

Invited Review Article

Autoinflammatory Diseases in Childhood

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Autoinflammatory diseases are characterized by recurrent fever attacks and clinical findings that arise from impaired natural immunity and spread to a wide variety of organ systems. The concept of autoinflammatory disease emerged after the definition of familial Mediterranean fever (FMF) and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS). Firstly, it is thought that this new group differs from the standard concept of autoimmune diseases, which is relatively better known in terms of basic features such as defects in innate immunity and the absence of antibodies. We have come a long way in understanding the genetic and pathogenetic mechanisms of this relatively new disease group in the past twenty years since they were first diagnosed. This growing understanding leads to some changes in the concept of autoinflammatory diseases. Recently, the definition of the autoinflammatory disease includes a wide range of diseases with different clinical features, mainly accompanied by changes in innate immune and rarely in humoral immunity. Owing to recent developments in molecular sciences and genetics, the spectrum of autoinflammatory diseases is rapidly expanding. In this review, clinical features, classification criteria, treatment options and long-term prognoses of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome, and other common autoinflammatory diseases are discussed in the light of current literature.

Keywords: Autoinflammatory diseases, CAPS, childhood, familial Mediterranean fever, FMF, TRAPS

Autoinflammatory diseases are a group of diseases that arise due to dysfunction or dysregulation in innate immunity and can cause serious morbidity and mortality by affecting multiple organ systems. This new group differs from the standard concept of autoimmune diseases, which is relatively better known in terms of basic features such as defects in innate immunity and absence of antibodies circulating in the bloodstream. The concept of autoinflammatory disease emerged after the definition of familial Mediterranean fever (FMF). Owing to recent developments in molecular sciences and genetics, the spectrum of autoinflammatory diseases is rapidly expanding.

Definition and the concept of autoinflammation:

To date, many definitions have been proposed to describe this group of rare diseases (1). The term of "autoinflammatory diseases" was firstly described by the National Institutes of Health (NIH) group as systemic diseases characterized by non-provoking attacks, without high-titrating antibodies and antigen-specific T lymphocytes (2). In 2010, Kastner et al. (3) defined autoinflammatory disease as "clinical disorders marked by abnormally increased inflammation, mediated predominantly by cells and molecules of the innate immune system, with a significant host predisposition". In 2017, Wekell et al. (4) modified this definition as "Autoinflammatory diseases are immunological diseases defined by abnormally increased inflammation, driven by dysregulation of molecules and cells of the innate immune system with a host predisposition as necessary and sufficient criteria, frequently associated with activation of the adaptive immune system and potentially with immune dysfunctions such as susceptibility to infections, autoimmunity or uncontrolled hyperinflammation". Finally, in 2018, the Paediatric Rheumatology International Trials Organization (PRINTO) defined autoinflammatory diseases as "clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants) and the lack of a primary pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)"(1).

The change in the definition of the disease reflects the expansion of the spectrum and the classification of new diseases under this group. Recently, the definition of the autoinflammatory disease includes a wide range of diseases including different clinical features, mainly accompanied by changes in innate immune and rarely in humoral immunity. Diseases classified under the group of autoinflammatory diseases today are summarized in **Table 1**. In this review, clinical features, classification criteria, treatment options and long-term prognoses of Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome and other common autoinflammatory diseases are discussed.

Approach to the patient with suspected autoinflammatory disease:

Fever is one of the most common reasons for hospital admission in childhood and infections are the leading cause of fever in children. The initial step of evaluation of a child with fever is the definition of fever and its characteristics. It should be kept in mind that the parents can subjectively exaggerate the symptoms and if the parents complain about recurrent fever episodes, a fever diary that is filled objectively should be requested. Fever diary is a useful tool for assessing whether it is really a fever and for identification of fever patterns like periodic, recurrent or prolonged.

In the case of recurrent or periodic fever, a detailed medical histories of the patients and the families should be taken, and cautious physical examination should be performed. Since, autoinflammatory diseases are rare, the other possible reasons of periodic/ recurrent fever like recurrent infections, malignancies, immunodeficiencies like cyclic neutropenia should be considered as well. Additionally, fever can be a sign of Munchausen by Proxy syndrome and physicians should be vigilant in every child with recurrent fever in this regard. While developmental delay, growth restriction and history of hospitalization for severe infections primarily suggest possible immunodeficiency; night sweats, night pains, weight loss, generalized lymphadenopathy or hepatosplenomegaly suggest malignancies first. On the other hand, signs and symptoms suggest autoinflammatory diseases are; having normal development and growth pattern, being asymptomatic between episodes, having positive family history, and having similar episodes before. A diagnostic approach algorithm is shown in **Figure 1**.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome is one of the most common periodic fever syndromes observed in childhood (5). The etiology and genetic basis of this unique disease is still unclear (6). In the literature, there is a common misuse of nomenclature of the diseases with recurrent or periodic fever. Most of the authors classify the autoinflammatory diseases under an umbrella of periodic fever, although most of these diseases have recurrent fever rather than periodic fever. The most important exception of this is PFAPA syndrome. The episodes of PFAPA syndrome have usually perfect periodicity that allows families to predict when will the next episodes come.

The genetic background of the disease is still an important topic of discussion and research. Although the high rate of positive family history in patients with PFAPA syndrome reported in the literature suggests the possible genetic transmission, Di Gioia et al. (7) could not find a causative gene by whole-exome sequencing studies and they suggested that PFAPA is related to oligogenic or complex inheritance of various genetic and non-genetic factors (8-10). The relationship between PFAPA syndrome and genes of the other autoinflammatory diseases is another topic of interest. Patients with underlying pathogenic variants of the other autoinflammatory diseases tend to have an atypical presentation of PFAPA syndrome (11, 12). There are studies reporting the increased frequency of MEFV mutations in patients with PFAPA syndrome in the literature. The frequency of the MEFV mutations in patients with PFAPA syndrome is reported to be 8-66% (8, 12-15). It is reported that PFAPA patients with MEFV mutations have a shorter episodes, longer intervals between episodes and need lower doses of corticosteroid for a cessation of the attacks (16-18). In contrast, Pehlivan et al. (15) found that patients with PFAPA syndrome, who have underlying MEFV mutations, have more severe clinical course.

Despite the sporadic reports of adult cases, the disease is usually seen in children younger than five years age (5). Periodic fever is the most prominent finding of the disease. The fever is usually accompanied with aphthous stomatitis, pharyngitis and adenitis. The episodes usually end within a week and recur every 2-8 weeks (11). The early disease episodes usually have a perfect periodicity that allow families to predict when will next episodes come. The periodicity of the episodes usually disappears during the course of the disease, the attack-free intervals become longer and finally episodes usually cease 3-5 years after the disease onset (5, 11). There is usually no development and growth delay in children with PFAPA syndrome. Fever in PFAPA syndrome can be as high as 39-40 °C, and it is usually not responsive to antipyretics. Despite the high fever, children do not appear ill and this is a useful clue for the PFAPA. Exudative tonsillopharyngitis/cryptic tonsillitis is another important finding of the disease and it is usually combined with aphthous stomatitis. Oral findings of the disease usually rapidly disappear within a day after a single dose of steroids. Cervical lymphadenitis is also commonly seen in disease attacks and is usually bilateral and tender (5). As, large cervical lymphadenitis is also one of the clinical findings of the hyper Immunglobulin D syndrome, the other autoinflammatory disease; sometimes HIDS is misdiagnosed as PFAPA syndrome. Therefore, HIDS should also be considered in PFAPA patients

unresponsive to tonsillectomy. Abdominal pain, arthralgia, myalgia and headache are rarely reported in disease episodes (11).

The diagnosis of PFAPA is made based on clinical findings. The most commonly used diagnostic criteria for PFAPA syndrome are modified Marshall's criteria (19). According to these criteria, regularly recurring fever with early onset (<5 years), absence of cyclic neutropenia, being completely asymptomatic between episodes, normal development and growth and at least one of the following three criteria: aphthous stomatitis, cervical lymphadenitis, pharyngitis, are needed for the diagnosis (19). In 2018, Vanoni et al. (20) proposed the new sets of classification criteria for PFAPA syndrome. The sensitivity and specificity of these new set of criteria were reported as 89.7% and 69.5% by Adrovic et al. (21) and they suggested that these newly proposed criteria are not sufficient enough for distinguishing FMF from PFAPA syndrome, especially in regions endemic for FMF. Eurofever/PRINTO suggested new sets of classification criteria for PFAPA syndrome with sensitivity of 97% and specificity of 93%(22). The diagnostic/classification criteria for PFAPA are shown in Table 2.

Although PFAPA syndrome is a benign condition and it usually ends spontaneously after 5 years of age, the recurrent episodes exhaust the families and children and lead them to seek treatment options for the disease. There are only a few drugs with proven efficacy for treatment of the PFAPA syndrome. Colchicine, cimetidine, vitamin D, anti-IL1 therapy and tonsillectomy are the recommended treatment options for the disease (23). Although steroids are highly effective for terminating the episodes, it is shown that using steroids shortens the intervals between fever attacks (23). Bearing on mind possible side effects of the steroid treatment, steroids should be considered as diagnostic test. It is shown that colchicine is effective for reducing the frequency of the episodes and this effect is more prominent in patients with MEFV mutation (11, 14, 15). Therefore, colchicine should be considered in certain percent of PFAPA patients, especially those in regions endemic for FMF, before tonsillectomy is performed. Another treatment option for PFAPA syndrome is a tonsillectomy. The efficacy of tonsillectomy is reported as %92 in the literature (11). As PFAPA syndrome is a benign condition, tonsillectomy should be discussed in detail with the family before a decision is made.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease with an autosomal recessive inheritance pattern, characterized by recurrent fever attacks and polyserositis (24, 25). The disease is most frequently seen in communities living in the Mediterranean basin and the highest prevalence has been reported among Sephardic Jews, Armenians, Turks, and Arabs(26).

MEDiterranean FeVer gene (MEFV) encoding pyrin protein is the causative gene of the disease (27). Although, the classical inheritance pattern of the disease is autosomal recessive, a vertical inheritance pattern has also been reported resembling to pseudo-dominant inheritance in some families from regions with high carrier frequency for MEFV gene variants (28). The carrier frequency rate was reported as about 1/6 among Sephardic Jewish, 1/5 among Armenian, and 1/8-1/5 among Turkish people. So far, 374 variants have been identified in this gene[<https://infevers.umai-montpellier.fr/web/>](29). The most common disease-causing mutations are M694V, V726A, M694I, M680I located in exon 10 (30). It is well-known that, unlike the other disease with autosomal recessive inheritance, the classical FMF phenotype can be seen in patients carrying only 1 MEFV mutation and even in patients without MEFV mutations. Therefore, the role of gene analysis in diagnosis is limited and it is usually used for predicting the prognosis and/or course of the disease. It is reported that patients with homozygous M694V mutations have severe disease and an increased risk of amyloidosis(24).

In majority of patients, the disease appears in childhood and the first disease episode usually occurs in the first 10 years of life (31). The mean age of the disease onset was reported to be 3-9 years (24). It is characterized by fever and an abdominal pain episode resembling acute abdomen. Contrary to the nomenclature that named these diseases as periodic fever syndromes, it is more accurate to define the disease episodes as recurrent instead of periodic (24). More or less, the episodes usually cease within 72 hours. Although the apparent prodromal period was reported in adult patients, episodes in children usually start suddenly, without any prodromal findings, and end spontaneously in children (25, 32). This contrast may be due to the fact that young children cannot express their pre-attack symptoms, and the prodromal period may be an overlooked finding of the disease in children (25). In spite of various types of disease episodes, the most commonly observed clinical phenotype is the coexistence of fever, abdominal pain and articular findings.

Fever is one of the most commonly reported findings of the disease (33). While it can be only finding of the episodes, it is often accompanied by at least one of the other findings. Another important finding of the disease is severe abdominal pain resembling an acute abdomen (34). Since abdominal pain is very severe, most of the patients are misdiagnosed as acute appendicitis during attacks and appendectomy is performed before the FMF is diagnosed (34). The reason of abdominal pain is aseptic serositis and it is also responsible for chest pain that can be caused by pericarditis or pleuritis (34). Another common finding of the disease is articular involvement and it can be only presentation of the disease. Typical articular involvement of the disease is a non-erosive, non-migratory mono/oligoarthritis of lower extremities that resolves spontaneously within a week. Chronic arthritis has been reported in 2-5% of patients (24). The erythematous rash can be seen over involved joint, and this unique sign is named as "red arthritis"(24). Seronegative sacroiliitis has also been reported in patients with FMF

(33, 35). The most common skin finding of FMF is erysipelas-like erythema that is usually seen on dorsum of the foot (24) (**Figure 2A**). Orchitis and aseptic meningitis have also been reported in FMF (24). Myalgia is another important symptom of the disease that is a frequent complaint of the patients with FMF (24). Apart from being the presenting symptom of FMF, myalgia can also be a sign of protracted febrile myalgia. It is a rare vasculitic manifestation of the disease, which is characterized by symmetric severe muscle pain, tenderness, elevated acute phase reactants, normal levels of muscle enzyme, excellent response to steroid and absence of articular findings (36).

Except for protracted febrile myalgia, a unique vasculitic manifestation, it is also well-known that the frequency of the other vasculitis such as Henoch Schoenlein purpura, polyarthritis nodosa, Behçet's syndrome and even some of the other inflammatory diseases such as juvenile idiopathic arthritis, psoriasis, inflammatory bowel diseases are increased in patients with FMF (37, 38).

The diagnosis of FMF is made based on clinical findings. Mutation testing is not required in all suspected patients. As mentioned earlier, knowing the genotypes of MEFV mutations is useful for taking an insight into the course and prognosis of the disease. Since the FMF represents the oldest autoinflammatory disease, many classification and/or diagnostic criteria have been suggested. The most commonly known and used ones are Tel Hashomer and Yalcinkaya-Ozen criteria (39, 40). According to Yalcinkaya-Ozen criteria; at least two of the following five criteria is needed for diagnosis: fever, abdominal pain, chest pain, oligoarthritis and positive family history for FMF. The mentioned clinical symptoms should be observed at least 3 times and should last between 6-72 hour to be considered as a criterion (39). Recently, the new two sets of classification criteria (combined and only clinical) were proposed by PRINTO (Table 3)(22). The main difference between this new criteria and earlier one is genotype of the patients being included. Sag et al. reported that this new set of criteria is more sensitive (96%) and less specific (73.1%) than Tel-Hashomer and Yalcinkaya-Ozen criteria(41).

The main aim of the treatment is to prevent amyloidosis, as the most important complication of the disease. The mainstay of FMF treatment is colchicine. Colchicine was firstly shown to be effective in FMF by Emir Ozkan and then Goldfinger (42, 43). The recommended dose is 0.5 mg (or 1 mg) for children under 5 years old, 0.5-1 mg for children between 5-10 years old and 1-1.5 mg for children older than 10 years old. The maximum dose of colchicine for children is 2 mg per day. If the episodes cannot be controlled by 2mg colchicine per day, it should be checked whether there is a drug compliance problem. Another treatment options like biologic agents should be considered in patients unresponsive to maximum tolerable dose of colchicine, in order to prevent amyloidosis. Although there are many definitions of colchicine resistant FMF in the literature, according to the most used one, colchicine resistance can be defined as three or more attacks in 6 months or, six or more attacks per year, despite the appropriate drug compliance (44). In our daily practice, we observed that some of the patients benefit from changing the brand of colchicine in the case of colchicine resistance and this approach sometimes helps also to get rid of the colchicine side effects like diarrhea. In a recent study, Emmungil et al. (45). Showed that adult patients who are not responsive to domestic coated colchicine tablets can benefit from compressed colchicine preparations. Although there is not enough evidence for this approach in children, it may be cost-effective and logical to try another brand of colchicine before the biologic agents are started. In the case of colchicine resistant disease, anti-IL1 agents like anakinra, canakinumab are recommended (46, 47).

Hyper Immunoglobulin D syndrome (HIDS) or Mevalonate kinase deficiency (MKD)

Hyper Immunoglobulin D syndrome is an autosomal recessive autoinflammatory disease. It is caused by mutations in MVK gene which encodes mevalonate kinase that is an enzyme takes a role in cholesterol biosynthesis (48). Among about 100 described mutations in MVK gene, V377I has been reported as the most common variant (49). Mutations in MVK lead to a decrease in the downstream product of the mevalonate kinase pathway, resulting in IL-1 β secretion and resulting autoinflammation (50).

Disease severity is highly correlated with remaining enzymatic function (51). Whereas in MVK/HIDS, MVK enzyme activity is reduced to 1-8% of normal, in mevalonic aciduria (MA) this activity is below 1% (52).

MVK/HIDS is milder condition, characterized by febrile episodes, combined with nonspecific skin rashes, cervical lymphadenitis, arthritis/arthralgia and severe gastrointestinal complaints, sometimes provoked by vaccination or infections (Figure 2C) (53). Episodes usually last 3-7 days and recur every 4-6 weeks (54).

Frequency and severity of episodes are tended to decrease by age (55). Contradictory to the nomenclature of the disease, 28% of patients do not have elevated immunoglobulin D levels (48). MA course is more severe, characterized by episodes similar to those in MKD/HIDS, but with chronic disease course (56). Additionally, mental retardation, dysmorphic features and failure to thrive can also be rarely seen in MA (57).

According to recently proposed classification criteria, presence of pathogenic (or likely pathogenic) MVK variants (homozygous or in trans compound heterozygous) and at least one of the following symptoms are needed: gastrointestinal symptoms, cervical lymphadenitis and aphthous stomatitis (22) (Table 4). The sensitivity and specificity of new criteria is reported as 98% and 100%(22).

Corticosteroids have been shown effective to reduce symptoms, particularly during episodes (58). If steroids are unable to suppress the flares, treatment with a biological agent such as anti-IL-1 agents or anti TNF agents should be considered (59, 60).

Tumor Necrosis Factor Receptor Associated Periodic Syndrome

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome (TRAPS) is an autoinflammatory disease with periodic fever, musculoskeletal symptoms, skin changes and eye findings (61). Although its exact prevalence is unknown, it is thought to be the most common autoinflammatory disease with an autosomal dominant inheritance pattern (34, 62).

The causative gene of the disease is “*TNF Receptor Super Family 1A (TNFRSF1A)*” that is located on chromosome 12 (63-65). Most of the disease-related genes are located on exon 2, 3, 4 and one hundred and sixty-seven sequence variants have been identified so far [<https://infevers.umai-montpellier.fr/web/>](29). Mutations of the *TNF Receptor Super Family 1A* gene are divided into two main groups: structural and non-structural mutations. Structural mutations, especially in which cysteine bonds are affected, are reported to be associated with more severe disease and increased risk for amyloidosis (61-63, 66). The most common mutations detected in patients with TRAPS are T50M and T50K related to hydrogen-bonds (67). Mutations in which cysteine bonds are affected like C29S, C29Y, C29F, C29G, C29R, C30F, C30Y, C30S, C30R, C33G, C33Y and in which proline residues are affected such as P46L, L67P, S86P, R92P are another important example of the structural mutations (61, 62, 67). It is reported that R92Q and P46L mutations, which are among the non-structural mutations, are frequently seen in healthy individuals, therefore their pathogenic significance is still controversial (6, 61, 67). Patients with these mutations can develop clinical findings consistent with TRAPS but have a milder clinical course than patients with structural mutations (6, 47).

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome can affect most of the organ systems and has highly variable clinical findings. The most prominent finding of the disease is recurrent fever attacks that usually last 1 to 3 weeks and recur every six weeks (68). Duration of the disease attacks is usually longer than the other autoinflammatory diseases and a persistent inflammatory course with intermittent flares is reported in some patients (34). Episodes of the disease usually start with muscle cramps and/or myalgia, followed by fever, skin rash, arthralgia, arthritis and findings of the eye involvement. The most commonly reported skin rash is a migratory, centripetal and erythematous rash (69). Rashes are usually detected on the muscle group that the myalgia arises from. Migratory myalgia is one of the most important clues for the disease and is reported to be detected in majority of patients (62). Findings of ocular involvement like ocular pain, conjunctivitis, optic neuritis, uveitis can be seen. Periorbital edema is pathognomonic for TRAPS and in every patient with periodic fever should be questioned (61, 62) (Figure 2B). Polyserositis is another well-defined finding of the disease and it can be only disease presentation (70-72). It can cause severe abdominal and thoracic pain (70, 71). Recurrent pericarditis was also reported as the only finding of some patients with TRAPS in the literature (72).

Additionally, non-erosive mono/oligo arthritis, sacroiliitis, headache, scrotal pain, urethral stricture and behavior changes can also be seen (62, 73, 74).

As in the other autoinflammatory disease, the most important complication of the disease is amyloidosis. It is reported that the risk of amyloidosis increases, especially in the presence of structural mutations that affect cysteine residues (75).

The most recently proposed classification criteria for TRAPS is Eurofever/PRINTO criteria (22) (Table 5). In that study, researchers suggested two sets of criteria. While one of them consists only of clinical criteria, other has genetic and clinical issues. The sensitivity and specificity of new criteria is reported as 95% and 99% (22). The main purpose of the disease treatment is to control the disease activity as quickly as possible, to prevent the illness and treatment-related damages and to increase the quality of life of the patients (47). Although nonsteroidal anti-inflammatory drugs (NSAID) have some symptomatic benefits in the vast majority of patients, they often fail to cease the attacks (34). Steroids are generally successful in terminating attacks when used at a dose of 0.5-1mg / kg, but in most patients their efficacy decreases over time and their long-term use is not recommended due to their serious side effects (34, 47). Moreover, steroids are reported not to prevent amyloidosis, and often relapse is reported after cessation (76). Ter Haar et al. reported that patients with R92Q mutation respond better to NSAIDs and colchicine. In the light of this information, it may be a logical strategy to try NSAIDs and steroids in patients with mild clinical findings, if needed, for a short period of time. Etanercept has been shown to be effective in preventing attacks and reducing steroid dose in some of the patients with TRAPS (62, 77). The effectiveness of etanercept treatment decreases over time and generally another biological agent is needed in the process (76). Other anti-TNF agents, such as infliximab, adalimumab, have been shown to be ineffective in treatment and can paradoxically increase attacks (76). Another group of drugs used in the treatment of TRAPS are anti-IL1 agents. Anakinra and canakinumab have been shown to be effective in both ending and preventing attacks (78, 79).

Cryopyrin Associated Periodic Syndrome

Cryopyrin Associated Periodic Syndrome (CAPS) is an autoinflammatory disease with well-defined three subtypes named as: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and Chronic Infantile Neurological, Cutaneous and Articular (CINCA)/Neonatal Onset Multisystem Inflammatory disease (NOMID) (80). These three subtypes are thought to be a spectrum of a disease instead of separate ones.

Some authors suggest that the name of the disease should be changed as “NLRP3 Associated Autoinflammatory Diseases” which reflects the responsible gene and covers all the three sub-types(6, 80).

Gain of function mutations are responsible of CAPS in *NLRP3(CIAS1)* gene encoding cryopyrin protein (81). So far, 230 sequence variants have been identified in this gene[<https://infefers.umai-montpellier.fr/web/>](29). Most of the diseases causing mutations are located in 3th exon of the gene. In **Figure 3**, mutations classified as pathogenic by Infefers database and related phenotypes are shown. Somatic mosaicism was reported in some patients with clinical findings consistent with CAPS but none of the mutations was shown (82, 83). Therefore, it should be kept in mind that the absence of the NLRP3 gene mutation in patients with a strong suspicion of CAPS will not exclude the diagnosis, and if necessary, patients should be evaluated in terms of somatic mosaicism.

All of the 3 subtypes of the disease reflect the disease’s different levels of severity and have both common and unique findings. Fever, flu-like symptoms, rashes, ocular and central nervous system involvement can be seen in all of the subtypes (80, 84). Disease episodes usually start with fever, fatigue and flu-like non-specific findings.

While the episodes usually end within a day in FCAS, it can continue three or more days in MWS and CINCA/NOMID. Furthermore, in CINCA/NOMID, a persistent inflammatory course with intermittent flares is also reported in some patients (80). Skin rashes are usually the first and prominent finding of the disease.

Although, urticaria is the most common skin finding, erythematous rash, edematous papule and plaque like skin changes can be seen (Figure 2D). The histopathological evaluation of the urticaria like rashes, showing the absence of mast cells is thought these rashes are not real urticarial (85).

Musculoskeletal findings are another important sign of the disease. While pain in the extremities, myalgia and arthralgia can be seen in all forms of the disease, arthritis is usually seen in MWS and CINCA/NOMID and can be erosive in patients with CINCA/NOMID (84, 86). Rarely, patients can develop bone deformities due to uncontrolled growth of the patella, articular cartilage or epiphysis of long bones and this abnormal bone formation is unresponsive to anti-IL1 treatment unlike other symptoms of the disease (84).

Progressive hearing loss is one of the main findings in patients with MWS and CINCA / NOMID but can be prevented and even partially regressed with timely treatment (34, 84). Like the other symptoms of the disease, severity of the findings of the ocular involvement increases from FCAS to CINCA/NOMID. Uveitis, papilledema and optic atrophy have been reported in CINCA / NOMID and rarely in MWS(80, 84, 87, 88).

Central nervous systemic involvement is an important cause of morbidity. Kılıç et al. (89), reported that central nervous system involvement was detected in 50% of their patients with CAPS. The mildest form of central nervous system involvement is a headache and it can be seen in all subtypes of the disease. Aseptic meningitis and increased intracranial pressure are among the common findings in patients with CINCA / NOMID(84).

Chronic leptomenigeal inflammation can cause adhesions and hydrocephalus(89). Developmental retardation, seizures, stroke, and vascular occlusions are other central nervous system findings of the disease (84).

Although, various classification criteria for CAPS have been proposed, the most recent one is Eurofever/PRINTO criteria(22) (Table 6). The sensitivity and specificity of these criteria were both reported as %100(22).

As in all the other autoinflammatory diseases, the main purpose of the disease treatment is to control the disease activity as quickly as possible, to prevent the illness and treatment-related damages and to increase the quality of life of the patients (47).

Since the increase of IL-1 is the main cytokine in the pathogenesis of the disease, the appropriate treatment approach is to antagonize the effect of IL-1(47, 80, 84). Anakinra, canakinumab and riloncept were all shown to be affective in patients with CAPS in various studies(84, 90-93).

In conclusion, the number of autoinflammatory diseases is increasing day by day. These groups of diseases should be considered in the presence of skin and musculoskeletal system findings accompanying periodic or recurrent fever in childhood. The diagnostic algorithm for suspected autoinflammatory diseases according to clinical findings are summarized in Figure 1. While clinical findings of this diseases are so variable, the detection of pathogenic mutations strengthens diagnosis and treatment approaches(94). Since the majority of this group of diseases are associated with the interleukin-1 pathway, anti-IL1 treatment is highly effective in most of them.

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Table 1. Classification of the autoinflammatory diseases based on the pathogenesis.

•	Interleukin-1 regulation defects
○	Periodic fever syndromes
▪	<i>Familial Mediterranean Fever</i>
▪	<i>Mevalonate Kinase Deficiency/Hyperimmunoglobulin D (HIDS) syndrome</i>
▪	<i>Cryopyrin Associated Periodic (CAPS) Syndrome</i>
○	Pustular skin rashes
▪	Inflammatory bone disease
•	<i>Majeed diseases</i>
▪	Pyogenic arthritis
•	<i>Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) syndrome</i>
•	<i>Deficiency of IL-1 Receptor Antagonist (DIRA) syndrome</i>
•	Related to NF-KB activation
○	Granulomatous skin lesions
▪	<i>Blau syndrome</i>
○	Neutrophilic urticaria
▪	<i>Familial Cold Autoinflammatory (FCAS) syndrome</i>
•	Protein-misfolding disorders
○	<i>Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)</i>
•	IL-36 regulation defect
○	<i>Deficiency of IL-36 Receptor Antagonist</i>
•	Unknown
○	<i>Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) syndrome</i>

- **Syndromes caused by interferonopathy**
- *Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy (JMP)*
- *Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)*
- *Nakajo-Nishimura syndrome*
- *Aicardi-Goutières syndrome*
- **Syndromes with immunodeficiency**
- *Deficiency of Adenosine Deaminase 2 (DADA2) syndrome*
- *PLCG2 associated antibody deficiency and immune dysregulation (PLAID)*
- *Autoinflammation, antibody deficiency, and immune dysregulation (APLAID)*
- *HOIL-1 deficiency*

Uncorrected proof

Table 2. The proposed classification criteria for Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis syndrome

Modified Marshall's Criteria(19)	Criteria by Vanoni et al.(20)	Eurofever/PRINTO criteria(22)
<ul style="list-style-type: none"> • Recurring fever with regular intervals (onset <5 years of age) • Constitutional symptoms with 1 of following 3: <ul style="list-style-type: none"> ○ Aphthous stomatitis ○ Cervical Lymphadenitis ○ Pharyngitis • Absence of cyclic neutropenia • Asymptomatic intervals between episodes • Absence of developmental delay or growth restriction 	<ul style="list-style-type: none"> • Periodic fever for at least 6 months: <ul style="list-style-type: none"> ○ Daily fever of 38.5°C for 2-7 days ○ At least 5 fever attacks with regular intervals (maximum of 2 months) • Pharyngitis, cervical adenitis, oral aphthae: at least one in every episode and at least two in the most of episodes. • Exclusion of other causes of recurrent fever • Exclusion of infections, immunodeficiency, cyclic neutrophilia • Disease onset <6 years • Being asymptomatic between episodes • Normal growth 	<p>At least seven of eight:</p> <p>Presence of:</p> <ul style="list-style-type: none"> • Pharyngotonsillitis • 3-6 days long episodes • Cervical lymphadenitis • Periodicity <p>Absence of:</p> <ul style="list-style-type: none"> • Diarrhea • Chest pain • Skin rash • Arthritis

Table 3. Eurofever/PRINTO classification criteria for Familial Mediterranean Fever (22)

Classification Criteria	Clinical Classification Criteria
<p>Presence of pathogenic (or likely pathogenic) MEFV variants (homozygous or in trans (or biallelic) compound heterozygous) and at least one of the following:</p> <ul style="list-style-type: none"> • 1-3 days long attacks • Arthritis • Chest pain • Abdominal pain <p>OR</p> <p>Presence of in trans compound heterozygous for one pathogenic MEFV variants and one variant of uncertain significance (VUS) or biallelic VUS or heterozygous for one pathogenic MEFV variant and at least two of the following:</p> <ul style="list-style-type: none"> • 1-3 days long attacks • Arthritis • Chest pain • Abdominal pain 	<p>At least six of nine:</p> <p>Presence of:</p> <ul style="list-style-type: none"> • Eastern Mediterranean Ethnicity • 1-3 days long attacks • Chest pain • Abdominal pain • Arthritis <p>Absence of:</p> <ul style="list-style-type: none"> • Aphthous stomatitis • Urticaria • Maculopapular rash • Painful lymphadenopathy
*Adopted from reference (22)	

Table 4. Eurofever/PRINTO Hyper Immunoglobulin D Syndrome classification criteria (22)	
Classification Criteria	Clinical Classification Criteria
<p>Presence of pathogenic (or likely pathogenic) MVK variants (homozygous or in trans (or biallelic) compound heterozygous) and at least one of the following:</p> <ul style="list-style-type: none"> • Gastrointestinal symptoms • Cervical lymph nodes • Aphthous stomatitis 	<p>Presence of at least three of six:</p> <ul style="list-style-type: none"> • Onset < 1 year of age • Gastrointestinal symptoms • Painful lymphadenopathy • Aphthous stomatitis • Triggers • Maculopapular rash
*Adapted from reference (22)	

Table 5. Eurofever/PRINTO Tumor Necrosis Factor Receptor–Associated Periodic Syndrome classification criteria (22)	
Classification Criteria	Clinical Classification Criteria
<p>Presence of pathogenic (or likely pathogenic) TNFRSF1A variants (heterozygotes) and at least one of the following:</p> <ul style="list-style-type: none"> • Duration of episodes ≥ 7 days • Myalgia • Migratory Rash • Periorbital Edema • Relatives affected <p>OR</p> <p>Presence of variant of uncertain significance (VUS) of TNFRSF1A and at least 2 of the following:</p> <ul style="list-style-type: none"> • Duration of episodes ≥ 7 days • Myalgia • Migratory Rash • Periorbital Edema • Relatives affected 	<p>Score ≥ 5 points:</p> <p>Presence of</p> <ul style="list-style-type: none"> • Fever ≥ 7 days (2 points) • Fever 5-6 days (1 point) • Migratory Rash (1 point) • Periorbital Edema (1 point) • Myalgia (1 point) • Positive Family History (1 point) <p>Absence of:</p> <ul style="list-style-type: none"> • Aphthous stomatitis (1 point) • Pharyngotonsillitis (1 point)
*Adapted from reference (22)	

Table 6. Eurofever/PRINTO classification criteria Cryopyrin Associated Periodic Syndrome (22)	
Classification Criteria	Clinical Classification Criteria*
<p>Presence of pathogenic (or likely pathogenic) <i>NLRP3</i> variants (heterozygotes) and at least one of the following:</p> <ul style="list-style-type: none"> • Urticarial Rash • Red eye (conjunctivitis, episcleritis, uveitis) • Neurosensorial hearing loss <p>OR</p> <p>Presence of variant of uncertain significance (VUS) of <i>NLRP3</i> gene and at least 2 of the following:</p> <ul style="list-style-type: none"> • Urticarial Rash • Red eye (conjunctivitis, episcleritis, uveitis) • Neurosensorial hearing loss 	<p>Presence of at least two of five:</p> <ul style="list-style-type: none"> • Urticarial Rash • Cold/Stress triggered episodes • Sensorineural hearing loss • Chronic aseptic meningitis • Skeletal abnormalities (epiphysial overgrowth/frontal bossing) <p>Absence of:</p> <ul style="list-style-type: none"> • Aphthous stomatitis (1 point) • Pharyngotonsillitis (1 point)
<p>*Modified version of the classification criteria by Kuemmerle -Deschner et al.(95) **Adapted from reference (22)</p>	

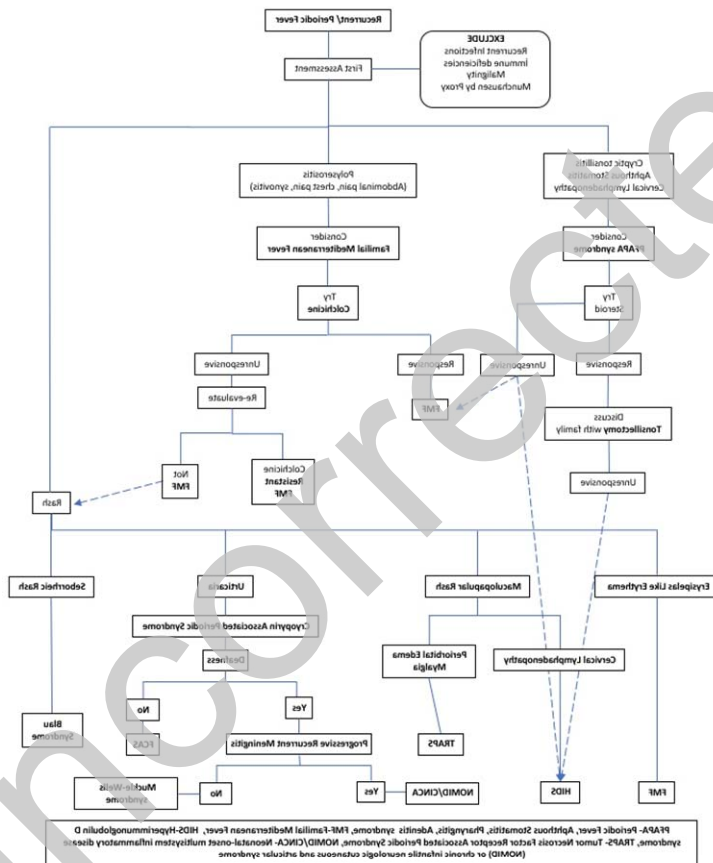


FIG. 1. Diagnostic approach algorithm to child with recurrent fever



FIG. 2. Skin findings of the autoinflammatory diseases. A) Erysipelas-like erythema B) Periorbital Edema C) Cervical lymphadenopathy in patients with Hyper Immunoglobulin D Syndrome D) Urticarial rash in patients with familial cold autoinflammatory syndrome.

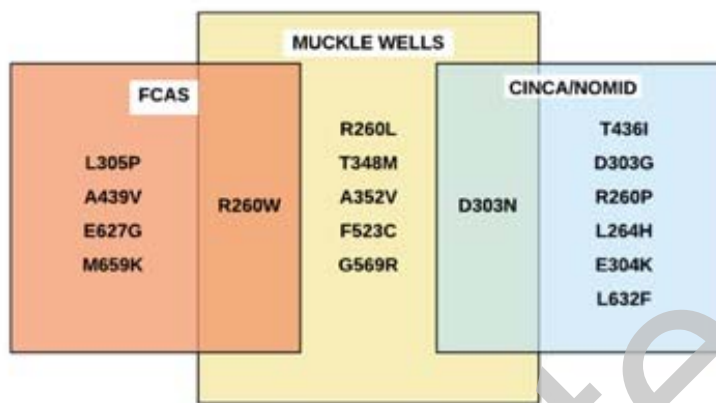


FIG. 3. Pathogenic *NLRP3* gene variants according to Infevers database (29) and related phenotypes.