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PEDIATRIC RHEUMATOLOGY (S OZEN, SECTION EDITOR)

Autoinflammatory Diseases with Periodic Fevers

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Abstract
Purpose of Review One purpose of this review was to raise awareness for the new autoinflammatory syndromes. These diseases are increasingly recognized and are in the differential diagnosis of many disease states. We also aimed to review the latest recommendations for the diagnosis, management, and treatment of these patients.
Recent Findings Familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), and hyperimmunoglobulinemia D and periodic fever syndrome/mevalonate kinase deficiency (HIDS/MVKD) are the more common autoinflammatory diseases that are characterized by periodic fevers and attacks of inflammation. Recently much collaborative work has been done to understand the characteristics of these patients and to develop recommendations to guide the physicians in the care of these patients. These recent recommendations will be summarized for all four diseases.
Summary FMF is the most common periodic fever disease. We need to further understand the pathogenesis and the role of single mutations in the disease. Recently, the management and treatment of the disease have been nicely reviewed. CAPS is another interesting disease associated with severe complications. Anti-interleukin-1 (anti-IL-1) treatment provides cure for these patients. TRAPS is characterized by the longest delay in diagnosis; thus, both pediatricians and internists should be aware of the characteristic features and the follow-up of these patients. HIDS/MVKD is another autoinflammatory diseases characterized with fever attacks. The spectrum of disease manifestation is rather large in this disease, and we need further research on biomarkers for the optimal management of these patients.

Keywords Autoinflammatory syndromes · Periodic fever diseases

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Introduction

Fever is used to be the subject of infectious disease experts only. In a young child, the most common cause of fever is still an infection. However, in the twenty-first century, fever has become a major topic of pediatric rheumatologists as well. The main reason is our expanding knowledge of the autoinflammatory diseases (AIDs). AIDs are disorders of the innate immune system characterized by episodes of systemic inflammation. Hereditary periodic fever syndromes are a group of mainly monogenic disorders (except for periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)), which are characterized by attacks of fever episodes, accompanied by signs of clinical and laboratory inflammation. The features of clinical inflammation vary according to the underlying genetic defect, and the patients always have elevated acute phase reactants during the inflammatory episodes, manifesting as elevation of mainly erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) [1, 2]. The spectrum of AIDs is expanding. Although other AIDs may also present with fever,

they have other prominent features such as pyogenic lesions and granulomatous lesions and are classified according to the leading feature. The reader is referred to reviews on the classification of AIDs elsewhere [3•]. However, the AIDs with periodic fevers are the most common. Furthermore, they present as an important differential in the pediatric practice.

In this review, our aim is to discuss recent data on the pathophysiology and the recent recommendations for the management of monogenic AIDs that present as periodic fever diseases. We shall start with a nonmonogenic periodic fever syndrome PFAPA, and then continue with the monogenic AIDs (Fig. 1).

A group of international experts has recently reached consensus for classification criteria for the four periodic fever syndromes that are discussed here (work in progress).

Fig. 1 Diagnostic approach to recurrent fever. Infections and malignancies must be excluded as a first step in a patient with recurrent fever. If the fever attacks follow a regular period with exudative pharyngitis, oral aphtae, and/or lymphadenopathy, PFAPA should be considered. If infections, malignancies, and PFAPA are excluded, monogenic autoinflammatory diseases should be taken into account and necessary testing including genetic analysis should be done depending on the specific clinical features and the hereditary pattern of the disease. *LAP* lymphadenopathy, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and adenitis, *HIDS* hyperimmunoglobulinemia D and periodic fever syndrome, *FMF* familial Mediterranean fever, *CAPS* cryopyrin-associated periodic syndromes, *TRAPS* tumor necrosis factor receptor-associated periodic fever syndrome, *NOMID* neonatal-onset multisystem inflammatory disease, *MVK* mevalonate kinase, *MEFV* Mediterranean fever, *NLRP3* nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3, *TNFRSF1A* tumor necrosis factor receptor superfamily member 1A, *anti-TNF* anti-tumor necrosis factor, *Anti-IL-1* anti-interleukin-1

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

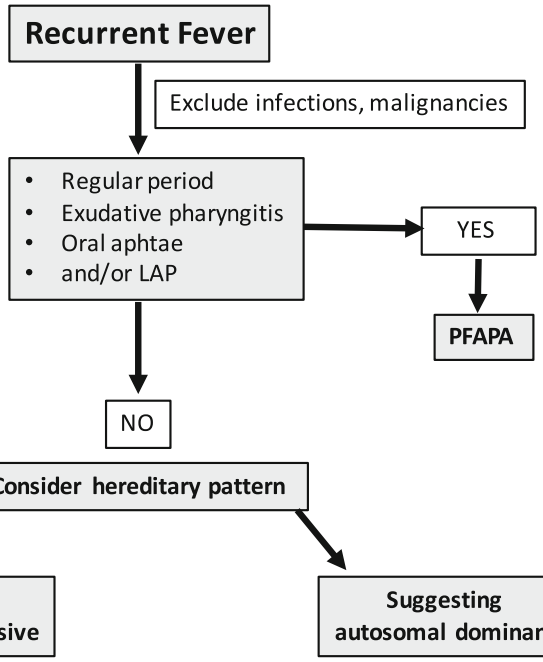
PFAPA syndrome, first described in 1987 by Marshall et al., is one of the most common periodic fever syndromes in children [4]. PFAPA is not a monogenic disease. Recently the characteristic features of the disease were once again shown in a large cohort of 301 patients: the disease usually presents with a median age of 4 years, with recurrent fever; exudative tonsillitis with negative throat culture; cervical lymphadenopathy; oral aphthae; and less commonly abdominal pain, arthralgia, myalgia, and headache [5••]. Each period lasts 4–6 days regardless of antibiotics and antipyretics and recurs every 3–5 weeks regularly [5••]. There is a male predominance (M/F:1.8:1) and a positive family history in about 30% of PFAPA patients [5••, 6]. There is no specific laboratory test to confirm the diagnosis PFAPA; however, leukocytosis and high CRP values are common during flares, with normalization between fever episodes [5••, 6]. There are no causative genes identified for PFAPA [2]. On the other hand, previous studies have shown that Mediterranean fever (MEFV) variants might have a modifier role in PFAPA [7].

PFAPA is considered a self-limited disease since the disease generally tends to fade away after 6 years of age. On the other hand, the attacks with prolonged high fevers may become a serious concern for the family. Corticosteroids are the most effective nonsurgical treatment causing dramatic cessation of fever during attacks, but this does not prevent the future episodes [5••, 8••, 9]. Furthermore, the attack-free periods may shorten in patients who used corticosteroids during attacks [9]. There are also reports suggesting long attack-free periods with colchicine; however, the best chance of cure of the disease is with tonsillectomy [9, 10].

Familial Mediterranean Fever

Pathophysiology

Familial Mediterranean fever is the most common monogenic inflammatory disease. It is inherited autosomal recessively. The causative gene in patients with Familial Mediterranean fever (FMF) is MEFV, encoding pyrin protein. Pyrin is an essential protein in the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome complex; mutation of this protein causes excess inflammation via caspase-1 activation and IL-1b production [3•]. Chae et al. have shown that in FMF knock-in, pyrin mutations lead to a gain of function through an apoptosis-associated speck-like protein containing CARD (ASC) and caspase-1-dependent pathway [11]. It is also shown that pyrin mediates caspase-1 activation in response to pathogen modification and inactivation of RhoA-GTPases by several bacterial toxins [12]. In normal individuals, RhoA-activated serine-threonine kinases (PKN1 and PKN2) bind and phosphorylate pyrin. Phosphorylated pyrin binds to regulatory 14-3-3 proteins, which in turn blocks the pyrin inflammasome. Mutations that affect the C terminal of the B30.2 domain, where the most of the common and severe FMF mutations are clustered, are important in controlling the pyrin phosphorylation by inhibiting the binding of the kinases, such as PKN1, thus resulting in a lowered threshold for pyrin inflammasome activation [13]. Colchicine both activates RhoA and reverses the inhibition of RhoA by bacterial toxins [13]. Besides that, sterile activators can also provide pro-inflammatory signals through damage-associated molecular patterns (DAMPs), which may elicit why patients have attacks triggered by stress as well [3•].



	HIDS	FMF	CAPS	TRAPS
Onset	<1 yrs (0.1-1.4 yrs)	2.7 yrs (1.1-5.3 yrs)	<1 yrs (0-3 yrs)	4.3 yrs (0-63 yrs)
Attack duration	4 days (3-6 days)	1-3 days	<2 days – continous	>7-14 days (median 10.8 days, 33% less than 7 days)
Trigger	Vaccination, stress, infection	Stress, menstruation, infection	Cold	Stress, menstruation, fatigue, infection, vaccination
Cutaneous	Maculopapular rash	Erysipelas-like erythema	Urticeria-like rash	Migratory rash over myalgia
Musculoskeletal	Arthralgia, myalgia	Monoarthritis	Artralgia, arthritis, abnormal bony growth (NOMID)	Severe myalgia, arthralgia
Abdominal	Severe abdominal pain, diarrhea, vomiting, Splenomegaly	Severe abdominal pain	-	Abdominal pain
Eye	-	-	Conjunctivitis, episcleritis, uveitis, optic disc edema	Periorbital edema, pain, conjunctivitis
Spesificities	Cervical LAP, aphtous ulcers, headche, mental retardation (in severe form)	Erysipelas-like eryhtema, severe serositis (abdominal pain, pleurisy, pericarditis), arhtritis	Urticeria-like rash, chronic aseptic meningitis, sensorineural hearing loss	Migratory myalgia and rash, periorbital edema
Gene	MVK	MEFV	NLRP3	TNFRSF1A
Treatment	Anti-TNF, Anti-IL1	Colchicine, Anti-IL1	Anti-IL1	Anti-TNF, Anti-IL1

Classification Criteria

FMF is not only characterized by attacks but with a chronic inflammatory state as well. Thus early diagnosis and treatment are crucial. The diagnosis of FMF relies on clinical findings and the genetic analysis of the MEFV gene. There are three sets of classification criteria. The first criteria were proposed for adult FMF patients at Tel Hashomer Hospital, and these criteria had been revised by Livneh, which include major and minor criteria as well as supportive criteria [14]. The four major criteria are typical attacks (defined as ≥3 attacks of the same type, with rectal temperature ≥38 °C, lasting 12–72 h) with any one of peritonitis, pleuritis, monoarthritis (of the hip, knee, or ankle), or fever alone. The minor criteria were defined as incomplete attacks, exertional leg pain, and favorable response to colchicine [14]. The authors suggested that one major or two minor criteria, or one minor plus five supportive criteria, should be satisfied to establish a diagnosis [14]. As there are differences between adult and children patients, in 2009, our group proposed a new set of criteria for pediatric FMF patients [15]. According to these criteria, the presence of at least two of the following characteristics is required for FMF classification: fever (lasting 6–72 h, ≥3 attacks), abdominal pain (lasting 6–72 h, ≥3 attacks), chest pain (lasting 6–72 h, ≥3 attacks, unilateral), arthritis (lasting 6–72 h, ≥3 attacks, monoarthritis), exertional leg pain, and family history of FMF. These pediatric criteria are tested in a large cohort of 339 patients and 377 control patients. The Turkish pediatric criteria had 88% sensitivity and 41% specificity. On the other hand, Tel Hashomer and Livneh criteria displayed a sensitivity of 45 and 77%, respectively. Both of the latter criteria displayed a better specificity than the Turkish pediatric criteria: 97.2 and 41.1% for the Tel Hashomer and Livneh criteria, respectively [16].

Diagnosis

The diagnosis of a child with periodic fever is much more challenging in a multiethnic population than in regions of high FMF prevalence. Thus, the first step is to decide on who to test, and then it is crucial to correctly analyze the genetic data. Shinar et al. proposed a set of guidelines for the genetic testing of hereditary recurrent fevers including FMF. The consensus was to test for a total of 14 variants (the first nine are defined as clearly pathogenic, while the remaining five variants have unknown significance): M694V, M694I, M680I, V726A, R761H, A744S, E167D, T267I, I692del, K695R, E148Q, P369S, F479L, and I591T. According to this guideline, there five different possible scenarios about genetic test results (with the assumption that the patient has symptoms compatible with FMF, at least unexplained fever attacks) [17]:

- If the patient is homozygote for pathogenic mutations, FMF diagnosis is confirmed and treatment should be initiated with no need of parental testing.
- If the patient is compound heterozygote for two pathogenic mutations and the mutations are on separate alleles, FMF diagnosis is confirmed and treatment should be initiated.
- If there is one pathogenic mutation and one uncertain mutation on separate alleles, there must be further clinical confirmation such as high CRP levels during attacks and/or high SAA levels between attacks to initiate treatment.
- If two variants of unknown significance are reported or if there is only one clearly pathogenic mutation, physician should reconsider the other periodic fever syndromes and testing acute-phase reactant levels.
- If only one variant of uncertain significance has been reported, FMF is very unlikely.

Since the first description of the MEFV gene, most experts and studies show that M694V is related with a severe phenotype. Both Shinar et al. and Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) recommendations defined E148Q as a variant of unknown significance [17, 18••]. SHARE is a European initiative where experts have suggested consensus guidelines for the management of the main pediatric rheumatic diseases. One task was to develop recommendations for the diagnosis of FMF. Some highlights of the recent SHARE recommendations for the genetic diagnosis of FMF are as follows [18••]:

- FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing.
- FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations at position 680–694 on exon 10, must be considered at risk of having a more severe disease.
- The E148Q variant is common, of unknown pathogenic significance, and, as the only MEFV variant, does not support the diagnosis of FMF.
- For individuals with two pathogenic mutations for FMF who do not report symptoms, if there are risk factors for amyloid A (AA) amyloidosis (such as the country, family history, and persistently elevated inflammatory markers, particularly SAA protein), close follow-up should be started and treatment considered.
- Consultation with an AID specialist may be helpful to aid in the indication and interpretation of the genetic testing and diagnosis.

Treatment and Management

Colchicine is still the main treatment of FMF, which decreases attack frequency, increases quality of life, and prevents the

complication of secondary amyloidosis [19, 20]. A starting dose of ≤0.5 mg/day for children <5 years of age, 0.5–1.0 mg/day for children 5–10 years of age, 1.0–1.5 mg/day for children >10 years of age and for adults is recommended. Although it is recommended to use twice daily, a recent randomized controlled study (RCT) has shown that using colchicine with either a once or twice-daily dosage provides similar clinical and laboratory improvements [21]. Patients should be followed closely for 3–6 months to observe the therapeutic effects of colchicine on attack frequency and severity and for the side effects mainly gastrointestinal symptoms [22••]. About 2% of the patients do not tolerate colchicine due to side effects or are resistant to the drug [23]. As FMF is an inflammasomepathy and IL-1 plays an important role in the pathogenesis, anti-IL-1 treatment can be used in treatment of colchicine-resistant (maximum dose of 2 mg in children) patients [24]. Response to treatment must be followed with a validated disease activity tool. Recently Demirkaya et al. proposed an International Severity Score for FMF and validated for both pediatric and adult FMF patients with severe disease ≥6, intermediate disease 3–5, and mild disease ≤2 out of maximum 10 points [25•].

Recent Recommendations

Recently a group of pediatricians and internists has suggested recommendations for the management of FMF, endorsed by the European League Against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PRES). Some of the important recommendations in this recent set of recommendations can be summarized as follows [22••]:

- The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimizing subclinical inflammation in between attacks.
- Treatment with colchicine should be started as soon as a clinical diagnosis is made.
- The persistence of attacks or subclinical inflammation represents an indication to increase colchicine dose. Compliant patients not responding to the maximum tolerated dose of colchicine can be considered nonresponders or resistant; alternative biological treatments are indicated in these patients.
- FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required.
- Periods of physical or emotional stress can trigger FMF attacks.
- Response, toxicity, and compliance should be monitored every 6 months
- Liver enzymes should be monitored regularly; if liver enzymes are elevated greater than twofold the upper limit of normal, colchicine should be reduced and investigated.
- In patients with decreased renal function, the colchicine dose reduced accordingly.
- Colchicine toxicity is a serious complication.
- Colchicine should not be discontinued during conception, pregnancy, or lactation; current evidence does not justify amniocentesis.
- In general, men need not stop colchicine prior to conception; however, further consultation is required for the rare case of azoospermia or oligospermia.
- In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; nonsteroidal anti-inflammatory drug (NSAID) and IL-1 blockade might also be a treatment option.

Tumor Necrosis Factor Receptor-Associated Periodic Fever Syndrome

Pathophysiology

Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS) is an autosomal dominant disease that was first reported in a large Irish/Scottish family and was originally described as familial Hibernian fever in 1982 [26]. After the discovery of the molecular basis of the disease showing the association with mutations in the gene of tumor necrosis factor receptor superfamily member 1A (TNFRSF1A), it was renamed as TRAPS [27]. Most sequence variants underlying TRAPS lie within exons 2 to 4 (Infevers database: http://fmf.igh.cnrs.fr/ ISSAID/infevers/) [28••]. Missense substitutions which disrupt structurally important cysteine–cysteine disulfide bonds in the extracellular domain demonstrate a higher penetrance than the other identified mutations and are usually associated with a more aggressive disease and an increased risk of renal amyloidosis [3•]. Two other most common variants of TNFRSF1A are R92Q and P46L; however, these mutations are also encountered in about 10% of West American and 2% of Caucasian [28••, 29]. P46L seems to be a benign polymorphism, whereas R92Q behaves as a variant of incomplete penetrance and results in atypical attacks of shorter duration [3•, 29]. In contrast to previously believed mechanism as reduced cleavage of the soluble extracellular domain of TNFR1, it is now suggested that additional and alternative mechanisms such as an abnormal oligomerization and misfolding of TNFR1 leading to retention in endoplasmic reticulum (causing increased levels of ER stress response protein X box binding protein 1 together with high reactive oxygen species—ROS generation may contribute to the pro-inflammatory state), decreased TNF binding, ligand independent signaling, and reduction in TNF-induced apoptosis could be involved in the pathogenesis [3•, 30–32]. The

TNFR1 aggregates are cleared by autophagy. This process becomes defective with that much TNFR1 aggregates, resulting in the TRAPS-associated induction of nuclear factor kappa B (NF-κB), and triggers innate immunity and excessive IL-1b secretion, leading to chronic inflammation [33].

Classification Criteria

In 2015, the Paediatric Rheumatology INternational Trials Organisation (PRINTO) proposed clinical classification criteria for autoinflammatory periodic fevers. Due to these criteria, presence of periorbital edema, duration of episodes >6 days, migratory rash (centrifugal migratory, erythematous patches most typically overlying a local area of myalgia, usually on the limbs or trunk), myalgia, family history and the absence of vomiting, and aphthous stomatitis were classified as TRAPS with 59% sensitivity and 84% specificity [34••].

Diagnosis

Lachmann et al. had recently reported largest cohort of 158 adult and pediatric patients from the Eurofever/EUROTRAPS registry [28••]. The median age of onset was 4.3 years; however, 9% of the patients presented after 30 years of age. Recurrent attacks of fevers with the median duration of 10.8 days were accompanied by myalgia (85%), abdominal pain (74%), urticarial rash (63%), and ocular involvement (45%, as periorbital edema and conjunctivitis) [28••]. Lymphadenopathy, periorbital edema, and abdominal pain were more common in children. In 10% of the patients, AA amyloidosis had developed. Among sequence variant, patients with R92Q mutation presented slightly later (median age 5.7 years) with less rash and orbital manifestation and more headaches [28••].

Shinar et al. suggested to test cysteine mutations of TNFRSF1A (C30R, C33Y, D42del, T50M, C52Y, C55Y, C73W clearly pathogenic), R92Q, and P46L of TNFRSF1A (variants of uncertain significance) [17]. That is due to this guideline: If one clearly pathogenic mutation is identified, it confirms the clinical diagnosis of TRAPS, but if one variant of uncertain significance is identified, the diagnosis relies on clinical judgement or criteria. Parental testing/familial segregation may help understanding the clinical significance of this variant. If no pathogenic variant is identified, the diagnosis relies on clinical judgement or criteria because rare undetected variants and mosaicism may exist.

Interpretation of the significance of the R92Q and P46L sequence variants can be difficult. These occur at a high frequency in healthy controls, and their pathogenic significance remains unclear. Some individuals develop a clinical phenotype of TRAPS, although sometimes with shorter and/or more frequent fever episodes [8••].

Treatment and Management

These patients should also be followed carefully with the necessary clinical and laboratory workup. NSAIDs, corticosteroids, IL-1 blocking agents, and TNF blocking agents are used in the treatment of TRAPS. NSAIDs and corticosteroids are often used to control the clinical manifestations and the acute fever attacks [30]. Anti-TNF treatment with etanercept has been reported to be effective in nearly 87% of the patients in the Eurofever registry [30]. In another study, etanercept provided significant improvement in symptoms and inflammatory parameters in most patients, but its efficacy declined over time; thus, there was a need to switch to anti-IL-1 therapy [35]. Other anti-TNF agents, infliximab and adalimumab, are not recommended [8••]. Anakinra is one of the best options that was effective as on-demand as well as maintenance therapy in a study with five patients [36]. It induced complete response in 79% and partial response in 16% of the TRAPS patients in the Eurofever registry [30]. In a recent study, 19 out 20 patients responded rapidly to canakinumab and clinical benefits were sustained during long-term treatment [37].

Recent Recommendations

Recently SHARE has developed recommendations for the management and treatment of the three main periodic fever diseases. The treatment suggestions for TRAPS are as follows [8••]:

- NSAIDs may provide symptom relief during inflammatory attacks.
- Short-term glucocorticoids, with or without NSAIDs, are effective in stopping inflammatory attacks.
- The beneficial effect of corticosteroids can decline over time.
- IL-1 blockade is beneficial in the majority of patients with TRAPS.
- Etanercept can be effective in some patients, but the effect might decline over time.
- With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended to limit steroids.
- If one IL-1 blocking agent at adequate dose is ineffective or intolerable, a switch to etanercept or another IL-1 blocking agent should be considered. Similarly, if etanercept is ineffective, a switch to an IL-1 blocking agent should be considered.
- Although a beneficial effect is reported in a few cases, the use of anti-TNF monoclonal antibodies is not advised, due to the possible detrimental effect.

Cryopyrin-Associated Periodic Syndromes

Pathophysiology

Cryopyrin-associated periodic syndrome (CAPS) is associated with NLRP3 mutation, encoding cryopyrin. NLRP3 is a key protein of the NLRP3 inflammasome, which is activated by several stimuli and causes conversion of pro-IL-1 to mature IL-1 by caspase-1 activation [3•]. CAPS is inherited autosomal dominantly. The common clinical features are fever, urticarial rash, musculoskeletal symptoms, elevated acute phase reactants, and conjunctivitis. Conventionally the spectrum of the disease is separated into three disease subgroups: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome) [38–40]. However, since there may be an overlap of the mutations involved and since the borders between these three subgroups are not so clear-cut in children, there is a trend to assess CAPS patients as those with mild and severe disease.

Clinical Features and Classification

FCAS has been described to be characterized by cold-induced episodes of inflammation, associated with fever, urticaria, joint symptoms, and sometimes conjunctivitis that last <2 days. If cold is avoided, the quality of life is good in most cases [3•]. MWS, a more severe form, presents with fever, urticarial rash, and joint symptoms as well as hearing loss and eye manifestations (conjunctivitis, episcleritis) [3•]. Amyloidosis is also present in 25% of the MWS patients [40]. NOMID has been described as the most severe form and also one of the most severe monogenic AIDs. It has more chronic and persistent course [3•]. Patients display ongoing fever, continuous rash, optic disc edema, uveitis, abnormal bony overgrowth of the knees, and a variety of central nervous system (CNS) manifestations. The CNS features can vary, but include severe headaches, chronic meningitis, hydrocephalus, mental retardation, hearing loss, and lymphadenopathy. Mortality is high in untreated patients [3•, 38, 39].

Diagnosis

Recognizing the clinical manifestations is important in diagnosis. If possible, a genetic analysis should be sought. For the genetic testing of NLRP3, Shinar et al. guidelines suggest to test exon 3 with clearly pathogenic variants as R260W, D303N, L305P, E311K, T348M, L353P, A439V, and variant of unknown significance as V198M [17]. If one clearly pathogenic mutation is identified, it confirms the diagnosis of CAPS, but if one variant of uncertain significance or none is identified, the diagnosis relies on clinical judgement or criteria. Parental testing/familial segregation may help understanding the clinical significance of this variant.

On the other hand, we now know that a good portion of the CAPS patients may have mosaicism, and thus, the mutations may not be shown in routine genetic analysis. Thus if CAPS is strongly suspected, mosaicism in the CAPS gene should be sought for.

Treatment and Management

NLRP3 inflammasome and overproduction of IL-1 are the most important pathogenic mechanism underlying CAPS; thus, the mainstay of the treatment is based on anti-IL-1 drugs. Anakinra was reported to provide complete response in 64% and partial response in 34% of patients in the Eurofever project [30]. Canakinumab also induced 75% complete response and 25% partial response [30]. In another RCT, study revealed the efficacy of rilonacept for the treatment of CAPS patients. Some patients benefit from NSAIDs and corticosteroids, mostly as on-demand symptom relief; however, there is no evidence for the efficacy of disease-modifying anti-rheumatic drugs or biologic agents other than IL-1 blockers [8••, 30]. A recent warning was issued for the pneumococcal vaccine (PPV), which triggered serious local and systemic reactions in CAPS patients [41].

Monitoring these patients with routine follow-up with hearing and ophthalmological examinations as well as follow-up of well-being, functioning, and social participation is essential [8••]. Cognitive testing, lumbar puncture (pressure, cells, protein level), bone MRI, and skeletal X-ray and brain MRI (including imaging of the inner ear) may also be required.

Recent Recommendations

Treatment of CAPS according to the recent SHARE criteria is outlined as follows [8••]:

- IL-1 inhibition is indicated for the whole spectrum of CAPS, at any age.
- Long-term IL-1 inhibition should be started as early as possible to prevent organ damage.
- There is no evidence for the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) or other biological DMARDs.
- For symptomatic adjunctive therapy, short courses of NSAIDs and corticosteroids may be used, but they should not be used for primary maintenance therapy.
- In patients with CAPS, adjunctive therapy (e.g., physiotherapy, orthotic devices, hearing aids) is recommended as appropriate.

Mevalonate Kinase Deficiency/Hyperimmunoglobulinemia D and Periodic Fever Syndrome

Pathophysiology

Mevalonate kinase deficiency/hyperimmunoglobulinemia D and periodic fever syndrome (MKD/HIDS) is an autosomal recessive AID caused by mutations of the mevalonate kinase (MVK) gene which encodes MVK enzyme involved in cholesterol and isoprene biosynthesis [3•]. The disease spectrum is a continuum of two phenotypes, known as the hyperimmunoglobulinemia D and periodic fever syndrome and mevalonic aciduria [42, 43]. Besides elevation of mevalonic acid, lack of nonsterol isoprenoid end products which in turn leads to ectopic activation of small GTPases has also resulted in IL-1 increase via caspase-1 activation [44]. A role for impaired antioxidant response, mitochondrial dysfunction, and impaired autophagy (similar to TRAPS) is plausible and currently under investigation [45].

RhoA is an important protein that controls the pyrin inflammasome by activating kinases, PKN1 and PKN2, that causes phosphorylation of pyrin and blocking its effects. The deficiency in MVK function results in depletion of geranylgeranyl phosphate, which is needed for membrane targeting of RhoA. Thus inactivation of RhoA induces pyrin inflammasome activation which suggests an interesting molecular connection between FMF and HIDS [13]. On the other hand, unlike FMF, colchicine has no inhibitory effect on pyrin inflammasome activation of HIDS patients, probably because colchicine cannot activate RhoA that is not localized to cell membrane through geranylgeranylation [13].

Clinical Features and Classification

A recent report of 114 MKD/HIDS patients from the Eurofever registry has allowed us to better understand the disease features [46••]. MKD/HIDS is a disease with recurrent attacks (86% had attack-free periods, 14% had continuous disease with or without exacerbations), lasting approximately 3–6 days (median 4 days). In the aforementioned series, febrile attacks were provoked by specific triggers in 51 patients, mainly by vaccination, stress, and infection [46••]. Besides high fever, patients had lymphadenopathy (mostly cervical and tender) and gastrointestinal (abdominal pain, diarrhea, vomiting), mucocutaneous (aphthous stomatitis, painful erythematous macular, maculopapular, nodular, urticarial and morbilliform rash, pharyngitis), musculoskeletal (arthralgia, myalgia, arthritis), and neurological (headache, in severely affected patient mental retardation, cerebellar syndrome) symptoms. Five patients had AA amyloidosis and one patient had macrophage activation syndrome [46••].

Diagnosis

The onset is very early in life, with a median age of 0.5 years. Most patients have increased levels of IgD both during attacks and under basal condition. However 28% of the patients show no increase in IgD levels and the level of IgD is not related to the severity of the disease [46••, 47]. Thus the term "hyperimmunoglobulin D syndrome" is not completely appropriate [3•]. On the other hand, urinary excretion of mevalonic acid is increased in 93% of the patients during attacks and thus can be used as a diagnostic tool and biomarker of the disease [46••]. MKD/HIDS is the only AID in which a laboratory test other than genetic screening is useful [3•]. Still Shinar et al. suggested to test clearly pathogenic variants (V377I, I268T, S272F, H20P) and a variant of unknown significance (S52N) [17]. Due to 2015 PRINTO criteria, age at onset <2 years, presence of aphthous stomatitis, generalized enlargement of lymph nodes or splenomegaly, diarrhea, and absence of chest pain were classified as MKD with 53% sensitivity and 89% specificity [34••].

Treatment and Management

NSAIDs are used to treat symptomatic relief but rarely provide complete response. Attack of MKD/HIDS responds dramatically to corticosteroids and may be used on demand or continuous treatment [46••]. In a pediatric series, colchicine was not helpful in 13 out 21 patients; only one had complete response [46••]. As the mutant enzyme is involved in the cholesterol and isoprene pathway, statins have been used in the treatment. However there was no response in a trial of 15 patients; in 11 patients, treatment failed; moreover, three of them reported worsening of the disease [46••]. Anakinra was effective in 24 (89%) of 27 treated patients, inducing complete response in six patients (22%) [30, 46••]. Etanercept was effective in 16 (59%) of the 27 treated patients, with only two complete responses [46••]. In selected cases with severe refractory disease, allogeneic hematopoietic stem cell transplantation could be an option [48–50]. SHARE recommendations for the managements and monitoring of MKD/HIDS suggest routine follow-up with clinical and laboratory follow-up of these patients and specific neurological examination and muscle and liver enzyme testing in patients with more severe phenotypes [8••]:

Besides infections, physicians should also be alert to the possibility of macrophage activation syndrome in patients with MKD/HIDS.

Recent Recommendations

Treatment of MKD/HIDS according to the aforementioned SHARE recommendations is as follows [8••]:

- NSAIDs may provide symptom relief during inflammatory attacks.

- Short-term glucocorticoids, with or without NSAIDs, may be effective for suppressing inflammatory attacks.
- Colchicine or statins are not efficacious; therefore, we do not recommend their use.
- Short-term IL-1 blockade may be effective for terminating inflammatory attacks and should be considered to limit or prevent steroid side effects.
- With frequent attacks and/or subclinical inflammation between attacks, maintenance therapy with IL-1 blockade or etanercept is recommended.
- If one IL-1 blocking agent at adequate dose is ineffective or intolerable, a switch to another IL-1 blocking agent or another biological agent (including TNF-α blockade or IL-6 blockade) should be considered. Likewise, if TNF-α blockade is ineffective or intolerable, a switch to another biological agent should be considered.
- In selected cases with severe refractory disease with poor quality of life, consideration of allogeneic hematopoietic stem cell transplantation is recommended.

Conclusion

In a child presenting with fever, a large spectrum of diseases needs to be considered from infections to malignancy. However, the pediatrician and especially the pediatric rheumatologist should be aware of the features of AIDs and be able to take the correct measures for the diagnosis and management of the patient.

Compliance with Ethical Standards

Conflict of Interest Dr. Ozen reports personal fees NOVARTIS, SOBI, and R-PHARM, outside the submitted work.

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- • Of importance
- •• Of major importance

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