than half of the patients found NSAIDs effective during disease attacks [75]. There is no response to antibiotics in most cases [74]. Sometimes, patients/parents may report response to antibiotics, since the self-limited nature of the flares coincides with the initiation time of antibiotics.

Single-dose corticosteroid administration, usually in the form of prednisone at a dose of 1–2 mg/kg, results in abrupt cessation of PFAPA attacks in 85–95% of patients [9, 40, 50, 68, 74, 76–79]. Lower dose as 0.5 mg/kg could be effective, as well [80]. Several physicians prefer more than one dose of corticosteroids to abort the disease attacks [55]. After corticosteroid administration, fever subsides within 24 h. However, other symptoms may disappear more slowly [81]. Some physicians use single-dose corticosteroids only for diagnostic purpose and do not use it during the attacks afterwards. Some others might prescribe it in every attack and/or for only attacks that occur at an unsuitable time for the patient/family (e.g., during the exam week at school) [7, 82]. Increase in attack frequency could be observed in the long term after use of corticosteroid treatment during attacks [4, 9, 49, 55, 68, 77, 83, 84].

Abrupt cessation of acute attacks was observed by IL-1 inhibitors in several case reports/series [24, 85, 86].

Prevention of attacks

For the prevention of attacks or decreasing the attack frequency, several drugs such as cimetidine, colchicine, IL-1 inhibitors, vitamin D, pidotimod, and probiotic K12 have been used so far [5, 7, 9, 12, 24, 39, 40, 43, 50, 68, 74–78, 80, 85–94]. There are anecdotal reports on benefits of thalidomide and montelukast in PFAPA patients. However, these results have not been confirmed in current studies [3, 95, 96].

Cimetidine is a histamine H2-receptor antagonist [97]. It was found effective in prevention of PFAPA episodes in only 27–44% of patients [5, 9, 74, 75, 89, 91]. However, there is no report of cimetidine use in the recent large PFAPA cohorts [10, 12, 43].

There are increasing number of studies reporting effective use of colchicine in the prevention of PFAPA attacks [7, 12, 39, 40, 43, 88, 94]. Colchicine is the mainstay of FMF treatment [98, 99]. It blocks the assembly and polymerization of microtubules, which are the key components of cytoskeleton [100]. The previous studies in FMF suggest that colchicine affects the pyrin inflammasome through the re-organization of actin cytoskeleton [100–103]. It also inhibits IL-1β release from mononuclear cells in FMF patients [104]. The mechanism of action of colchicine in PFAPA has not been elucidated. However, it may be exerting its prophylactic effect through aforementioned mechanisms. In the only randomized controlled trial of colchicine in PFAPA, Butbul-Aviel et al. have demonstrated that it could be beneficial in decreasing attack frequency in PFAPA [39]. Dusser et al. reported that heterozygous *MEFV* mutations were more frequent, while chronic fatigue and oral aphthosis were less common among the colchicine-responder PFAPA patients compared to non-responders [88]. Similarly, the rate of response to colchicine was higher among PFAPA patients with *MEFV* variants than the ones without *MEFV* variants in two studies from Turkey [12, 43]. There is no consensus about the duration of colchicine treatment in PFAPA patients. In a preliminary study, we showed that colchicine treatment could be discontinued in *MEFV* heterozygote children with FMF if the patient is asymptomatic with normal acute phase reactants for at least 2 years [105]. Since PFAPA is self-limited, the duration could be shorter in PFAPA patients who are heterozygous for *MEFV* variants. However, further studies are required to determine the optimum duration of treatment.

Vitamin D has been reported to be effective in prevention of PFAPA attacks in a case report and a study including 25 patients [92, 93]. Pidotimod (an immunomodulatory molecule) and probiotic K12 have been found effective in the prevention of PFAPA attacks in two different studies, including 37 and 4 patients, respectively [87, 90, 93].

For IL-1 inhibitors, response to anakinra (recombinant IL-1 receptor antagonist) has been reported in 6 PFAPA patients so far [24, 85]. In addition, there is one report of effective canakinumab (humanized monoclonal anti-IL-1 antibody) use in an adult PFAPA patient after anakinra lost its efficacy [86]. Cost-effectiveness issues should be considered for IL-1 inhibitors, since the disease has a benign course with lack of major complications.

Tonsillectomy is a surgical therapeutic option in PFAPA management. In a recent literature review on the role of tonsillectomy in PFAPA, Førsvoll et al. identified 28 case series including 555 children with PFAPA treated with (adeno)tonsillectomy [106]. Tonsillectomy was curative in 509 (92%) of these children [106]. To date, there are only two randomized controlled trials on the efficacy of tonsillectomy in PFAPA, one in 2007 by Renko et al. [107] and another one in 2009 by Garavello et al. [108]. Renko et al. demonstrated that disease was cured in all children with PFAPA in the tonsillectomy group, while only half of the children in the control group were free of symptoms at the 6th month follow-up [107]. The main limitations of this study were vague diagnostic criteria used for PFAPA (there were patients with fever as the only symptom) and the short follow-up period. However, the same group performed another study in 2006 and showed that tonsillectomy was effective in patients with disease onset later than 5 years of age and when fever was the only symptom during episodes [109]. Based on these results, they suggested that tonsillectomy should be considered in children who had recurrent fever attacks with no other explanations and were asymptomatic in inter-attack periods. Garavello et al. randomized 39 PFAPA patients to either adenotonsillectomy (surgery group, $n=19$) or expectant management (control group, $n=20$) [108]. The complete resolution rate was higher in surgery group compared to control group (63% versus 5%, respectively). This study serves the best evidence for the effect of tonsillectomy in PFAPA. Of note, according to the last Cochrane systematic review, it is uncertain whether adenotonsillectomy has any additional benefit over tonsillectomy alone [110]. Although tonsillectomy seems curative in most cases, relapses may rarely be observed several years after tonsillectomy [109, 111]. A recurrence of aphthous stomatitis or cervical lymphadenopathy without febrile episodes was also described after tonsillectomy in several reports [75, 112–114].

It could be difficult to recommend a surgery as the primary treatment option in PFAPA, since the disease is usually self-limited. Moreover, in a long-term observational study, Vigo et al. showed no significant difference in terms of clinical remission in the percentage of PFAPA patients responding to tonsillectomy versus standard medical treatment and the search for possible predictors of tonsillectomy efficacy failed to show any significant results [114]. Thus, it is important to weigh the risks/benefits and involve the family to the

decision process while choosing the best therapeutic option for PFAPA patients.

Disease course and prognosis

PFAPA is usually considered a benign disease with spontaneous resolution within 3–5 years after disease onset. However, occasionally the disease can persist up to adolescence [5, 8, 48, 68, 75]. Spontaneous resolution of disease has been reported at different rates in different studies. The difference is probably due to different lengths of follow-ups. Thomas et al. reported spontaneous remission in 41% of patients after an average duration of 4.5 years [5]. Feder et al. demonstrated that PFAPA resolved spontaneously in 20% of patients with a mean disease duration of almost 3 years [9]. Førsvoll et al. reported disease resolution in 37 out of 46 patients, 17 promptly after tonsillectomy, and 20 spontaneously at a median age of 5 years [8]. Of these 20 patients with spontaneous remission, one-third experienced a prompt resolution of disease, while the attack frequency gradually decreased in the rest of the patients. In the study with the longest follow-up, the time from the inclusion to the PFAPA registry to the last control ranged from 12 to 21 years [75]. They reported disease resolution in 50 out of 59 PFAPA patients (spontaneous in 44, after tonsillectomy in 6). Of these 50 patients, 16 continued to have aphthous stomatitis episodes and 1 patient continued to have lymphadenopathy attacks without fever [75]. It is important to note that relapses could be observed and the disease could reappear in adulthood in around 20% of cases [4, 49, 115]. In addition, even though it is a self-limited disease without any long-term sequela, it considerably affects the quality of life. Grimwood et al. have recently shown that the disease had a major impact on psychosocial functioning and caused increased fatigue in the first study on health-related quality of life in children with PFAPA syndrome [116].

PFAPA in adults

Although the previous diagnostic/classification criteria and most of the studies in the literature focus on patients with disease onset before 5–6 years of age, we know that PFAPA could also be seen in adulthood [3, 4, 83, 115, 117, 118]. There are prominent differences between adult and pediatric PFAPA patients (Table 2). These changes suggest that children with PFAPA are more typical by definition, while adult patients present a wider repertoire of inflammation-related signs and symptoms [3, 4, 115]. Cardinal symptoms along with chills are more prevalent during attacks in children when compared to adults [4, 83]. On the other hand, other signs and symptoms such as arthralgia/myalgia and headache are more common in adults than children [4, 83]. Of note, the clock-work regularity of attacks seems to be more typical of the pediatric PFAPA rather than adult-onset disease. Response to treatment also varies significantly between children and adults [3, 4]. Efficacy of NSAID treatment is higher during attacks in adults compared to children. Moreover, in adults, single-dose corticosteroid and tonsillectomy are not as effective as they are in children with PFAPA [3, 4, 115].

Unsolved issues and unmet needs in PFAPA

The exact etiopathogenesis and the reason why the inflammation is restricted to the oropharyngeal lymphoid tissue in PFAPA remain unknown currently although recent studies focus on tonsillar pathology and microbiota.

There are three diagnostic/classification criteria sets for PFAPA. Two of them exclude late-onset cases. There is need for a single diagnostic criteria set which has a high performance in diagnosis of both pediatric and adult PFAPA patients.

The reason for clock-work regularity of disease episodes is also unknown. The nature of the trigger (reactivation

Table 2 Differences between adults and children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome

Features	Children with PFAPA	Adults with PFAPA
Gender	Slight male predominance	No gender predominance
Clock-work regularity of attacks	Common	Not so common
Symptoms in attacks	More common chills, oral aphthosis, pharyngitis	More common arthralgia, myalgia, headache, fatigue, chest pain, conjunctivitis, rashes
Response to medical treatment	Abrupt cessation of attacks is more frequent with single corticosteroid dose	Efficacy of NSAIDs is higher during attacks
Response to tonsillectomy	Effective in > 90% of patients	Less effective
Outcome	Self-limited (relapses could be observed)	Not self-limited (?) (long term data missing)

NSAID nonsteroidal anti-inflammatory drug, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis

of an infectious agent?), the epithelial cell turnover, the unique biokinetics of immune cells may take role in determining periodicity.

The disease is self-limited in most pediatric patients. The reason for this disease course remains unknown. Padeh et al. hypothesized that some form of delayed maturation of the immune system may be the underlying pathology, which also explains the self-limiting course of the disease as being due to the full maturation of the immune system when the child grows older [83]. They considered adult PFAPA patients as individuals whose immune systems never reach maturation [83].

There is no consensus on PFAPA treatment. There are wide discrepancies in clinical practice with regard to prescribing corticosteroids and choosing tonsillectomy. There is a need for a PFAPA treatment guideline that will be formed based on the evidence coming from controlled studies.

Although PFAPA patients have recurrent inflammatory attacks for a relatively long period (around 5–6 years), the disease does not cause any major sequela, which remains to be an unexplored aspect.

Conclusion

PFAPA is considered to be the most common periodic fever syndrome of childhood. It is mainly an early childhood disease. However, late disease onset should not be a reason to exclude PFAPA diagnosis. Recently, the main challenge is to differentiate PFAPA from monogenic AIDs, especially in countries endemic for a monogenic AID. It could be wise to check for mutations in monogenic AID genes in endemic areas especially in PFAPA patients with clinical characteristics and/or disease course which are atypical for PFAPA. Single dose corticosteroid seems effective in treatment of attacks. However, it could increase the attack frequency in the long term. For surgical treatment, some experts recommend tonsillectomy at the diagnosis, while some never recommend surgery, since the disease is self-limited without major sequela in most cases. Colchicine treatment is promising for decreasing the attack frequency especially in patients carrying *MEFV* variants. There are still lack of knowledge in the etiopathogenesis, disease mechanisms, and the self-limited disease course. These issues will probably be addressed in future studies with large numbers of PFAPA patients.

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