Chapter 16
Autoinflammatory Diseases

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High-Yield Review of Autoinflammatory Diseases
Key Points on Autoinflammatory Diseases

- Autoinflammatory diseases are a genetically heterogeneous group of rheumatic inflammatory diseases and are driven by abnormal activation of the innate immune system.
- Autoinflammatory diseases are distinct from systemic autoimmune diseases in that autoantibodies and antigen-specific T cells are generally absent in the former conditions.
- Autoinflammatory diseases compass monogenic and polygenic disorders, and molecular genetic analysis usually aids in the diagnosis.

Clinical Pearls on Autoinflammatory Diseases

- FMF is an autosomal recessive disorder generally, and patients have two copies of the *MEFV* mutations, but approximately 30% of patients carry only one copy and up to 20% of patients lack detectable mutations.
- CAPS has three subtypes that are caused by *NLRP3* mutations and is associated with inflammasome. Patients have good response to interleukin-1 inhibitors.

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P. Efthimiou (ed.), *Absolute Rheumatology Review*,
https://doi.org/10.1007/978-3-030-23022-7_16

- TRAPS is characterized by periorbital swelling and localized myalgia underlying rash.
- HIDS occurs in children and the disease onset is extremely rare in adults. Elevated IgD levels are not specific to the disease.
- NLRP12-AID and CAPS (FCAS1) share very similar phenotypes, and molecular analysis of *NLRP12* and *NLRP3* aids in the differentiation between the two diseases.
- NOD2-associated diseases include Blau syndrome, Crohn disease, and Yao syndrome, and they are distinct in clinical phenotypes and genotype.

Introduction

Autoinflammatory diseases (AIDs) are a genetically heterogeneous group of rheumatic diseases that are driven by abnormal activation of the innate immune system [1–3]. In its inception of this group of diseases, AIDs were defined to have recurrent episodes of fever and systemic inflammation without high titer of autoantibodies or high number of antigen-specific T lymphocytes. Most recently, AIDs have been defined as clinical disorders caused by defects or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute-phase reactants) and by the lack of a primary pathogenic role of the adaptive immune system (autoreactive T cells or autoantibody production) [4, 5]. The prototypic AIDs are hereditary monogenic periodic fever syndromes, including familial Mediterranean fever (FMF), TNF receptor-associated periodic fever syndrome (TRAPS), mevalonate kinase deficiency (MKD) (formerly named as hyper-IgD with periodic fever syndrome), *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID) (formerly known as cryopyrin-associated periodic syndrome (CAPS)), and *NLRP12*-associated autoinflammatory disease (*NLRP12*-AID) [6]. With application of more advanced molecular techniques notably next-generation sequencing, the disease spectrum is rapidly expanding, including those associated with *PSMB8*, *ADA2*, *NLRC4*, and *NLRP1* genes as well. Monogenic AIDs are classified (Table 16.1).

Individual Disease

Familial Mediterranean Fever

Pathophysiology

Familial Mediterranean fever (FMF) is the most prevalent AID worldwide, which is characterized by recurrent episodes of fever and serosal inflammation. It is generally considered an autosomal recessive disorder, and the pathogenic mutations are

Table 16.1 The classification of autoinflammatory diseases

Monogenic periodic fever syndromes
FMF (familial Mediterranean fever)
MKD (mevalonate kinase deficiency)
NLRP3-AID (*NLRP3*-associated autoinflammatory disease)
TRAPS (TNF receptor-associated periodic fever syndrome)
NLRP12-AID (*NLRP12*-associated autoinflammatory disease)
NOD2-associated diseases
Blau syndrome
Crohn disease
Yao syndrome
PRAAS (proteasome-associated autoinflammatory disease)
DIRA (deficiency of the IL-1 receptor antagonist)
DITRA (deficiency of the IL-36 receptor antagonist)
PAPA (*PSTPIP1*-associated arthritis, pyoderma gangrenosum, and acne)
APLAID (*PLCG2*-associated antibody deficiency and immune dysregulation) syndrome
SAVI (STING-associated vasculopathy with onset in infancy)
DADA2 (ADA2 deficiency)
Schnitzler syndrome
CNO (chronic nonbacterial osteomyelitis)
Other rare AIDs

located in the *MEFV* gene on the chromosome 16. Four mutations, M694V, M694I, M680I, and V726A, account for most cases in the Mediterranean populations. The mutations in exon 10 of the *MEFV* gene tend to be associated with more severe disease as compared with variants found in exons 2 and 3. However, approximately 30% of patients who meet clinical diagnostic criteria for FMF have only one copy of *MEFV* mutations. Moreover, *MEFV* mutations are absent in up to 20% of patients who fulfill the clinical diagnostic criteria for FMF [7–9].

The *MEFV* gene, identified in 1997, encodes a protein of 781 amino acids, pyrin, which plays an important role in the innate immune system defending against external pathogens. In patients with FMF, the mutations in the *MEFV* gene result in the production of pyrin even in the absence of external triggers, leading to the formation of the NLRP3 inflammasome, which in turn causes the secretion of interleukin (IL)-1βand other inflammatory mediators, and eventually FMF attacks [7, 8].

Clinical Presentation

FMF mainly affects patients of Mediterranean descent, such as Turks, Armenians, North Africans, Jews, and Arabs, but it has also been reported in other parts of the world at a lower prevalence. Most patients experience the initial attack during early childhood, with 90% of patients exhibiting their first symptoms by the age of 20 years [7, 8].

FMF is characterized by recurrent attacks of fever and serositis resulting in abdominal and chest pain. The onset of symptoms is usually abrupt without consistent triggers. The disease attacks generally last fewer than 3 days before spontaneous resolution. Between attacks, irregular asymptomatic intervals range from weeks to years [7, 8].

1. Fever is present in almost all episodes, and the temperature usually rises to above 38°. Chills often herald the onset of fever, and the typical duration of fever only lasts between 12 h and 3 days.
2. More than 90% of the FMF patients have abdominal pain during attacks mostly as a result of sterile peritonitis. The pain is usually generalized, and guarding, rebound tenderness, and rigidity are often present. The abdominal pain is so severe that can mimic an acute surgical abdomen. Some patients also experience pleuritic chest pain which is usually unilateral. Concomitant pericarditis can also develop.
3. Other two common symptoms are joint pain which is usually mono- or oligoarticular affecting large joints (knee, ankle, hip, or wrist) and erysipelas-like skin changes which typically occur as a tender erythematous plaque in the lower extremities.
4. Sometimes, children with FMF can develop exertional myalgia of the lower limbs, and rarely, patients with M694V mutation may present with severe, debilitating "protracted febrile myalgia" lasting up to 8 weeks, which is thought to be due to vasculitis. Other rare manifestations also include acute scrotal swelling and tenderness and aseptic meningitis.
5. The laboratory tests during attacks demonstrate nonspecific systemic inflammation, including leukocytosis, neutrophilia, and elevated acute-phase reactants, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen. Mild to moderate, transient pleural, and pericardial effusion can be detected by imaging. Between attacks, persistent elevation of the acute-phase reactants may be present, and persistent proteinuria requires a renal biopsy to rule out amyloidosis.
6. Secondary (AA) amyloidosis is a major cause of mortality in FMF patients. Renal amyloidosis can present with nephrotic syndrome and gradually lead to end-stage renal disease. Amyloidosis can also involve other organs such as the liver, spleen, gastrointestinal tract, and heart. Colchicine treatment has markedly decreased the incidence of amyloidosis. Peritoneal adhesions leading to small bowel obstruction and infertility or subfertility are other long-term complications in the pre-colchicine era.
7. In addition, immunoglobulin A vasculitis, polyarteritis nodosa, Behçet's syndrome, and ankylosing spondylitis have higher prevalence among FMF patients.

Diagnosis

FMF is diagnosed based upon clinical ground, which can be supported but not excluded by genetic testing. Genetic testing is also performed to exclude other

hereditary periodic fever syndromes. The detection of biallelic pathogenic mutations in the *MEFV* gene confirms the diagnosis [9]. At present, the most widely used clinical diagnostic criteria were proposed by the Tel Hashomer Medical Center in Israel in 1997 [10]. Using this set of criteria, a diagnosis can be made with both a specificity and sensitivity of >95%. In this set of criteria, typical attacks are defined as recurrent (≥3 of the same type), febrile (rectal temperature of 38 °C or higher), and short (lasting between 12 h and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in one or two features, as follows: (1) the temperature is normal or lower than 38 °C; (2) the attacks are longer or shorter than specified (but not shorter than 6 h or longer than a week); (3) no signs of peritonitis are recorded during the abdominal attacks; (4) the abdominal attacks are localized; (5) the arthritis is in joints other than those aforementioned. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks. The requirements for the diagnosis of FMF are:

1. ≥1 major criteria
2. ≥2 minor criteria
3. 1 minor criterion plus ≥5 supportive criteria
4. 1 minor criterion plus ≥4 of the first 5 supportive criteria

The major differential diagnoses for FMF include other autoinflammatory periodic fever syndromes, such as TRAPS, CAPS, MKD, and periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA). These diseases all present with periodic or episodic fevers, but the durations of fever vary. The attacks of TRAPS typically last 1–3 weeks, CAPS 1–2 days, HIDS 3–7 days, and PFAPA 3–7 days with a true periodicity of 3–4 weeks. Genetic testing is used to help distinguish these diseases clearly. Systemic juvenile idiopathic arthritis or Still disease usually may be differentiated from FMF by its typical quotidian or persistent fever. The etiologies for fever of unknown origin, for instance, rheumatic diseases, infection, and malignancy, should also be considered and excluded based upon their specific clinical features [11].

Treatment

The initial treatment for FMF is daily oral colchicine at doses of 1–2 mg/day to prevent acute attacks and the development and progression of amyloidosis [11]. Compliance is very important for its efficacy. Colchicine should generally be started at a low dose and gradually increased as tolerated to minimize the gastrointestinal toxicities, such as diarrhea, cramping, and bloating. Dose adjustment is necessary in patients with renal or liver impairment. Higher dosage above 2 mg/day is rarely used for long periods because of intolerance.

Regular safety monitoring should include measurements of blood cell counts for leukopenia, urinalysis for proteinuria, serum chemistries, and the acute-phase reactants [11]. The efficacy of colchicine in FMF has been proven in several double-blind, placebo-controlled trials. It can induce a near cessation of FMF attacks in

about 70% of patients and provides at least some relief in more than 90%. In FMF patients with amyloidosis, colchicine could prevent the progression of nephrotic syndrome. Patients with elevated ESR, CRP, or SAA between attacks despite maximal colchicine are considered colchicine resistant because of the risk of amyloidosis.

For patients who are non-responders to colchicine (up to 15%) or those who are intolerant to colchicine (up to 5%), IL-1 inhibition is the preferred treatment. Concomitant colchicine at a tolerable dose should be given for the prevention of amyloidosis. Among the three IL-1 inhibitors, canakinumab, rilonacept, and anakinra, canakinumab is approved by FDA to treat the disease. TNF inhibitors or IL-6 receptor antagonist, tocilizumab, may be tried [11].

NLRP3-*Associated Autoinflammatory Disease*

Pathophysiology

NLRP3-associated autoinflammatory disease (*NLRP3*-AID), formerly known as cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies [6], consists of a clinical continuum of three overlapping disorders of increasing severity, including 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. All three cryopyrinopathies are caused by mutations in the *NLRP3* gene in chromosome 1, encoding a protein called cryopyrin (also known as NALP3, CIAS1, or PYPAF1). Thus, in 2018, it was proposed that a single name, *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID), should be used, and adjectives mild, moderate, and severe phenotypes may be added instead of using the historical names FCAS, MWS, and NOMID/CINCA [6, 12, 13].

Cryopyrin belongs to the NOD-like receptor (NLR) family that is intracellular sensors of molecular danger signals. It serves as a scaffold for the assembly of the NLRP3 inflammasome, a multimolecular complex activating the protease, caspase-1, which cleaves pro-IL-1β and pro-IL-18 to their biologically active forms. Nearly 200 disease-causing mutations of the *NLRP3* gene have been reported in CAPS, and more than 75% of them are located in exon 3, which encodes the central regulatory NACHT domain of the cryopyrin protein. Point mutations in CAPS promote aberrant formation of the inflammasome and production of the active IL-1β, which leads to inappropriate inflammation. Phenotypic differences among the three cryopyrinopathies are thought to be caused by the different impact of mutations on the activity of the inflammasome, modulated by individual genetic background [12, 13].

Clinical Presentation [12, 13]

CAPS are rare autosomal dominant disorders with an incidence of 1/1,000,000 in the USA. The clinical features of the three subtypes of CAPS are described below.

FCAS, formerly known as familial cold autoinflammatory syndrome, is at the mildest end of the CAPS spectrum. The onset of symptoms typically occurs in early childhood, usually in the first year of life. FCAS flares are triggered by generalized cold exposure and present with a systemic inflammatory response including urticarial rash (100%), polyarthralgia (96%), and low-grade fever (93%). Patients may also experience conjunctivitis, which is rather distinctive among periodic fever syndromes, as well as fatigue, dizziness, headache, and nausea. Symptoms often develop within hours after cold exposure and last 12–48 h. FCAS rarely leads to secondary amyloidosis (<2%).

Muckle-Wells syndrome (MWS) is characterized by intermittent episodes of fever, urticarial rash, headache, conjunctivitis, and arthralgia/arthritis and may lead to severe sequelae such as progressive sensorineural hearing loss and renal amyloidosis. Febrile episodes are not typically precipitated by cold exposure. The self-limiting systemic inflammation may last between 12 h to days, and the intervals between attacks range from weeks to months. Patients who suffer from aseptic meningitis often complain of headache and may progress into increased intracranial pressure (ICP) with papilledema. Sensorineural hearing loss caused by chronic inflammation of inner ear typically develops in the late childhood or the early adulthood. Secondary amyloidosis has been described in 25–33% of untreated patients.

NOMID/CINCA is the most severe of the CAPS spectrum. In addition to the systemic symptoms similar to FCAS and MWS, such as urticarial rash, conjunctivitis, and fever, patients with NOMID/CINCA have characteristic abnormalities, including frontal bossing, protruding eyes, and saddle-shaped nose, generally manifesting at or near the time of birth. Focal exuberant cartilaginous proliferation at growth plates and epiphyses frequently leading to joint deformities is seen in up to 70% of patients, most commonly involving the epiphyses of the distal femur and proximal tibia and the patella. Chronic aseptic meningitis, presenting with irritability, headaches, nausea, and vomiting, can lead to increased ICP, papilledema, seizures, hydrocephalus, and cerebral atrophy. Other features include sensorineural hearing loss, uveitis, lymphadenopathy, hepatosplenomegaly, and arthralgia. NOMID/CINCA leads to growth retardation and cognitive disability and may cause premature death and secondary amyloidosis.

Laboratory findings in CAPS include leukocytosis with neutrophilia, thrombocytosis, and elevation of acute-phase reactants. Biopsies of urticarial rash show a marked perivascular infiltration of neutrophils, in contrast to the lymphocytic and eosinophilic infiltrate found in classical allergic urticaria. Lumbar punctures in patients with chronic meningitis may show increased ICP, neutrophilic leukocytosis, and elevation of protein. Radiographs of the long bones can demonstrate epiphyseal lesions.

Diagnosis

The diagnosis of CAPS should be suspected in patients with recurrent episodes of unexplained fever and/or urticarial rash, especially in patients with a positive family history. The diagnostic criteria for CAPS proposed by a multidisciplinary team of

international experts in 2017 require one mandatory criterion plus ≥two of six CAPS typical signs/symptoms [14]. In patients with typical manifestations, the presence of *NLRP3* mutations is confirmatory, but is not necessary to initiate therapy.

Treatment

Nearly all patients with CAPS respond dramatically to IL-1 blockade. Three IL-1 blocking agents are approved by the US Food and Drug Administration for the treatment of CAPS: anakinra, rilonacept, and canakinumab. Anakinra, an IL-1 receptor antagonist, is given subcutaneously on a daily basis. Rilonacept is a fusion protein consisting of a ligand-binding portion of the human IL-1 receptor linked to the Fc region of human IgG1. Rilonacept is given subcutaneously once a week. Canakinumab is a human anti-IL-1β monoclonal antibody, which is given subcutaneously every 8 weeks. Optimal treatment with these agents leads to complete resolution of symptoms in most cases [15].

NLRP12-*Associated Autoinflammatory Disease*

Pathophysiology

NLRP12-associated autoinflammatory disease (*NLRP12*-AID) is also known as familial cold autoinflammatory syndrome 2 (FCAS 2), and it is a rare autosomal dominant disease that is characterized by recurrent fever and musculoskeletal symptoms associated with the mutations in the *NLRP12* gene.

Studies have shown that *NLRP12* is closely related to the inflammasome scaffold, *NLRP3*. While the precise function of *NLRP12* is debatable, it forms inflammasome or regulates inflammasome function. *NLRP12* is reported to regulate inflammation by activation of caspase-1 via inflammasome, leading to the processing and secretion of IL-1β. Meanwhile, caspase-1 induces cell apoptosis and attenuates the negative regulation of NF-κB signaling induced by TNF [16, 17].

Clinical Presentation and Diagnosis

NLRP12-AID can occur in multiple ethnic groups, sporadically in both children and adults. The clinical features of *NLRP12*-AID are similar to *NLRP3*-AID, notably FCAS, including periodic fever, rash (primarily urticaria), myalgia, polyarthralgia/arthritis, abdominal pain/diarrhea, thoracic pain, headache, sensorineural deafness, lymphadenopathy, and splenomegaly. Most patients report cold exposure as a trigger. Elevated acute-phase reactants are common in episodes. The *NLRP12* gene variant, F402, is the most frequent, and some other rare *NLRP12* gene variants have been reported as well. *NLRP12*-AID is diagnosed based on the characteristic clinical phenotype and genotype [16, 18–20].

Treatment

Therapeutically, glucocorticoids and antihistamine drugs are largely effective in the majority of patients with *NLRP12*-AID. IL-1 inhibitors may be beneficial. However, it has been reported that some patients albeit initially responsive eventually developed resistance to anakinra within a few months of treatment. Unlike their definite therapeutic roles in FCAS, IL-1 antagonists may be further evaluated for its potential efficacy in the treatment of the disease [19, 20].

TNF Receptor-Associated Periodic Fever Syndrome

Pathophysiology

TRAPS is caused by mutations in the *TNFRSF1A* gene in chromosome 12p13 which encodes the 55-kD, the TNF receptor 1 (TNFR1) for TNF-α. Most mutations associated with TRAPS (94%) are single-nucleotide missense variants within exons 2, 3, 4, and 6. The pathogenic mechanism of TRAPS is not fully understood. Studies suggest that TRAPS mutations might result from impaired metalloprotease-dependent cleavage of *TNFRSF1A*, producing soluble "shed" receptors. TNFR 1 on the cell surface does not neutralize TNF perhaps due to mutant TNFR1 protein misfolding and endoplasmic reticulum retention. In vitro studies show possible causative links between TRAPS-associated *TNFRSF1A* mutations and impaired TNF-α binding, abnormal apoptosis, and altered NF-kB pathway, as well as defective receptor trafficking to the cell surface [21].

Clinical Presentation

TRAPS often occurs in childhood (age 3) and causes variable and heterogeneous clinical manifestations. The disease is characterized by recurrent fever attacks, typically lasting from 1 to 3 weeks. Febrile attacks recur either spontaneously or after minor triggers (local injury, minor infection, stress, exercise, and hormonal changes) at varying intervals and usually initiate with muscle cramps or myalgia underlying the rash that migrate in a centrifugal pattern. Skin lesions usually start as painful and warm macules and papules, which progressively expand at the periphery, subsequently coalescing into large patches or plaques. Skin biopsies usually show dermal perivascular lymphocytic and monocytic infiltrates. Other less common skin lesions may include erysipelas-like erythema and urticarial rash. Eye involvement can include peculiar periorbital edema, conjunctivitis, and/or uveitis. Arthralgia occurs during febrile attacks in about two-thirds of patients, including mono- or oligo-arthralgia. Arthritis is less common, and joint effusion may occur. Serositis is also common, and amyloidosis can occur as a long-term complication of TRAPS [22, 23].

Diagnosis

TRAPS is diagnosed based on clinical ground and genetic confirmation of specific *TNFRSF1A* mutations. Patients with TRAPS should be regularly screened for proteinuria from renal amyloidosis [21].

Treatment

Patients gain some symptomatic relief from nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, while colchicine or immunomodulators such as methotrexate, cyclosporine, and thalidomide produce very little benefit. TNF-α blockers, such as etanercept, can be used. IL-1 inhibitor, canakinumab, has been approved by FDA to treat the disease [21].

Mevalonate Kinase Deficiency

Pathophysiology

Mevalonate kinase deficiency (MKD), also known as hyperimmunoglobulin D syndrome (HIDS), is a rare monogenic disorder characterized by recurrent febrile attacks associated with rash, lymphadenopathy, abdominal pain, and elevated serum immunoglobulin D (IgD). HIDS can be divided into classic and variant forms. If the genetic defect is known, it is called the classic form, which accounts for 75% of cases. The variant form has similar clinical symptoms, but there is unclear genetics.

The classic HIDS is an autosomal recessive disorder, caused by loss-of-function mutations in the *MVK* gene which lead to mevalonate kinase (MK) deficiency. The most common mutation found in classic HIDS is the V377I mutation. The MK protein, encoded by the *MVK* gene in the chromosome 12, is an enzyme in the cholesterol synthesis pathway. Mutations in *MVK* that cause a mild to moderate reduction (normal 5–15%) in the enzymatic activity of MK lead to the periodic fever syndrome, HIDS, whereas mutations that cause more severe reduction or loss of MK activity result in a potentially fatal condition with marked developmental delay and mevalonic aciduria. The diminished activity of MK results in accumulation of its substrate mevalonic acid in serum and urine. However, the pathophysiologic mechanism underlying MK deficiency and self-limiting inflammation is still unclear. The cause of the characteristic high concentration of IgD in this syndrome is unclear. It has been suggested that neither elevated level of IgD nor accumulated mevalonic acid is responsible for the pathogenesis in HIDS [24–26].

Clinical Presentation [24–26]

HIDS occurs almost exclusively in childhood, and 90% of patients experienced the first attack within the first year of life, with a median age of 6 months. HIDS affects female and male equally. Most patients reported are of Dutch or French ancestry.

The potential triggers for HIDS attacks include vaccinations, minor trauma, surgery, or stress. Symptom-free intervals between attacks usually last 1–2 months without obvious periodicity. The durations of interval vary greatly and may become longer with increasing age. HIDS attacks are characterized by the rapid onset of moderate to high fever, which typically lasts 3–7 days. The prodrome may include nasal congestion, sore throat, fatigue, backache, and headache. More than 90% of patients have diffuse lymphadenopathy, mostly cervical, during febrile attacks. Palpable splenomegaly is found in 50% of patients. Abdominal pain is reported in 85% of patients, which is often accompanied by vomiting and/or diarrhea; the severity of pain may suggest acute abdomen. Skin rashes are noted in over 80% of patients, and erythematous macular rash is the most common type. Aphthous ulcers may occur in 50% of patients. Polyarthralgia/polyarthritis develops in 80% of patients during febrile episodes. Larger joints are involved more commonly and often in a symmetrical pattern. Secondary amyloidosis is rare.

Laboratory findings during HIDS attacks include leukocytosis with neutrophilia; elevation of acute-phase reactants such as ESR, CRP, SAA, ferritin, and fibrinogen; and increase in urinary mevalonate. The acute-phase reactants commonly return to normal or are only mildly elevated between attacks except for SAA, which may remain elevated in 50% of patients. Elevated serum IgD (>100I U/mL) and IgA levels are seen in over 80% of patients and remain elevated between attacks; elevated serum IgD levels are nonspecific.

Diagnosis

The diagnosis of HIDS should be entertained in patients with early-onset recurrent fever lasting 3–7 days, accompanied by a combination of characteristic clinical findings, such as lymphadenopathy, splenomegaly, arthralgia/arthritis, abdominal pain, and rash. The Eurofever clinical diagnostic/classification criteria may be used [27]. If the diagnostic cutoff score of ≥42 is reached, serum IgD should be measured to confirm the HIDS diagnosis. Clinical suspicion of the diagnosis in normal serum IgD can be corroborated by genetic testing [27].

Treatment

Most patients with HIDS have a normal lifespan and carry a good prognosis. However, if the attacks are frequent and severe, the quality of life will be significantly affected. The goal of treatment is to improve quality of life and to minimize

the risk of drug adverse effects. NSAIDs and/or short courses of oral glucocorticoid may be used; IL-1 inhibitors can be used, and canakinumab is approved by FDA to treat the disease [24–26].

Blau Syndrome [28–30]

Pathophysiology

Blau syndrome (BS) is characterized by an early-onset clinical triad of arthritis, dermatitis, and uveitis, and it is a rare autosomal dominant autoinflammatory granulomatous disorder. It is caused by gain-of-function mutations in the nucleotide-binding domain of the nucleotide-binding oligomerization domain protein 2 (*NOD2*), also called caspase recruitment domain-containing protein 15 (*CARD15*) gene in chromosome 16. In 2018, an international expert committee proposed that a general name, *NOD2*-associated granulomatous disease, should be used to encompass BS, early-onset sarcoidosis, and familial Crohn disease due to the fact that all the disorders are linked to *NOD2* mutations. Similar to NLRP3 protein, NOD2 protein is also a member of the NOD-like receptor family, which plays important roles in innate immune system. Mutations in BS are predominantly located in exon 4 of the *NOD2* gene. The two most common mutations are two missense mutations, R334Q and R334W.

Clinical Presentation

The disease onset of BS typically occurs before the age of 4 years. Three typical sites affected by granulomatous inflammation are joints, eyes, and skin. Joints are affected in over 90% of patients. The chronic granulomatous arthritis is almost always polyarticular, presenting as minimally symptomatic swelling involving the wrists, ankles, and knees. Arthritis of proximal interphalangeal joints of hands can lead to progressive flexion contractures of the fingers (camptodactyly). Symmetric hypertrophic tenosynovitis develops in up to 40% of patients, resulting in the typical periarticular “boggy” appearance, especially about the knees. Granulomatous uveitis is frequent (80%) and usually chronic and persistent. Acute anterior uveitis can be a presenting feature and often extends to panuveitis. Most patients have bilateral ocular involvement, leading to cataracts, glaucoma, and even blindness. Ocular involvement is the most significant morbidity in BS. The BS-associated dermatitis is typified by ichthyosis-like popular-nodular erythematous rash. The typical clinical triad of dermatitis, arthritis, and uveitis is seen in up to 80% of patients, usually in a consecutive fashion. Other manifestations include lymphadenopathy, vasculitis, cranial neuropathies, and granulomatous involvement of visceral organs. Fever and abdominal pain can occur infrequently.

Laboratory findings include leukocytosis, thrombocytosis, and elevation of acute-phase reactants such as ESR and CRP. Biopsies of synovium and skin show noncaseating granulomas in typical cases.

Diagnosis

The diagnosis of BS is based upon characteristic clinical phenotype. Histological findings of granulomas are the most supportive of the disease in the proper clinical setting. Molecular testing for the *NOD2* mutations provides more definitive diagnosis.

Treatment

Optimal therapy for BS has not been well defined. NSAIDs can be used for mild clinical manifestations, and severe symptoms are often treated with systemic glucocorticoids. Immunosuppressants such as methotrexate and cyclosporine are used as glucocorticoid-sparing agents. Biologic agents such as TNF-α blockers (infliximab and adalimumab) can be used. IL-1 and IL-6 inhibitors were anecdotally reported. Uveitis should be managed with both topical and systemic therapies. Early diagnosis and proper management is crucial to avoid long-term ocular complications.

Yao Syndrome

Pathophysiology

Yao syndrome (YAOS, OMIM 617321), formerly called *NOD2*-associated autoinflammatory disease (NAID), is a polygenic AID characterized by periodic fever, dermatitis, arthritis, swelling of the distal extremities, as well as gastrointestinal and sicca-like symptoms. The disorder has a genetic association with certain *NOD2* variants [31].

The pathogenesis of YAOS remains elusive, and it is postulated that the interplay between the NOD2 defect as a risk factor and environmental factors may play a role. It has been recently reported that *NOD2* transcript level was significantly elevated in the peripheral blood mononuclear cells from IVS8^{+158} YAOS patients. Moreover, these patients' cells had elevated basal IL-6 secretion. In contrast, NF-κB activity and TNF-α secretion were uniquely suppressed in haplotype IVS8^{+158}/R702W patients. Specific *NOD2* genotypes may result in distinct NOD2 expression and cytokine profiles. Further study is needed to dissect its pathomechanism [32, 33].

Table 16.2 The diagnostic criteria for Yao syndrome

Clinical criteria	Comments
Major	
1	Periodic occurrence ≥ twice
2	Recurrent fever of dermatitis or both
Minor	
1	Oligo- or polyarthralgia/inflammatory arthritis, or distal extremity swelling
2	Abdominal pain or diarrhea or both
3	Sicca-like symptoms
4	Pericarditis or pleuritis or both
Molecular criterion	*NOD2* IVS8^{+158} or R702W or both, or other rare variants
Exclusion criteria	High-titer antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjögren syndrome, and monogenic autoinflammatory diseases

Adapted from Yao et al. [36]

Clinical Presentation and Diagnosis [31, 34, 35]

YAOS is a multisystem inflammatory disease. Recurrent fever occurs in >60% of patients, and typically each febrile episode lasts several days. The fever occurs at varying intervals ranging from several weeks to several months. Intermittent dermatitis is common, manifesting as erythematous patches and plaques on the face, trunk, and limbs. Skin biopsies are usually consistent with spongiotic dermatitis, and other types of dermatitis can be present. Granulomatous changes are extremely rare. Arthritic symptoms are common with oligo- and polyarticular involvement. Some patients (25%) have distal lower extremity swelling involving the ankle and foot with unilateral distribution often. Recurrent or intermittent abdominal pain and/or diarrhea of varying degrees occurs in about two-thirds of patients. Sicca-like symptoms occur in 60% of patients. Other less common manifestations include recurrent chest pain with pleuritis and/or pericarditis, headache, oral ulcers, lymphadenopathy, and sore throat. The diagnosis criteria for YAOS are listed in Table 16.2. YAOS is diagnosed if two major criteria, one or more minor criteria, and the molecular and exclusion criteria are fulfilled.

Treatment

Glucocorticoid therapy is beneficial for reducing the disease frequency and severity. A short course of prednisone (30–40 mg daily for 1–3 days) initiated at the prodromal phase of the disease can shorten the disease flares and severity. A long-term use of prednisone can sustain control of the more frequent flares. Sulfasalazine is also beneficial in 50% of patients. In patients with more frequent disease flares or poor

responses to steroids or sulfasalazine, biologic agents such as IL-1/IL-6 antagonists may offer a long-term benefit for refractory cases. YAOS generally does not respond to colchicine treatment [36].

Summary of the Main Phenotypes and Genotypes of the Above Diseases

The main phenotypes and genotypes of the above diseases are summarized in Table 16.3. The rashes in each of the above diseases are represented in Fig. 16.1 [37].

Table 16.3 Brief summary of the main phenotypes and genotypes of above autoinflammatory diseases

Disease	Gene	Inheritance	Characteristic clinical features	Treatment
FMF	*MEFV*	AR	Fever, polyserositis, arthralgia/arthritis, erysipelas-like eruption on the leg, and amyloidosis	Colchicine, IL-1 inhibitors TNF-α inhibitors
CAPS	*NLRP3*	AD		
FCAS			Fever, cold-induced urticarial rash, conjunctivitis, and arthralgia	
MWS			Fever, urticarial rash, conjunctivitis, episcleritis, arthralgia, neurosensory deafness, and amyloidosis	IL-1 inhibitors
CINCA			Fever, urticarial rash, uveitis, papilledema, deforming arthritis involving large joints, aseptic chronic meningopathy, neurosensory deafness, and amyloidosis	
NLRP12-AID	*NLRP12*	AD	Fever, arthralgia, and cold-induced urticarial rash	Glucocorticoids, antihistamine drugs, and anakinra
TRAPS	*TNFRSF1A*	AD	Fever, myalgia, conjunctivitis, periorbital edema, oligo-arthralgia/oligo-arthritis, serosal involvement, and amyloidosis	Glucocorticoids, etanercept, IL-1 inhibitors
MKD	*MVK*	AR	Fever, polymorphous rash, arthralgia, abdominal pain, diarrhea, lymph node enlargement, and splenomegaly	Anti-inflammatory drugs, glucocorticoids, IL-1 inhibitors
BS	*NOD2*	AD	Granulomatous polyarthritis, dermatitis, panuveitis, occasional fevers, and cranial neuropathies	Glucocorticoids, methotrexate, infliximab
YAOS	*NOD2*	Polygenic	Fever, erythematous patches and plaques, arthritis/arthralgia, distal extremity swelling, gastrointestinal and sicca-like symptoms	Glucocorticoids, sulfasalazine, IL-1 inhibitor, and IL-6 inhibitors

New Monogenic Diseases [38–44]

Some new monogenic diseases has been described in Table 16.4.

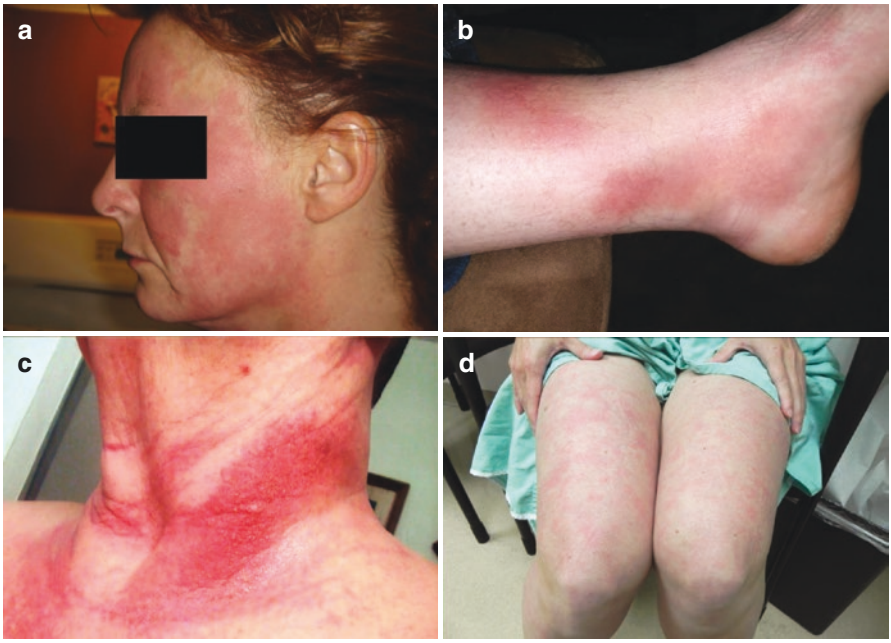

Fig. 16.1 Rashes in autoinflammatory diseases. Erythematous patches on the face in Yao syndrome (NAID) (**a**), erysipelas-like rash on the distal lower extremity in FMF (**b**), plaques on the neck in TRAPS (**c**), and urticaria in CAPS (**d**) (Reprinted with permission from Yao et al. [37])

Table 16.4 New monogenic diseases [38–44]

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Full disease name	STING-associated vasculopathy with onset in infancy	Deficiency of adenosine deaminase 2, also childhood-onset polyarteritis nodosa	Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome, also known as proteasome-associated autoinflammatory syndrome (PRAAS), or autoinflammation, lipodystrophy, and dermatosis syndrome (ALDD), or joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) syndrome, or Nakajo-Nishimura syndrome	Congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay	PLCG2-associated antibody deficiency and immune dysregulation, also known as familial cold autoinflammatory syndrome 3 (FCAS3)	Deficiency of the interleukin-1 receptor antagonist, also called osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP)	A20 haploinsufficiency, also known as familial Behçet-like autoinflammatory syndrome (AISBL)
Gene	TMEM173	CECR1/ADA2	Mostly PSMB8	TRNT1	PLCG2	IL1RN	TNFAIP3
Inheritance	AD	AR	AR	AR	AD	AR	AD
Pathogenesis	Interferonopathy	Small-vessel vasculopathy	Proteasome-associated interferonopathy	Dysregulation in protein clearance pathways and mitochondrial dysfunction	Immune dysregulation	Unopposed interleukin-1 activity	Inappropriate activation of inflammatory cytokines
Age of onset	Infancy, usually before 8 weeks	As early as infancy, most patients have onset of symptoms in the first decade, adult onset has been described	First months of life	Neonatal period or infancy, mostly prior to 3 months of age. Median survival 48 months	Most patients have onset in the first 6 months of life. Most patients note a subjective improvement of the severity of the symptoms after age 30 years	Early infancy	Disease onset before 10 years of age

(continued)

Table 16.4 (continued)

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Disease pattern	Continuous, cold-induced worsening	Intermittent or recurrent	Almost daily, can't be triggered by cold, stress, infections	Recurrent, commonly every 2–4 weeks	Evaporative cooling is the most common trigger	Continuous inflammation	Recurrent
Fever	Recurrent	Recurrent fever	Recurrent fever	Periodic fevers typically last 5–7 days	UK	Recurrent low-grade fevers	Episodic
Cutaneous	Telangiectasia, pustules, and/or blisters, affecting the face, ears, nose, and digits and resulting in ulceration, eschar formation, necrosis, and even amputation. Livedo reticularis, Raynaud phenomenon	Livedo racemosa or reticularis with an inflammatory vasculitis on biopsy, urticarial papules and plaques, purpura	1. Acral, perniotic lesions in newborns and infants 2. Perioral and periocular edema 3. Erythematous or purpuric edematous lesions often with annular shape 4. Progressive lipodystrophy usually well-established before puberty. Histopathology of skin lesions shows an infiltration of immature, myeloid, mononuclear cells, resembling leukemia cutis	Oral ulcers, cellulitis	1. Localized cutaneous urticaria, erythema, and pruritus and sometimes angioedema over unprotected skin after exposure to generalized cold or at the site of exposure to evaporative cooling 2. Onset <5 min after exposure. Resolved within 30 min of rewarming 3. Ulcerative and cutaneous lesions from cold exposure 4. Oropharyngeal swelling after ingestion of cold foods or beverages 5. Cutaneous nodular granulomatous disease	1. Pustular skin rash ranging from discrete crops of pustules to generalized severe pustulosis or ichthyosiform lesions 2. Biopsies of skin lesions show extensive infiltration of epidermis and dermis by neutrophils 3. Nail changes similar to the onychomadesis as in psoriasis 4. Aphthous ulcers	Recurrent painful oral, genital ulcers, rashes, and abscesses

Neurologic	Normal cognition, rarely basal ganglia calcification	Recurrent ischemic stroke affecting the small vessels of the brain, sometimes hemorrhagic stroke. The first stroke often occurs before 5 years of age	Attacks of aseptic meningitis or meningoencephalitis, bilateral basal ganglia calcifications	Delayed psychomotor development mainly manifests as hypotonia and communication problems. Variable neurodegeneration, seizures, ataxia, cerebral atrophy	UK	Cerebral vasculitis or occasional vasculopathy on MRI	Central nervous system vasculitis
Auditory	UK	UK	Otitis, recurrent sinusitis	Sensorineural hearing loss	UK	UK	UK
Ophthalmic	UK	Optic nerve atrophy	Conjunctivitis, keratitis, and nodular episcleritis	Vision impairment, retinitis pigmentosa	UK	Conjunctivitis	Anterior uveitis, retinal vasculitis
Cardiopulmonary	Tachypnea, interstitial lung disease, and lung fibrosis	Coronary aneurysms	Carditis, pneumonitis,	Dilated cardiomyopathy. Cardiac failure was the leading cause of death	Syncope or near syncope usually related to emergence from water	Pulmonary hemosiderosis with progressive interstitial fibrosis in one patient	Pericarditis with effusion, venous thrombi
Abdominal	Failure to thrive	Necrotizing vasculitis of the bowel, abdominal pain, portal hypertension in some patients	Large abdomen and diarrhea during attacks	Poor feeding, vomiting, and diarrhea, enteropathy, failure to thrive, nephrocalcinosis	UK	Poor feeding and failure to thrive are common	Recurrent gastrointestinal ulcers leading to abdominal pain, bloody diarrhea, bowel perforation
Musculoskeletal	Polyarthralgia or polyarthritis, myositis, and joint stiffness	Myalgias	Clubbing of the fingers and/or toes. Arthralgia, disabling joint contractures on the hands and feet usually occur in the long term, muscle wasting, and sometimes myositis. Short stature is common	Dactylitis, arthralgias/arthritis	UK	Sterile multifocal osteomyelitis and periostitis with articular pain. Joint swelling	Polyarthritis

Table 16.4 (continued)

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Reticuloendothelial	Paratracheal or hilar lymphadenopathy, occasionally general lymphadenopathy	Lymphadenopathy, hepatosplenomegaly	Generalized lymphadenopathy, hepatosplenomegaly	Lymphadenopathy, mild hepatosplenomegaly	UK	Splenomegaly	UK
Vasculitis	Skin biopsies showed marked vascular inflammation limited to capillaries, as well as microthrombosis	Renal aneurysms and stenosis, ischemic necrosis of the digits	UK	UK	UK	Histopathologic evidence of vasculitis was observed in the connective and fat tissue adjacent to bone lesions in one patient	Central nervous system vasculitis
Amyloidosis	UK	UK	UK	UK	UK	UK	UK
Lab tests	Elevated ESR, CRP, chronic anemia, thrombocytosis, T-cell lymphopenia with normal B cells, leukopenia, and hypergammaglobulinemia. Normal or low positive ANA, ANCA, antiphospholipid antibodies	Elevated acute-phase proteins, tenfold decrease in serum ADA2 level, abnormal liver enzymes, mild immunodeficiency with hypogammaglobulinemia, pancytopenia, and leukopenia, negative for antiphospholipid antibodies, but lupus anticoagulant can develop over time	Elevation of acute-phase reactants, chronic hypochromic anemia, liver enzymes usually moderately elevated, increased triglyceride, elevated muscle enzymes	1. Elevation of acute-phase reactants during flares 2. Congenital sideroblastic microcytic anemia 3. B-cell deficiency and hypogammaglobulinemia, progressive reduction in T and NK cells 4. Peripheral blood smears typically showed hypochromasia, schistocytosis, and nucleated erythrocytes 5. Hemophagocytic lymphohistiocytosis 6. Aminoaciduria	1. Negative cold stimulation time test with ice-cube and cold-water immersion 2. Antibody deficiency, decreased numbers of B cells, defective B cells, decreased natural killer cells 3. Most had increased IgE 4. Presence of autoantibodies or autoimmune diseases	Markedly elevated inflammatory markers, leukocytosis, thrombocytosis, chronic anemia	Elevated acute-phase reactants during flares. Variable presence of autoantibodies
Year	2014	2014	2010	2013	2012	2009	2016
MIM #	615934	615688	256040	616084	614468	612852	616744

AD autosomal dominant, *AR* autosomal recessive

Board-Style Multiple-Choice Questions with Detailed Explanations

1. A 15-year-old boy of Turkish descent presents with recurrent fever and abdominal pain for 8 years. Ever since the age of 7, he has experienced intermittent episodes of high-grade fevers without consistent triggering events. During the attacks, severe generalized abdominal pain also developed along with the fever, which would confine him to bed for a few days. The patient often suffered from transient unilateral arthritis in his knee or ankle during the febrile attacks. Occasionally, he noted a patch of tender, warm, erythematous skin change on one of his lower legs. During the attacks, laboratory tests showed only leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein. The symptoms typically lasted for 2–3 days and resolved spontaneously. The intervals between attacks range from weeks to months. He was asymptomatic during intervals, and the abnormal test results returned to normal rapidly. What is the most appropriate management for the patient?

   A. Long-term colchicine on a daily basis
   B. Short course of high-dose colchicine during attacks
   C. Short course of high-dose glucocorticoid during attacks
   D. Anti-IL-1 treatment during attacks

   Correct answer: A
   Explanation: The presence of childhood onset of short (12–72 h), recurrent (≥3) febrile episodes accompanied by severe abdominal pain, monoarticular arthritis, and erysipelas-like skin change without discernible infectious cause in a patient from the Mediterranean region established the clinical diagnosis of familial Mediterranean fever (FMF). Although molecular analysis of the *MEFV* gene provides genetic confirmation of the diagnosis, 10–20% of patients who meet the diagnostic criteria for FMF have no detectable MEFV mutations. The differential diagnosis of FMF includes other periodic fever syndromes. However, the duration of episode and accompanying symptoms in this patient are not typical for other syndromes, such as TRAPS, CAPS, HIDS, and PFAPA. The ultimate goal of treatment in FMF is to prevent acute attacks and minimize subclinical inflammation. The initial treatment choice is a long-term use of colchicine.
   B: Administering colchicine only during attacks or increasing its dose during attacks is usually not quite effective for symptom relief. High-dose colchicine is associated with significant side effects. Intermittent colchicine does not prevent subclinical inflammation during intervals, which may lead to amyloidosis.
   C: Because colchicine prophylaxis is highly effective, high-dose glucocorticoid is neither very effective nor necessary for the self-limiting flares in FMF. Short courses of high-dose glucocorticoid are typically for the treatment of the attacks of TRAPS.

D: Colchicine is the first-line therapy for all FMF patients. Only 10–15% of FMF patients who are resistant or intolerant to colchicine need second-line treatments such as anti-IL-1 agents.

2. A 9-year-old girl presents to your clinic with periodic fever and oral ulcers for 6 years. She experienced periodic fever every 4 weeks. The temperature usually rose abruptly to over 39.5 °C, accompanied with chills and sore throat without cough or coryza. Her parents often noticed small oral ulcers on the inner lips or buccal mucosa and tender cervical adenopathy when fever developed. Physical examinations in other hospitals during attacks found bilateral exudative tonsillitis and no rashes or genital ulcers. The fever always abated suddenly after 4–5 days without antibiotics. Between febrile attacks, this girl appeared healthy and had normal growth and development. Moderate leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein were present during fever but normalized between attacks. Throat cultures when performed yielded no positive findings. What is your next step in management?

   A. Reassure the patient and family of the benign nature of the diagnosis and that observation without treatment is acceptable.
   B. Glucocorticoids at a dose of 1–2 mg/kg per day should be given orally throughout the whole duration of the attack, usually 4–5 days.
   C. Short course of cimetidine or colchicine at the onset of each attack is the first-line treatment.
   D. Tonsillectomy is ineffective so should be avoided.

   Correct answer: A
   Explanation: Recurrent fevers accompanied by aphthous ulcers, pharyngitis, and cervical adenopathy with clockwork periodicity in a child of less than 5 years old highly suggests the diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Cyclic neutropenia and recurrent infections should be excluded, and complete lack of symptoms during intervals and normal growth and development should also be confirmed before the definite diagnosis of PFAPA. It is a relatively benign and self-limiting disease with resolution in most patients by the age of 10 years, so treatment is only optional.
   B: If the patient and family wish to treat, a single dose of 1–2 mg/kg prednisone at fever onset is highly effective to relieve the symptoms.
   C: Prophylactic therapy with cimetidine or colchicine is used in patients with frequent attacks.
   D: Tonsillectomy is an effective option for many patients with PFAPA, even in those who fail medical therapy.

3. A 40-year-old Caucasian female presented with a 2-year history of recurrent rash, fever, and arthritis. The rash commonly manifested as erythematous patches and plaques on her forehead, face, neck, and upper chest, which usually lasted 3–7 days before disappearing. Her recurrent fever typically lasted several days, and the afebrile intervals ranged from weeks to months. She experienced intermittent mono- and oligoarthritis in her lower extremities, accompanied by unilateral pedal swelling. Moreover, she also complained of intermittent abdominal

pain and mild diarrhea. A skin biopsy showed spongiotic dermatitis, and colonoscopy examination showed no evidence of inflammatory bowel disease. Laboratory tests including erythrocyte sedimentation rate, C-reactive protein, and autoantibodies were all normal. Doctors in another hospital who ordered gene sequencing for *MEFV* and *TNFRSF1A I* found no pathogenic mutations. What is this patient's most likely diagnosis?

A. Familial Mediterranean fever (FMF)
B. Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS)
C. Blau syndrome
D. Yao syndrome (YAOS)

Correct answer: D
Explanation: This patient's presentations are suggestive of Yao syndrome (YAOS), formerly called NOD2-associated autoinflammatory disease (NAID). It occurs predominantly in Caucasian adults. Patients typically have intermittent episodes of fever, dermatitis, mostly spongiotic dermatitis, arthritis, gastrointestinal symptoms, and/or pedal swelling. These patients don't have detestable or high titers of autoantibodies or convincing evidence of inflammatory bowel disease. Acute-phase reactants are elevated in 50% of patients. Genotyping typically shows the *NOD2* gene mutations $IVS8^{+158}$ and/or R702W.
A: Patients with FMF typically experience episodic fever lasting fewer than 3 days, serositis, especially acute abdominal pain, erysipeloid rash on the lower extremities, and arthritis. *MEFV* gene mutations are present in 80% of patients.
B: Blau syndrome is an autosomal dominant disease, caused by mutations in the *NOD2* gene. It is characterized by an early-onset clinical triad of granulomatous dermatitis, uveitis, and arthritis classically leading to finger flexion deformities (camptodactyly). In addition, GI symptoms and fever are infrequent.
C: TRAPS is an autosomal dominant disease, characterized by recurrent fever attacks, typically lasting from 1 to 3 weeks, various forms of rashes with underlying myalgia, and mild mono- or oligo-arthritis. Genetic testing for *TNFRSF1A* is employed to confirm the diagnosis.

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