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REVIEW

Familial Mediterranean fever and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: shared features and main differences

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Abstract
Autoinflammatory diseases are characterized by fever attacks of varying durations, associated with variety of symptoms including abdominal pain, lymphadenopathy, polyserositis, arthritis, etc. Despite the diversity of the clinical presentation, there are some common features that make the differential diagnosis of the autoinflammatory diseases challenging. Familial Mediterranean fever (FMF) is the most commonly seen autoinflammatory conditions, followed by syndrome associated with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). In this review, we aim to evaluate disease characteristics that make a diagnosis of FMF and PFAPA challenging, especially in a regions endemic for FMF. The ethnicity of patient, the regularity of the disease attacks, and the involvement of the upper respiratory systems and symphonies could be helpful in differential diagnosis. Current data from the literature suggest the use of biological agents as an alternative for patients with FMF and PFAPA who are non-responder classic treatment options. More controlled studies are needed to evaluate the efficacy and safety of this strategy.

Keywords Familial Mediterranean fever · PFAPA syndrome · Colchicine · Recurrent fever · Anti-interleukin-1 agents

Introduction

Term of autoinflammation covers disorders associated with the unprovoked hyperactivity of the innate immune system leading to excessive inflammation, without confirmed influence of adaptive immune system mechanisms. Autoinflammatory conditions are characterized by fever attacks of varying duration, associated with variety of symptoms including abdominal pain, lymphadenopathy, polyserositis, arthritis, etc. [1]. Despite the diversity of the clinical presentation, there are some common features that make the differential diagnosis challenging (Fig. 1).

The marked improvement in understanding the nature of the autoinflammation has been registered after discovery of genes responsible for the different autoinflammatory conditions. Furthermore, identification of the underlying pathologic mechanisms and the role of interleukin-1 (IL-1) production resulted with successful treatment of these diseases [3].

Familial Mediterranean fever (FMF) is the most commonly seen autoinflammatory conditions in Turkey, followed by syndrome associated with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). Despite the different origin of these two separated conditions, recent studies suggest that there are many common features [1, 2].

In this review, we aim to evaluate disease characteristics that make a diagnosis of FMF and PFAPA challenging, especially in a regions endemic for FMF. It is important to add that the expanding spectrum of autoinflammatory conditions, including hyper IgD syndrome (HIDS), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), etc., should be considered in differential diagnosis of PFAPA and FMF. The main disease features and differences are presented in Table 1.

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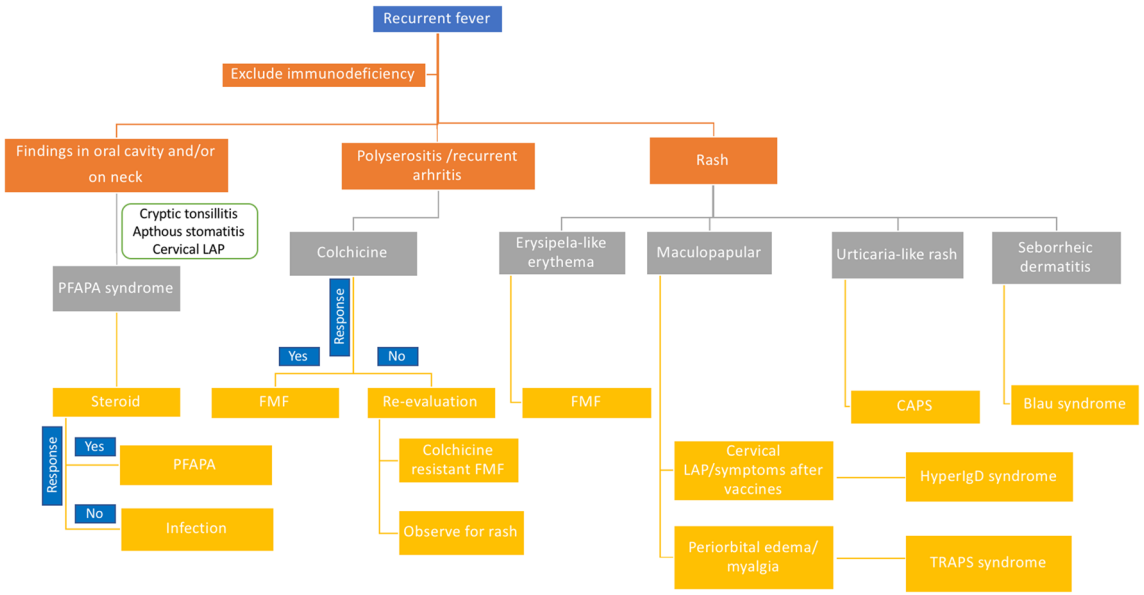

Fig. 1 Diagnostic algorithm in children with recurrent fevers

Table 1 Periodic fever, adenitis, pharyngitis, and aphthous stomatitis syndrome versus familial Mediterranean fever: main disease features

Disease feature	PFAPA syndrome	FMF
Regularity of the disease episodes	+	−
Fever	+	+
Cervical lymphadenopathy	++	−
Pharyngitis	++	−
Aphthous stomatitis	+	−
Abdominal pain	+/−	++
Pleurisy	−	+
Arthritis	−	+
Erysipelas like erythema	−	++
Response to single dose of glucocorticoids	++	+/−
Response to colchicine	+/−	++
Response to anti IL-1 agent	+/−	++
MEFV gene mutation	−	+
Family history	+/−	+

IL-1 interleukin 1, *FMF* familial Mediterranean fever, *PFAPA* periodic fever, adenitis, pharyngitis, and aphthous stomatitis

++ severe clinical presentation

Methods

Search strategy

A systematic literature searches for the review have been performed to optimize the relevance and the impact of this manuscript. Therefore, an electronic of the most frequently used medical databases (PubMed/MEDLINE, Web of Science, and SCOPUS) for peer-reviewed studies published in the English language during the last 6 years has been provided. We searched studies for the following words: childhood familial Mediterranean fever, FMF, periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome, PFAPA, Marshall's syndrome, autoinflammatory disease, *MEFV*, and colchicine. Consequently, papers published from January 2012 to January 2018 were primarily chosen; with a note that main reports published before the mentioned period of time have been included, as well.

The preparation of this manuscript was generated in accordance with the recommendations from the previously published review for writing a narrative biomedical paper [4].

Eligibility criteria

All observational studies, clinical trials, and reviews on the childhood FMF and PFAPA syndrome, published in English in peer-reviewed journals during the last 5 years, were considered for inclusion. No limitations were made regarding the results, findings, and clinical outcome.

Selection of studies

Selected papers were further screened for eligibility by the first author (AA), based on title, abstracts, and key words. After full-text retrieval, the senior author (OK) reviewed included papers to confirm compliance with study inclusion

criteria. All the four authors finally made a consensus on the eligibility of the finally selected papers.

Familial Mediterranean fever (FMF)

Familial Mediterranean fever is the most common monogenic autoinflammatory disease, presenting with recurrent, self-limiting attacks of polyserositis and arthritis [5, 6]. It is generally seen among subjects with Turkish, Armenian, Arabic, and Jewish origin. Clinical manifestations develop secondary to autosomal recessive mutations in the Mediterranean fever (*MEFV*) gene [7]. Since the disease symptoms usually emerge early in childhood, nearly 90% of the patients experience their first disease attack prior to 20 years of age [5].

Pathophysiology

The pathophysiology of the FMF is still unclear. In general, mutations in the gene encoding proinflammatory protein called pyrin (*MEFV*) represent the main cause of FMF. However, the physiological function of pyrin remains unknown, despite many studies investigating its role in the innate and adaptive immunity. Xu et al. [8] show that pyrin mediates caspase 1 inflammasome activation secondary to Rho-glucosylation activity of cytotoxin TcdB. Thus, pyrin is responsible for modification and inactivation of Rho GTPases, opening a new horizon in human innate immunity.

Similarly, Park et al. [9] found that mutations in the genes encoding pyrin and mevalonate kinase (MVK) cause interleukin-1β (IL-1β)-mediated autoinflammatory conditions, such as FMF and HIDS. They found that RhoA activated the serine-threonine kinases (PKN1 and PKN2) that bind and phosphorylate pyrin. Phosphorylated pyrin bound to regulatory proteins that blocked the pyrin inflammasome. Their findings suggest an important association between those two seemingly autoinflammatory conditions [9].

Genetics

The responsible gene (*MEFV*) is located on 16p13, encoding the proinflammatory protein called pyrin. As previously mentioned, pyrin is involved in the activation of caspase-1 and releasing of active IL-1, as a part of the inflammasome complex. Consequently, mutated pyrin enhances the IL-1β overexpression and inflammation [5–7]. Approximately 175 pathogenic mutations have been registered so far (mostly in exon 10) with four of them blamed for majority of diseases (M694V, M680I, M694I, V726A) [3]. In studies from Turkey, the most common *MEFV* mutation patterns were M694V homozygosity (21.8%) and heterozygosity (19.2%), followed by M694V/M680I (7.2%) compound heterozygosity [5, 7]. Patients homozygous for M694V are shown to be at greater risk for severe clinical course and for development of systemic AA amyloidosis, while the E148Q was not associated with significant clinical symptoms [3, 5].

Diagnosis

The disease is most prevalent among eastern Mediterranean populations, predominantly affecting the Turks, Armenians, Arabs, and non-Ashkenazi Jewish populations [1–3].

According to the Turkish pediatric FMF criteria, the presence of ≥ 2 following in a patient is accepted as diagnostic criteria for FMF.

≥ 3 attacks with fever lasting for 6–72 h, abdominal pain, oligoarthritis, chest pain, and positive family history [10]. The oligoarthritis of the FMF is acute arthritis of the lower extremities. Arthritis lasting more than 6 weeks in a patient with confirmed FMF is accepted as chronic arthritis.

Clinical presentation

Up to date, data on pediatric FMF, including relationship between MEFV gene mutation and clinical manifestations, treatment modalities, and efficacy and disease outcome are spare. Our group has recently reported the largest pediatric FMF cohort from the single center [5].

Fever associated with abdominal pain is the most frequently reported complaint by the FMF patients. Arthritis is the second commonly seen manifestation, seen in 288/708 (40.7%) pediatric FMF cases reported by Barut et al. [5]. Interestingly, in the mentioned study, 39/708 (5.5%) subjects had recurrent attacks of arthritis, without fever and signs of serositis. The FMF arthritis is the acute arthritis of large joints of the lower extremities, healing without sequelae. Among the large joints, the knee is the most common, while the shoulder girdle is the least frequently affected joint. However, the chronic arthritis is not rare in FMF. Except for symptoms resembling chronic idiopathic arthritis, signs of juvenile spondyloarthropathies could be seen, as well [5, 11]. The previous studies reported the coexistence of FMF and vasculitis [IgA vasculitis; polyarteritis nodosa (PAN)] [12, 13]. Alterations in the *MEFV* gene were found to be important susceptibility factors for the development of IgA vasculitis. In addition, mutations in *MEFV* gene provided a basis for the development of PAN both by forming a proinflammatory state and by possibly giving exaggerated response to streptococcal infections.

Since the autoinflammation represents the basic mechanism of the disease, the main aim of treatment is to take an inflammation under control. Uncontrolled, prolonged inflammation in FMF patients can lead to devastating complications, namely amyloidosis. Fortunately, the frequency

of FMF-related amyloidosis is quite low (0.2–1.5%), according to the data from recent studies [3, 5].

Laboratory findings

The elevation of the acute phase markers [erythrocyte sedimentation rate and C-reactive protein (CRP)], leukocytosis, thrombocytosis, and anemia could be seen during the disease attack. Patients with continuous elevation of the acute phase markers during the attack-free period are considered to have the subclinical inflammation. In a study by Korkmaz et al. [14], CRP was the only acute phase protein that was increased during all attacks. Interestingly, neither thrombocytosis nor an increase in ferritin levels was noted in any attack. Serum albumin levels remained unchanged, as well.

Proteinuria has been reported in 1.4% of pediatric FMF patients. Patients with M694V mutation of the *MEFV* gene have been shown to be more prone to have anemia, thrombocytosis, and proteinuria. Fortunately, the percentage of amyloidosis is extremely rare in pediatric population [5].

Treatment

Colchicine represents the main treatment option, decreasing the attack frequency and preventing the amyloidosis. Moreover, it has been proven that long-term usage of colchicine prevents the development of severe complications due to systemic amyloidosis [5, 15–17]. The recommended dose of colchicine is 1.2 mg/m^2/day, depending on the age of patient: 0.5, 1 mg/day for children < 5; 1 mg/day for children between 5 and 10 years and 1.5 mg/day for children older than 10 [15]. The maximum tolerable colchicine dose is reserved for colchicine-resistant FMF patients: 1.5 mg/day between 5 and 10 years and 2 mg/day for those older than 10. Colchicine resistance is defined as recurrence of disease attacks at least one per month, for 3 consecutive months (despite the adequate colchicine dose and good compliance) [15]. Anti-interleukin 1 agents are shown to be effective in decreasing attack frequency and severity in colchicine-resistant FMF cases [5, 15, 16]. In our previous study, the colchicine resistance has been reported in 6.6% cases [5]. In a study by Ozcakar et al. [18], 15/330 (4.5%) childhood-onset FMF patients were treated with anti IL-1 agent: 8 with colchicine resistance and 7 with FMF-related amyloidosis. Ozen et al. [19] proposed FMF 50 outcome criteria that define response to treatment in FMF patients. The items of this FMF50 included: frequency and duration of disease attacks, frequency of arthritis attacks, patients/parents'/physicians' global assessment of disease severity, C-reactive protein, erythrocyte sedimentation rate, or serum amyloid A level. Authors reported the FMF 50 to be user-friendly measurement tool, useful especially for clinical trials. Recently published multicentric study showed that canakinumab was effective in controlling and preventing flares in patients with colchicine-resistant FMF, mevalonate kinase deficiency, and TRAPS [20].

Prognosis

Regular treatment with optimal colchicine doses and appropriate drug compliance leads to favorable clinical course [5, 18]. Although quite rare, amyloidosis remains the most devastating disease complication. Barut et al. [5] reported the amyloidosis only in 2/708 (0.28%) of childhood FMF patients. In another study from Turkey, the frequency of amyloidosis has been reported as 6/330 (1.81%), which is still quite low [18]. Especially, the M694V homozygosity has shown to be associated with increased risk for amyloidosis [3, 5, 18].

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome is the most common periodic fever of childhood worldwide. PFAPA includes many challenges for the clinicians, due to difficulty in early establishing the diagnosis, the lack of reliable diagnostic test, and/or biomarkers that would be helpful in distinguishing the PFAPA from other conditions with similar symptoms [21].

Although considered to be specifically limited to pediatric age, an increasing number of reports suggest that PFAPA syndrome can also affect adults [22–24].

Pathophysiology

The exact pathogenesis of the disease is still unknown. The occurrence of symptoms in young children, its periodicity, and presence of cryptic tonsillitis like features bring to mind infections as a main etiologic factor. However, the regularity of PFAPA attacks and its prompt responsiveness to corticosteroids suggest the immune dysregulation as a potential basic mechanism of this disorder [21, 25]. Stojanov et al. [26] showed that complement, IL-1-related, and IFN-induced genes were significantly overexpressed, while the T-cell-associated transcripts were down-regulated during the PFAPA attacks. The investigation by Kolly et al. [27] showed elevation in peripheral blood of proinflammatory cytokines, which activates IL-1β that plays a role in the clinical presentation of the disease. The increase in IL-1 level during PFAPA flares reported in mentioned opens new horizons in PFAPA treatment.

Genetics

Many studies have been provided, but no single genetic variant has been shown to date to be relevant to the etiology of PFAPA. However, a significant number of patients have a history of recurrent tonsillitis and/or tonsillectomy among parents and first-degree relatives. Those data suggest the potential genetic basis of disease, with potential epigenetic factors modifying the disease phenotype.

Our group has previously reported the *MEFV* as a factor that potentially influences the presentation of PFAPA. Patients with underling *MEFV* gene mutation (especially exon 10 mutation) seem to have more severe clinical course and poorer response to treatment [2]. Yamagami et al. described recently an adult case of PFAPA with P369S/R408Q exon3 variant in *MEFV* [28]. However, in several studies, it was shown that the presence of *MEFV* mutations in PFAPA patients had a favorable effect on disease phenotype [29–31]. Those findings open new questions that need to be answered in further clinical studies.

Clinical presentation

The PFAPA is a condition generally seen among young children, < 5 years of age. It is characterized by the recurrent episodes of fever, accompanied with different features including aphthous stomatitis, pharyngitis, and adenitis. The onset of fever is abrupt, with a sudden cessation 3 or 4 days later [21]. Fever is generally as high as > 39 °C, resistant to antibiotics and antipyretics. Interestingly, the general condition of the patient is good, despite the high fever and other disease features. There is no prodromal stage of the disease attack. The disease is seen in "generally healthy" patients with mental and motor development appropriate for the patients' age. Patients are completely healthy between the attacks. Attacks show no seasonal differences and could be seen at any time of the year. These features reduce the possibility of the infectious etiology of the disease.

Fever responds rapidly to the corticosteroid treatment, decreasing and remaining in the normal level until the next disease attack. Findings in the oral cavity are typical those of aphthous stomatitis, sometimes complicated with the oral candidiasis and infectious gingivostomatitis. Tonsils are generally enlarged with the findings of cryptic tonsillitis (Fig. 1). Signs of pharyngitis could be seen, as well. The throat culture and the streptococcus quick test remain negative. Tonsillo-pharyngitis shows no response to antibiotic treatment but disappears promptly after the corticosteroids are induced. Lymphadenopathy, predominantly cervical, is a common clinical finding. The abdominal pain due to abdominal lymphadenopathy could be rarely seen. Rash and other skin findings are not expected among PFAPA patients. Myalgia could be present in some of cases but never accompanied by the signs of arthritis [21, 25].

The main characteristic of the episodes is their regularity. Despite the almost unique of clinical presentation, gentle differences between patients suggest the influence of the epigenetic and environmental factors on the clinical course. In regions with high frequency of *MEFV* mutations, such as our country, clinical presentation of PFAPA could be more severe due to previously induced inflammatory pathway. A study by Batu et al. [32] underlines the differences between PFAPA patients from the Turkish and the US cohorts regarding the clinical features.

Laboratory findings

There is a lack of single diagnostic test that could simplify the diagnosis of PFAPA. Typically, the acute phase reactants are elevated during the disease episodes and normal between episodes. During the attack-free period, there is no possibility to distinct the patients from the healthy control. However, the exclusion of cyclic neutropenia and similar signs of immunodeficiency (e.g., lymphopenia) is of high importance [21, 25].

Diagnosis

Diagnostic criteria for PFAPA differ with a lack of unique consensus on PFAPA diagnosis. There is few set of criteria, all of them based on the main clinical features. Criteria proposed by the Marshall et al. [33] are still widely in use. The additionally sets of criteria are sporadically used, depending on the clinical experience and the choice of the practitioners [34–36].

Based on the comparison of clinical features of different periodic fevers and PFAPA, which was used as a negative control, the evidence-based classification criteria for inherited periodic fevers were recently proposed [37]. Hyper IgD syndrome could be misdiagnosed as PFAPA, due to some common disease features. Recurrent attacks of fever, tonsillopharyngşitis, and lymphadenitis that persist after the tonsillectomy indicate possible diagnosis of HIDS.

Treatment

Episodes dramatically resolve with corticosteroids, given even in a single dose of 1 mg/kg [21]. However, the antinflammatory treatment does not represent the permanent solution, since the disease attacks recur. The tonsillectomy remains the option that leads to the cessation of the disease attacks, in general. It is important to mention that some PFAPA patients continue to experience the periodic fever attacks despite the surgical treatment (namely tonsillectomy) [2, 25, 38]. Some data from the literature suggest the

potentially underlying *MEFV* mutation in PFAPA patients unresponsive to tonsillectomy [2]. There are some evidences of colchicine efficiency in PFAPA patients, especially those with underlying of *MEFV* mutation [2, 38–40]. The increase in IL-1 during PFAPA flares demonstrated in previously mentioned studies suggests a possible role of IL-1 inhibition in PFAPA treatment [26, 27]. Stojanov et al. [26] treated five PFAPA patients with a recombinant IL-1 receptor antagonist and all of them showed excellent clinical response.

Prognosis

A PFAPA syndrome is a commonly seen autoinflammatory disease, characterized with benign clinical course and favorable prognosis. Disease symptoms disappear spontaneously until the 7–8 years of age. The tonsillectomy represents the cure, especially for patients with frequent disease attacks that influence the quality of life. Rarely, the disease attacks persist during the adolescence and adulthood. According to data from the literature, the underlying FMF and other autoinflammatory conditions should be considered in PFAPA patients unresponsive to standard treatment options [2, 3, 21, 37, 38].

FMF and PFAPA: common features and main distinctions

Although FMF and PFAPA represent two separate conditions, there are some noteworthy confusing points that make the differentially diagnosis challenging. The episodes of the FMF attacks appear in irregular cycles, while the PFAPA episodes show regularity. Both of patients (FMF and PFAPA) are completely healthy between the episodes. The subacute disease state of the FMF is exception, due to poor general condition and fatigue of patients even during the attack-free period.

The abdominal pain accompanied with fever is the main stone of the clinical presentation of FMF [2, 5]. Abdominal pain could be seen during the PFAPA attacks, but its severity never reaches the level of acute peritonitis [2, 5, 21]. Lymphadenitis of the mesenteric lymph nodes is considered responsible for the pain of PFAPA patients [21, 25].

The PFAPA patient usually does not have systemic symptoms including rash, joint complaints, and signs of serositis. Although the acute arthritis of the large joints is typical for FMF patients, the chronic arthritis could be seen, as well [5, 6]. Skin involvement is not expected in none of the mentioned conditions, expect for erysipelas like erythema seen in FMF patients [5, 6].

Cervical lymphadenopathy and pharyngitis are exclusively seen in PFAPA patients [2, 5, 21]. Roughly, we can conclude that clinical features of the head and neck should be attributed to PFAPA, while symptoms of the trunk and extremities are characteristic for the FMF patients. The most relevant point in differential diagnosis of FMF/PFAPA is that patients with FMF never complaint of head and neck symptoms. On the other side, PFAPA patients do not report the abdominal pain, except for those with mesenteric lymphadenopathy.

Family history of some PFAPA patients suggests the autosomal dominant pattern of inheritance, but no single gene has been documented to be responsible for the condition, up to date [2, 21]. In some of cases, the parents of PFAPA patients may have history of recurrent fevers or adenoidotonsillectomy as young children [21]. In contrary, the strong genetic basis of the FMF has been confirmed with MEFV mutation being documented in majority of patients [1, 3, 5]. Furthermore, recent studies and case reports imply the possible role of the *MEFV* gene in PFAPA patients [2, 41–44]. It seems that future studies would bring us new insights in pathophysiology and genetics of PFAPA and its common pathway with FMF.

Anti-inflammatory treatment (non-steroidal, anti-inflammatory drugs, and corticosteroids) works in both patients group, resulting with cessation of the disease attacks and prevention of disease complication. Both of patients group does response to corticosteroids treatment, but the FMF patients do not response to its single dose [2, 21]. Colchicine is the cornerstone of the FMF treatment, whose efficiency has been proven many times [5, 6, 17]. There are some evidences of good clinical response of PFAPA patients to colchicine treatment, as well [2, 34, 35]. The tonsillectomy remains exclusive treatment option of PFAPA patients, resulting with cessation of disease attacks, in general [2, 28]. Stojanov et al. [26] also reported that IL-1 inhibition could possibly be beneficial in PFAPA patients during attacks.

Conclusions

The FMF and the PFAPA are the most frequent autoinflammatory conditions, with many common disease features. The ethnicity of patient, the regularity of the disease attacks, and the involvement of the upper respiratory systems and symphonies could be helpful in differential diagnosis. Current data from the literature suggest the use of biological agents as an alternative for patients with FMF and PFAPA who are non-responders classic treatment options. More controlled studies are needed to evaluate the efficacy and safety of this strategy.

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Compliance with ethical standards

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References

1. Sag E, Bilginer Y, Ozen S (2017) Autoinflammatory diseases with periodic fevers. Curr Rheumatol Rep 19:41
2. Pehlivan E, Adrovic A, Sahin S, Barut K, Kul Cınar O, Kasapcopur O (2018) PFAPA syndrome in a population with endemic familial Mediterranean fever. J Pediatr 192:253–255
3. Pepper RJ, Lachmann HJ (2016) Autoinflammatory syndromes in children. Indian J Pediatr 83:242–247
4. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417
5. Barut K, Sahin S, Adrovic A, Sinoplu AB, Yucel G, Pamuk G, Aydın AK, Dasdemir S, Turanlı ET, Buyru N, Kasapcopur O (2018) Familial Mediterranean fever in childhood: a single center experience. Rheumatol Int 38:67–74
6. Ozen S, Bilginer Y (2014) A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol 10:135–147
7. Booth DR, Gillmore JD, Lachmann HJ, Booth SE, Bybee A, Soyturk M, Akar S, Pepys MB, Tunca M, Hawkins PN (2000) The genetic basis of autosomal dominant familial Mediterranean fever. QJM 93:217–221
8. Xu H, Yang J, Gao W, Li L, Li P, Zhang L, Gong YN, Peng X, Xi JJ, Chen S, Wang F, Shao F (2014) Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. Nature 513:237–241
9. Park YH, Wood G, Kastner DL, Chae JJ (2016) Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. Nat Immunol 17:914–921
10. Yalcinkaya F, Ozen S, Ozcakar ZB, Aktay N, Cakar N, Duzova A, Kasapcopur O, Elhan AH, Doganay B, Ekim M, Kara N, Uncu N, Bakkaloglu A (2009) A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology 48:395–398
11. Sönmez HE, Batu ED, Demir S, Bilginer Y, Özen S (2017) Comparison of patients with familial Mediterranean fever accompanied with sacroiliitis and patients with juvenile spondyloarthropathy. Clin Exp Rheumatol 35(Suppl 108):124–127
12. Ozçakar ZB, Yalçinkaya F, Cakar N, Acar B, Kasapçopur O, Ugüten D, Soy D, Kara N, Uncu N, Arisoy N, Ekim M (2008) MEFV mutations modify the clinical presentation of Henoch–Schönlein purpura. J Rheumatol 35:2427–2429
13. Yalçinkaya F, Ozçakar ZB, Kasapçopur O, Oztürk A, Akar N, Bakkaloğlu A, Arisoy N, Ekim M, Ozen S (2007) Prevalence of the MEFV gene mutations in childhood polyarteritis nodosa. J Pediatr 151:675–678
14. Korkmaz C, Ozdogan H, Kasapçopur O, Yazici H (2002) Acute phase response in familial Mediterranean fever. Ann Rheum Dis 61:79–81
15. Gul A, Ozdogan H, Erer B, Ugurlu S, Kasapcopur O, Davis N, Sevgi S (2015) Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. Arthritis Res Ther 17:243
16. Sozeri B, Kasapcopur O (2015) Biological agents in familial Mediterranean fever focusing on colchicine resistance and amyloidosis. Curr Med Chem 22:1986–1991
17. Kallinich T, Haffner D, Niehues T, Huss K, Lainka E, Neudorf U, Schaefer C, Stojanov S, Timmann C, Keitzer R, Ozdogan H, Ozen S (2007) Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 119:e474–e483
18. Özçakar ZB, Özdel S, Yılmaz S, Kurt-Şükür ED, Ekim M, Yalçınkaya F (2016) Anti-IL 1 treatment in familial Mediterranean fever and related amyloidosis. Clin Rheumatol 35:441–446
19. Ozen S, Demirkaya E, Duzova A, Erdogan O, Erken E, Gul A, Kasapcopur O, Kasifoglu T, Kisacik B, Ozdogan H, Tunca M, Acikel C, FMF Arthritis Vasculitis and Orphan Disease Research in Pediatric Rheumatology (FAVOR), Turkish FMF Study Group (2014) FMF50: a score for assessing outcome in familial Mediterranean fever. Ann Rheum Dis 73:897–901
20. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, Koné-Paut I, Lachmann HJ, Ozen S, Simon A, Zeft A, Calvo Penades I, Moutschen M, Quartier P, Kasapcopur O, Shcherbina A, Hofer M, Hashkes PJ, Van der Hilst J, Hara R, Bujan-Rivas S, Constantin T, Gul A, Livneh A, Brogan P, Cattalini M, Obici L, Lheritier K, Speziale A, Junge G (2018) Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med 378:1908–1919
21. Harel L, Hashkes PJ, Lapidus S, Edwards KM, Padeh S, Gattorno M, Marshall GS (2018) The first international conference on periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome. J Pediatr 193:265–274
22. Vitale A, Orlando I, Lopalco G, Emmi G, Cattalini M, Frediani B, Galeazzi M, Iannone F, Rigante D, Cantarini L (2016) Demographic, clinical and therapeutic findings in a monocentric cohort of adult patients with suspected PFAPA syndrome. Clin Exp Rheumatol 34:77–81
23. Rigante D, Vitale A, Natale MF, Lopalco G, Andreozzi L, Frediani B, D'Errico F, Iannone F, Cantarini L (2017) A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. Clin Rheumatol 36:463–468
24. Cattalini M, Soliani M, Rigante D, Lopalco G, Iannone F, Galeazzi M, Cantarini L (2015) Basic characteristics of adults with periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome in comparison with the typical pediatric expression of disease. Mediat Inflamm 2015:570418
25. Førsvoll J, Øymar K (2018) The role of tonsillectomy in the periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome; a literature review. BMC Ear Nose Throat Disord 22:18:3
26. Stojanov S, Lapidus S, Chitkara P, Feder H, Salazar JC, Fleisher TA, Brown MR, Edwards KM, Ward MM, Colbert RA, Sun HW, Wood GM, Barham BK, Jones A, Aksentijevich I, Goldbach-Mansky R, Athreya B, Barron KS, Kastner DL (2011) Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. Proc Natl Acad Sci USA 108:7148–7153
27. Kolly L, Busso N, von Scheven-Gete A, Bagnoud N, Moix I, Holzinger D, Simon G, Ives A, Guarda G, So A, Morris MA, Hofer M (2013) Periodic fever, aphthous stomatitis, pharyngitis,

cervical adenitis syndrome is linked to dysregulated monocyte IL-1β production. J Allergy Clin Immunol 131:1635–1643
28. Yamagami K, Nakamura T, Nakamura R, Hanioka Y, Seki K, Chiba H, Kobayashi K, Agematsu K (2017) Famillial Mediterranean fever with P369S/R408Q exon 3 varian in pyrin presenting as symptoms of PFAPA. Mod Rheumatol 27:356–359
29. Berkun Y, Levy R, Hurwitz A, Meir-Harel M, Lidar M, Livneh A, Padeh S (2011) The familial Mediterranean fever gene as a modifier of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome. Semin Arthritis Rheum 40:467–472
30. Taniuchi S, Nishikomori R, Iharada A, Tuji S, Heike T, Kaneko K (2013) MEFV variants in patients with PFAPA syndrome in Japan. Open Rheumatol J 19:7:22–25
31. Perko D, Debeljak M, Toplak N, Avčin T (2015) Clinical features and genetic background of the periodic Fever syndrome with aphthous stomatitis, pharyngitis, and adenitis: a single center longitudinal study of 81 patients. Mediat Inflamm 2015:293417
32. Batu ED, Kara Eroğlu F, Tsoukas P, Hausmann JS, Bilginer Y, Kenna MA, Licameli GR, Fuhlbrigge RC, Özen S, Dedeoğlu F (2016) Periodic fever, aphthosis, pharyngitis, and adenitis syndrome: analysis of patients from two geographic areas. Arthritis Care Res (Hoboken) 68:1859–1865
33. Marshall GS, Edwards KM, Lawton AR (1989) PFAPA syndrome. Pediatr Infect Dis J 8:658–659
34. Thomas KT, Feder HM, Lawton AR, Edwards KM (1999) Periodic fever in children. J Pediatr 135:15–21
35. Feder HM, Salazar JC (2010) A clinical review of 105 patients with PFAPA (a periodic fever syndrome). Acta Paediatr 99:178–184
36. Marshall GS, Edwards KM, Butler J, Lawton AR (1987) Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 110:43–46
37. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amaryan G, Woo P, Koné-Paut I, Dewarrat N, Cantarini L, Insalaco A, Uziel Y, Rigante D, Quartier P, Demirkaya E, Herlin T, Meini A, Fabio G, Kallinich T, Martino S, Butbul AY, Olivieri A, Kuemmerle-Deschner J, Neven B, Simon A, Ozdogan H, Touitou I, Frenkel J, Hofer M, Martini A, Ruperto N, Gattorno M, Paediatric Rheumatology International Trials Organisation (PRINTO), Eurofever Project (2015) Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. Ann Rheum Dis 74:799–805
38. Aktas O, Aytuluk HG, Caliskan SK, Erdur O, Cirik AA (2017) Long-term follow-up of tonsillectomy efficacy in children with PFAPA syndrome. Braz J Otorhinolaryngol. https://doi.org/10.1016/j.bjorl.2017.10.012
39. Gunes M, Cekic S, Kilic SS (2017) Is colchicine more effective to prevent periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis episodes in Mediterranean fever gene variants? Pediatr Int 59:655–660
40. Dusser P, Hentgen V, Neven B, Koné-Paut I (2016) Is colchicine an effective treatment in periodic fever, aphtous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome? Jt Bone Spine 83:406–411
41. Igante D, Gentileschi S, Vitale A, Tarantino G, Cantarini L (2017) Evolving frontiers in the treatment of periodic fever, aphthous stomatitis, pharyngitis, cervical aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome. Isr Med Assoc J 19:444–447
42. Yamagami K, Nakamura T, Nakamura R, Hanioka Y, Seki K, Chiba H, Kobayashi K, Agematsu K (2017) Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA. Mod Rheumatol 27:356–359
43. Salehzadeh F, Vahedi M, Hosseini-Asl S, Jahangiri S, Habibzadeh S, Hosseini-Khotbesara M (2014) PFAPA and 12 common MEFV gene mutations our clinical experience. Iran J Pediatr 24:64–68
44. Taniuchi S, Nishikomori R, Iharada A, Tuji S, Heike T, Kaneko K (2013) MEFV variants in patients with PFAPA syndrome in Japan. Open Rheumatol J 9:7:22–25