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Review

Systemic autoinflammatory disease in adults

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ABSTRACT

Systemic autoinflammatory disorders comprise an expanding group of rare conditions. They are mediated by dysfunction of the innate immune system and share a core of phenotypic manifestations including recurrent attacks of fever, cutaneous signs, chest or abdominal pain, lymphadenopathy, vasculopathy, and musculoskeletal symptoms. Diagnosis is often established in childhood, but a growing number of adult patients are being recognized with systemic autoinflammatory disorders, including adult-onset disease. In this review, we provide a concise update on the pathophysiology, clinical presentation, and diagnostic approach of systemic autoinflammatory disorders with an emphasis on the adult patient population. Despite the recent advances in genetic testing, the diagnosis of autoinflammatory disease in adult patients is often based on a thorough knowledge of the clinical phenotype. Becoming acquainted with the clinical features of these rare disorders may assist in developing a high index of suspicion for autoinflammatory disease in patients presenting with unexplained episodes of fever or inflammation.

1. Introduction

Systemic autoinflammatory disorders (SAIDs) comprise an expanding group of rare conditions. They are mediated by dysfunction of the innate immune system and share a core of phenotypic manifestations including recurrent attacks of fever, cutaneous signs, chest or abdominal pain, lymphadenopathy, vasculopathy, and musculoskeletal symptoms. Diagnosis is often established in childhood, but a growing number of adult patients are being recognized with SAIDs, including adult-onset disease. This review provides a concise update on the pathophysiology, clinical presentation, management, and diagnostic approach of SAIDs with an emphasis on the adult patient population.

We searched PubMed and Google Scholar for articles published from 1995 to 2020 using the terms autoinflammation, autoinflammatory disorder, autoinflammatory disease, adult, adulthood, age of onset, familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, NLRP12-associated disorder, hyperimmunoglobulin D syndrome, mevalonate kinase deficiency, haploinsufficiency A20, deficiency of ADA2, type I interferonopathy, adult onset Still disease, idiopathic recurrent pericarditis, Schnitzler syndrome, periodic fever with aphthous stomatitis pharyngitis and adenitis, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome. Starting from the articles retrieved in this search, we used a snowball search strategy, scanning useful references and related articles and including those that were considered relevant to our subject.

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2. Background

In 1999, the term 'autoinflammation' was introduced by Michael McDermott and Daniel Kastner, who described the tumor necrosis factor receptor-associated periodic syndrome (TRAPS), to label an expanding family of disorders characterized by seemingly unprovoked localized or systemic inflammation in the absence of primary features of autoimmunity (high titer antibodies and autoreactive lymphocytes) [1]. The elucidation of SAIDs on a genetic and molecular level, and the association with dysfunction of the innate immune system in contrast to the adaptive immune system, initially led to the belief of a clear distinction between autoinflammatory and autoimmune disease [2]. More recently, the concept of an immunological disease continuum was proposed to integrate the complex interplay between the innate and the adaptive immune system, with monogenic SAID and monogenic autoimmune disease being the respective extremes (Fig. 1) [3,4].

3. Pathophysiology

Monogenic SAIDs are caused by inborn errors of the innate immune system that lead to constitutive inflammation. Occasionally, an environmental stimulus can result in the transcriptional and post-transcriptional mechanisms not being able to mitigate cytokine synthesis and release, leading to their dysregulation and overproduction with overresponse of innate and adaptive mechanisms [2,5,6]. However, these triggers remain to be elucidated for most autoinflammatory disorders. Historically, the classification of SAIDs focused on the primary altered molecular pathways. A schematic overview of the pathophysiological pathways involved in SAIDs is presented in Fig. 2. Although many monogenic SAIDs can be sorted into this paradigm, other complex disorders and newly identified monogenic SAID seem to defy this classification, resulting in a significant overlap between autoinflammation, autoimmunity, and immunodeficiency [7–11].

4. SAID presenting in adults

SAIDs are generally regarded as early-onset recurrent fever syndromes. However, a growing number of adult patients are recognized with SAIDs due to increased awareness and a better understanding of these disorders [12–14]. As in autoimmune disease, precision medicine is becoming increasingly important in the diagnosis of autoinflammatory diseases [15]. The introduction of next generation sequencing, using targeted gene panels, whole-exome or whole-genome sequencing approaches, has significantly contributed to the understanding and discovery of monogenic SAID. In adults, both childhood-onset with delayed diagnosis as well as adult-onset cases have been recognized. Adult patients may present with the initial manifestations of a SAID, as can be seen in patients with Schnitzler syndrome, who have a mean age of 51 years at disease onset [16]. However, many adults with SAIDs have a long-standing history of unexplained recurrent fever

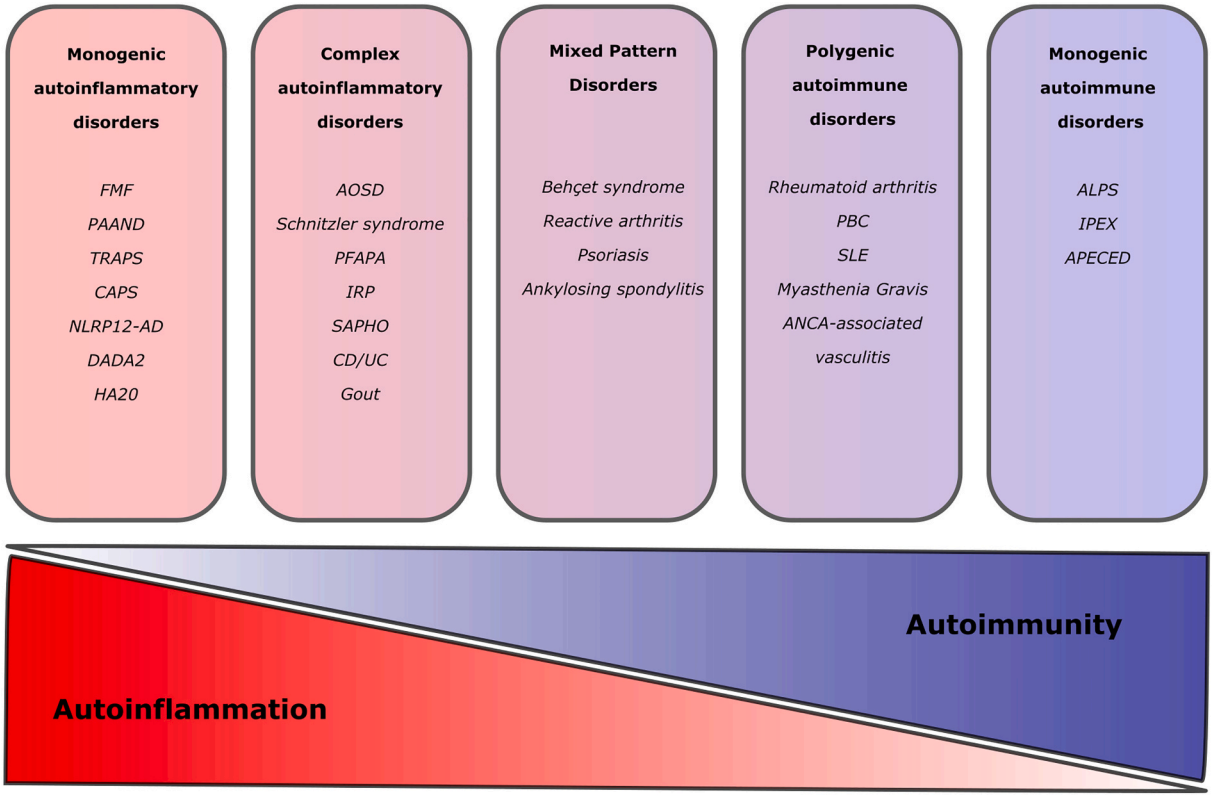

Fig. 1. Schematic representation of the immunological disease continuum.
Diseases classified according to involvement of the innate immune system (autoinflammation) or the adaptive immune system (autoimmune). Phenotypical heterogeneity within immunological diseases may reflect the variable role of autoinflammatory and autoimmune factors with regard to disease causation. A disease spectrum includes rare monogenic diseases at the polar ends of the spectrum and polygenic diseases in the center. The figure does not include all immunologically recognized diseases, because of their large number.
Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AOSD, adult-onset Still's disease; ALPS, autoimmune lymphoproliferative syndrome; CAPS, Cryopyrin-associated periodic syndrome; CD, Crohn's disease; DADA2, deficiency of ADA2; FMF, Familial Mediterranean Fever; HA20, haploinsufficiency A20; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked syndrome; IRP, idiopathic recurrent pericarditis; NLRP12-AD, NLRP12-associated autoinflammatory disease; PAAND, Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis; PBC, primary biliary cirrhosis; PFAPA, periodic fever with aphthous stomatitis pharyngitis and adenitis; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome; SLE, systemic lupus erythematosus; TRAPS, TNF-receptor associated periodic syndrome; UC, ulcerative colitis.

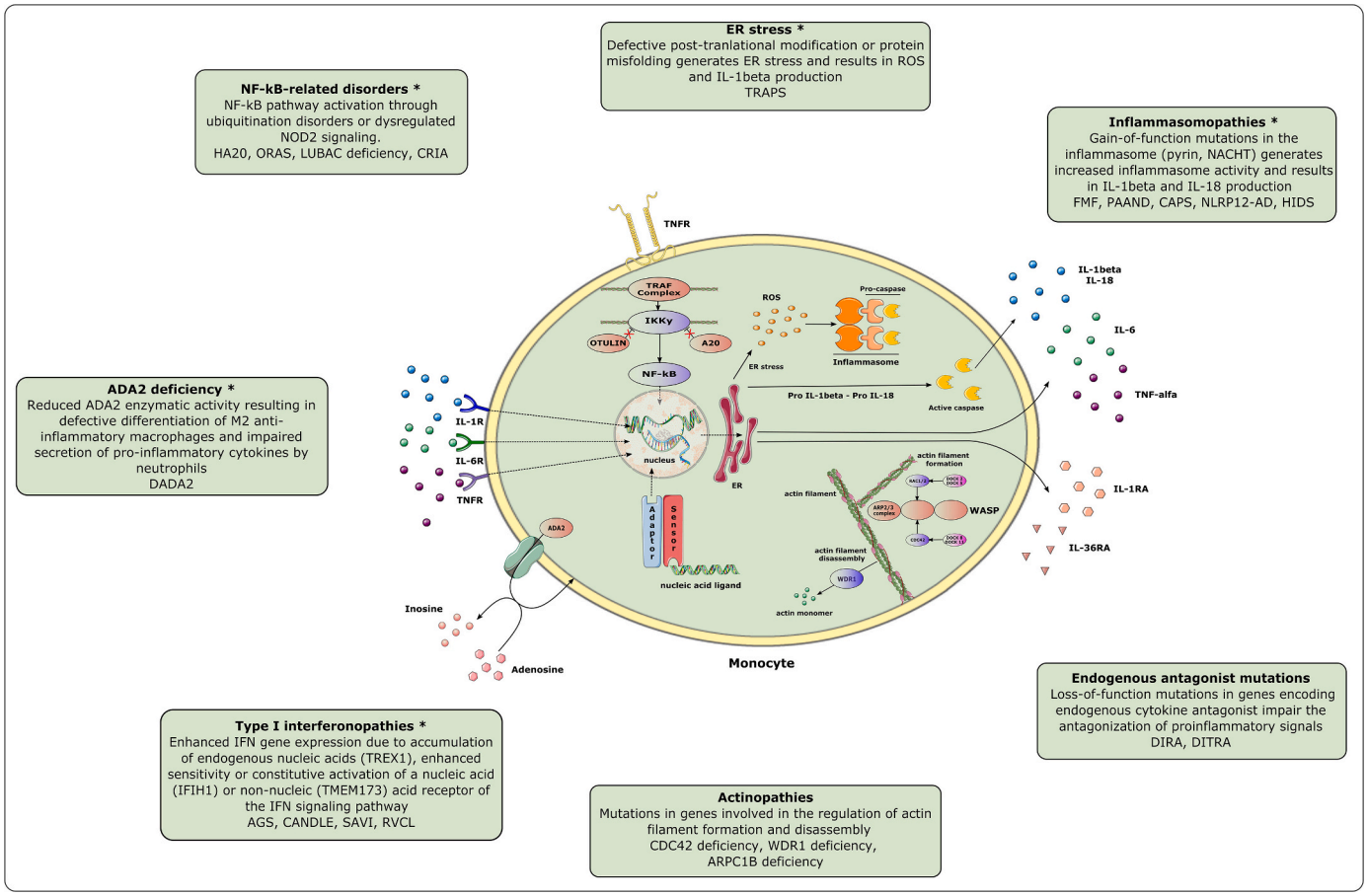

Fig. 2. Schematic representation of pathogenic mechanisms associated with autoinflammatory disease.
Simplified representation of the main pathophysiological pathways driving autoinflammatory disease with a short description of each mechanism and examples of associated conditions. Mechanisms associated with adult-onset cases are indicated by an asterisk.
Abbreviations: ADA2, adenosine deaminase 2; ARP2/3 complex, actin-related proteins-2/3 complex; CDC42, cell division control protein 42; DADA2, deficiency of ADA2; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated autoinflammatory syndromes; CRIA, cleavage-resistant RIPK1-induced autoinflammatory syndrome; DIRA, deficiency of IL-1Ra; DITRA, deficiency of IL-36Ra; DOCK, dedicator of cytokinesis; ER, endoplasmic reticulum; HA20, haploinsufficiency A20; HIDS, hyperimmunoglobulin D syndrome; IFN, interferon; IKKy, inhibitor of kappaB kinase gamma; IL, interleukin; IL-1R, IL-1 receptor; IL-1Ra, IL-1 receptor antagonist; IL-6R, IL-6 receptor; LUBAC, linear ubiquitin chain assembly complex; MKD, mevalonate kinase deficiency; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP12-AD, NLRP12-associated autoinflammatory disease; ORAS, OTULIN-associated autoinflammatory syndrome; OTULIN, OTU deubiquitinase with linear linkage specificity; PAAND, Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis; RAC1/2, Ras-related C3 botulinum toxin substrate 1/2; ROS, reactive oxygen species; RVCL, retinal vasculopathy with cerebral leukodystrophy; STING-associated vasculopathy with onset in infancy; TNF-alfa, tumor necrosis factor alfa; TNFR, TNF receptor; TRAF, TNF-receptor associated factor; TRAPS, TNF receptor-associated periodic syndrome; WASP, Wiskott-Aldrich syndrome protein; WDR1, WD repeat-containing protein 1.

episodes or recurrent inflammation dating back to childhood.

Individuals with a mild SAID phenotype may become accustomed to their symptoms, preventing them from seeking medical care. Disease manifestations may also be mistaken for other disorders, such as recurrent infections or inflammatory bowel disease in patients with Hyperimmunoglobulin D syndrome (HIDS) [17]. Next, the diagnosis of disease in a child may trigger a diagnosis in the parent with milder phenotype. Furthermore, a large proportion of SAIDs have only recently been described. In the past, patients with autoinflammatory manifestations were classified as having immune-mediated inflammatory disorders or an undifferentiated inflammatory disease [18]. Improvement in genetic tools, such as the use of amplicon-based deep sequencing, allowed detection of somatic mosaicism, which led to an increased identification of monogenic SAIDs in the adult population [19]. Monogenic SAIDs may also be present in individuals with low-penetrance germline mutations, which are associated with a delayed disease-onset and a variable clinical phenotype [19–21]. Finally, the rarity of SAIDs and the episodic nature of clinical features may complicate establishing a diagnosis during infancy. Development of other clinical features at an older age sometimes allows to connect the dots and lead to a definitive diagnosis.

5. Clinical spectrum in adult patients

A schematic overview of the most important disorders discussed in this section is provided in Fig. 3.

5.1. Monogenic autoinflammatory disease

5.1.1. Familial Mediterranean Fever (FMF) and Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND)

FMF is an autosomal recessive disorder, but a significant proportion of heterozygotes also express the phenotype [22]. The prevalence of FMF is associated with ethnicity, as it is primarily reported in people of Mediterranean ancestry (Turks, Arabs, and Armenians), but also in other parts of the world [23]. It is caused by homozygous or compound heterozygous mutations in the *MEFV* gene encoding the protein pyrin, which results in pyrin-mediated inflammasome assembly and secretion

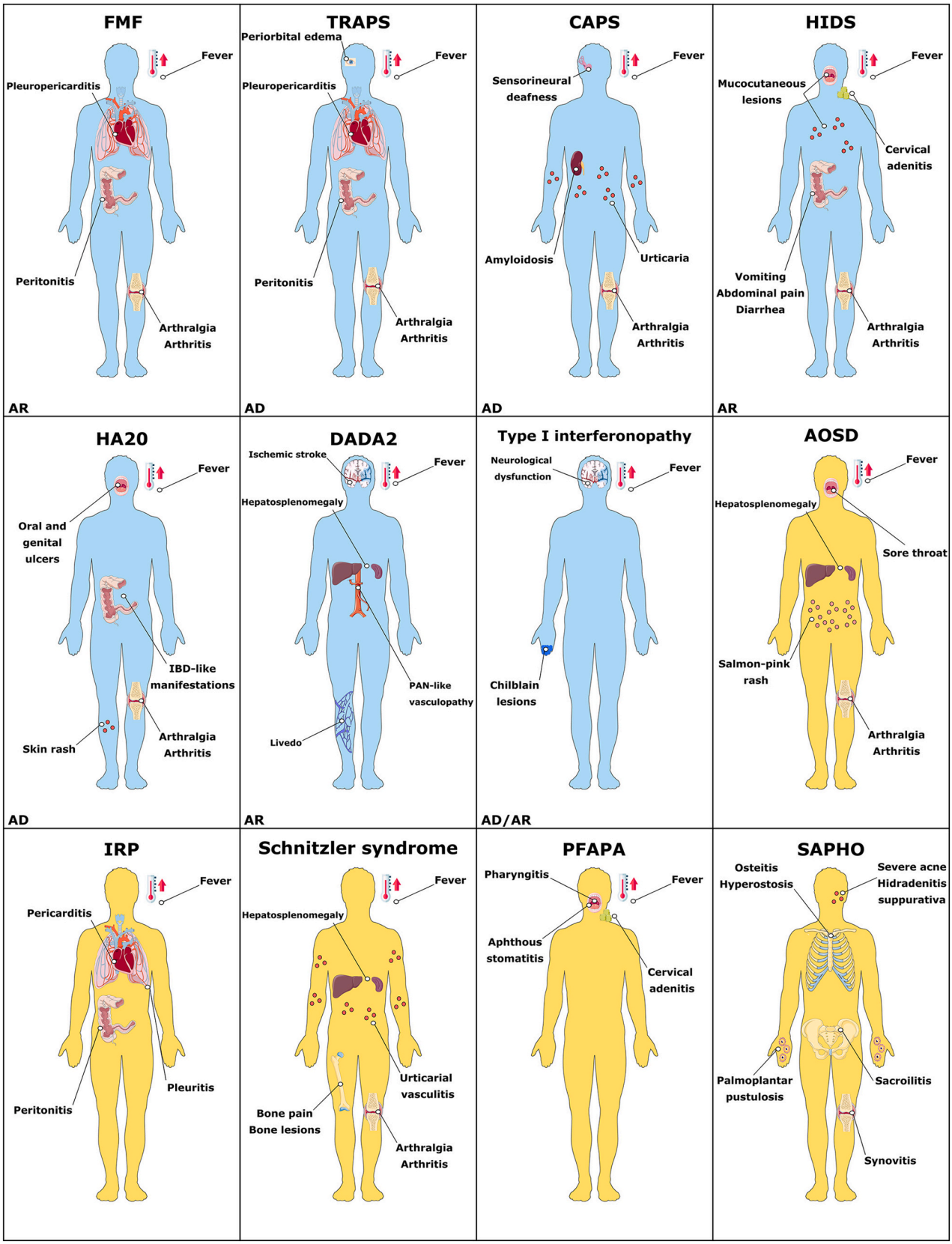

Fig. 3. Schematic representation of selected systemic autoinflammatory disorders in adults.
Cardinal features of the most important monogenic (blue) and complex (yellow) autoinflammatory disorders in adults.
Abbreviations: AD, autosomal dominant; AOSD, adult onset Still's disease; AR, autosomal recessive; CAPS, cryopyrin-associated periodic syndrome; DADA2, deficiency of adenosine deaminase 2; HA20, haploinsufficiency A20; HIDS, hyperimmunoglobulin D syndrome; FMF, familial Mediterranean fever; IBD, inflammatory bowel disease; IRP, idiopathic recurrent pericarditis; PAN, polyarteritis nodosa; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and adenitis; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; TRAPS, TNF-receptor associated periodic syndrome.

of the pro-inflammatory cytokines. Clinical symptoms usually start in childhood, but 5% of FMF patients develop disease manifestations only after the age of 30 years [24]. The clinical picture in adult patients is characterized by self-limiting attacks of fever and serositis, most commonly involving peritoneum and pleura. Pericarditis is present in a small percentage of patients [25]. The febrile episodes typically last three days or less, and patients appear healthy between attacks. Attacks may be triggered by fatigue, vigorous exercise, cold exposure, menstruation, and surgery [25]. Musculoskeletal manifestations include myalgia and arthritis, usually presenting as monoarthritis of the large joints [26]. Sacroiliitis may be present [27]. A self-limiting unilateral rash resembling cellulitis on the extensor surfaces of the leg is reported in 12–41% [24]. Protracted and uncontrolled inflammation can lead to anemia, splenomegaly, reduced bone mineral density, and tissue deposition of serum amyloid A, which ultimately leads to amyloidosis [28]. In this case, the kidney is most frequently affected, presenting as nephrotic range proteinuria and renal impairment. In some adult cases, this was reported to be the presenting feature [29].

Adult onset FMF has been extensively reported and seems to differ from childhood onset FMF in both genetic and clinical aspects. According to a large retrospective cohort study, late-onset FMF (defined as age of onset $\geq$20 years), had a lower prevalence of fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema compared to early-onset patients [30]. Genetic factors could partially explain the altered phenotype, since highly penetrant variants such as homozygous M694V mutations were less frequently observed in adult-onset FMF compared to early onset FMF[30].

During acute attacks, non-steroidal anti-inflammatory drugs (NSAIDs) often provide pain relief. Colchicine decreases the severity and frequency of attacks and drastically reduced the incidence of amyloidosis in this population [31]. IL-1 inhibition is an effective treatment in FMF but should be reserved for patients who are resistant or intolerant to colchicine [32].

PAAND is a recently described disorder that is also caused by *MEFV* mutations. However, PAAND is caused by a heterozygous *MEFV* mutation resulting in an altered 14–3-3 binding motif and constitutive activation of pyrin. This is associated with a distinct clinical phenotype characterized by period fever and neutrophilic dermatosis, including acne and pyoderma gangrenosum [33].

5.1.2. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)

TRAPS is an autosomal dominant disorder and is the most prevalent SAID in the Northern-European population [34]. Heterozygous mutations in *TNFR1SF1A*, which encodes TNF receptor 1, lead to enhanced NF-κB and NLRP3 activation through various mechanism such as increased endoplasmic reticulum stress, defective autophagy or defective shedding of soluble TNFR1 proteins which should act as decoy receptors which attenuate the proinflammatory signal [35]. Adult-onset disease is seen in 22% of TRAPS patients according to the Eurofever registry, with the oldest patient being 63 years at time of symptom onset [21].

In contrast to FMF, disease attacks last longer, ranging from one to three weeks, and may follow a more continuous course. Similar triggers as described in FMF can precede attacks, but often they are unprovoked. Symptoms consist of fever, serositis, myalgia, and a migratory erythematous rash [36]. A variety of other cutaneous manifestations have been described, including cellulitis-like erythema, periorbital edema, edematous plaques and urticaria [37]. Arthralgia is more frequent than arthritis and mainly involves the large joints [21]. Serositis may involve the pleura, pericardium, peritoneum, and tunica vaginalis, either simultaneously or isolated [21] Ocular symptoms such as conjunctivitis and ophthalmodynia may be present [21]. The incidence of amyloidosis is much lower compared to FMF [36].

Age of onset seems to impact the clinical course of TRAPS. A recent retrospective study compared 7 patients, aged 16 years and older, with adult-onset to 11 patients with infancy-onset TRAPS with a low-penetrance heterozygous R92Q mutation. Adult-onset patients tended to have a longer duration of disease attacks and had a higher prevalence of pericarditis and headache compared to infancy-onset patients. In contrast, peritonitis, vomiting, cervical adenitis, pharyngitis, and a family history of a SAID were more prevalent in early-onset patients [38].

NSAIDs and colchicine may be beneficial, especially in patients with the mild R92Q variant [39]. Corticosteroids are often used for the treatment of acute attacks in TRAPS, but long-term therapy is associated with diminished efficacy and significant toxicity [40]. Maintenance therapy with IL-1 or TNF-α (etanercept) inhibition is recommended as persistent disease activity may result in AA amyloidosis. TNF-α inhibitors other than etanercept are associated with treatment failure or even deterioration in TRAPS [41]. IL-1 inhibition appears superior to etanercept with regard to symptom control in retrospective studies [42].

5.1.3. Cryopyrin-associated periodic syndromes (CAPS) and NLRP12-associated disorder (NLRP12AD)

CAPS is an autosomal dominant disorder caused by gain-of-function mutations in NLRP3 resulting in a clinical spectrum of autoinflammatory disease, including neonatal-onset multisystem inflammatory disease, Muckle-Wells syndrome and familial cold autoinflammatory syndrome [43]. Neonatal-onset multisystem inflammatory disease (NOMID) is the most severe phenotype with an exclusive neonatal onset, and is more extensively reviewed by Hoffman et al. [44]

Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS) may start at any age and represent respectively the intermediate and mildest phenotype within CAPS [45]. Both syndromes are characterized by intermittent febrile episodes, neutrophilic urticaria, conjunctivitis, and arthralgia. Other symptoms such as fatigue, headache, and myalgia are associated with systemic inflammation. If left untreated, patients encounter daily symptoms in addition to intermittent disease flares that last hours to days and are triggered by infections, sleep deprivation, stress, and alcohol. Despite their similarities in clinical phenotype, symptoms in MWS are not precipitated by cold exposure. In addition, sensorineural hearing loss, meningitis, and oligoarthritis may be present in MWS. In untreated patients, chronic organ damage due to amyloidosis may develop in 25% of patients with MWS, but rarely in FCAS.

IL-1 inhibition is the first line treatment for CAPS and is effective for the entire clinical spectrum [46,47]. There is no evidence for efficacy of NSAIDs, corticosteroids or disease modifying antirheumatic drugs (DMARDs) without IL-1 inhibition, and it is essential to initiate IL-inhibition early, before irreversible organ damage occurs [39].

NLRP12AD is an autosomal dominant disorder caused by mutations in *NLRP12,* that shares a number of similarities clinical and biological similarities with CAPS [48]. The disease usually starts in early childhood, but multiple patients with disease onset in adulthood have been reported [49–51]. As in CAPS, patients experience attacks that are characterized by fever, arthralgia, myalgia, neutrophilic urticaria, and systemic inflammation They may also present with sensorineural hearing loss. Disease attacks may vary significantly both in frequency and duration. Disease episodes are often triggered by cold exposure. The treatment of NLRP12AD is mainly focused on avoiding cold exposure. Pharmacological therapy is mainly empirical, but a treatment approach similar to that in patients with CAPS may be adopted [48,49].

5.1.4. Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)

HIDS is an autosomal recessive disorder caused by loss-of-function mutations in the *MVK* gene, resulting in deficiency of mevalonate kinase and dysfunction of Ras homolog family member A, a small guanosine triphosphatase, which activates the pyrin inflammasome. Most patients are of Caucasian descent, with approximately 75% of patients originating from Western Europe. HIDS usually starts in early childhood,

but given a median diagnostic delay of 6 years (interquartile range of 1.9–14.2 years) reported in a study on 114 HIDS patients from the Eurofever registry, diagnosis may often be delayed until adolescence or adulthood due to various reasons [52–54].

In 87% of patients, the disease course is characterized by recurrent episodes of inflammation lasting 4 to 6 days. In 13% of patients, the symptoms are more continuous with or without intermittent disease flares [52]. Disease attacks are characterized by fever accompanied by tender (cervical) lymphadenopathy and abdominal pain with vomiting or diarrhea. Mucocutaneous involvement is present in 87%, including maculopapular rash, purpura, urticaria, oral and genital aphthous ulcers, and exudative pharyngitis. Over half of the patients have myalgia and arthralgia. Large joint arthritis is present in a minority of patients. Ocular involvement, including conjunctivitis and uveitis, is present in 15%.

Recurrent upper and lower respiratory tract infections are reported in patients with HIDS, and they may be hard to differentiate from disease attacks. The frequency of attacks varies between and within patients. Attacks may be triggered by infections, trauma, and stress, although an apparent trigger may not be present. Childhood vaccination is a characteristic trigger of the first disease flare of HIDS [52,54]. Amyloidosis and macrophage activation syndrome can occur but are considered rare complications of HIDS [52].

High IgD levels are commonly observed in HIDS. However, an elevated IgD level is not diagnostic of HIDS, as it occurs in other autoinflammatory disorders, including FMF, TRAPS, and Periodic fever with aphthous stomatitis pharyngitis and adenitis (PFAPA). Approximately 20% of cases with genetically confirmed HIDS do not have a high IgD, and IgD levels do not correlate with disease severity. Around 80% of patients may also have a high IgA level, often in correlation with elevated IgD levels [52]. HIDS also causes high levels of mevalonic acid in the urine during flares. However, this is a difficult test to perform and should not be mandatory before genetic analysis [55].

NSAIDs and corticosteroids may be beneficial for the treatment of acute attacks in HIDS [39]. Colchicine seems to be ineffective [39]. On demand IL-1 inhibition reduces all features of fever episodes, but for patients with frequent attacks or subclinical inflammation, maintenance therapy with IL-1 inhibition or TNF-α blockade is recommended [42].

5.1.5. Haploinsufficiency A20 (HA20) and NF-κB-related autoinflammation

HA20 is caused by heterozygous germline mutations in TNFAIP3 encoding the NF-κB regulatory protein A20 [56]. HA20 is most commonly reported in patients of European and Japanese descent. Although the disorder usually manifests in early-childhood, a number of patients have been reported with disease-onset in adolescence or adulthood [57].

The clinical overlap of HA20 with several other rheumatologic conditions resulted in patients being initially diagnosed with Behçet syndrome, juvenile idiopathic arthritis, rheumatoid arthritis, PFAPA, Crohn's disease, systemic lupus erythematosus, and adult onset Still disease prior to receiving a molecular diagnosis. In addition, clinical manifestations may vary significantly, even in patients with the same genetic variant [56].

Skin and mucosal manifestations are important features of HA20. Oral and/or genital ulcers are present in 64% of patients. A skin rash is present in 43% of patients, including nonspecific rash, malar rash, erythema nodosum-like lesions, psoriasis, and folliculitis. Recurrent fever is reported in 44% of affected individuals. Gastrointestinal symptoms, including abdominal pain, vomiting, diarrhea, abdominal lymphedema, and intestinal edema, and musculoskeletal symptoms, such as arthralgia and arthritis, are present in 44% and 33% respectively. Ocular manifestations, including anterior uveitis, retinal vasculitis, and episcleritis, are reported in a minority of patients [57].

Treatment strategies in HA20 are largely based on case series. Some patients respond well to colchicine monotherapy, but most patients require a combination of immunosuppressive drugs, including corticosteroids, DMARDs and cytokine inhibitors such as TNF-α inhibition, IL-1 inhibition, IL-6 inhibition, and JAK inhibition [18,57]. Some patients were treated with intravenous immunoglobulins (IVIG) for recurrent infections. In case of severe disease activity, hematopoietic stem cell transplantation may be considered [18].

Haploinsufficiency of the subunit p50 caused by heterozygous *NF-κB1* mutations is another disorder related to this pathway, which is associated with a complex phenotype characterized by infections, autoimmunity, inflammation, and lymphoproliferation and has a disease onset after 20 years of age in 31.5% of patients [58].

5.1.6. Deficiency of ADA2 (DADA2)

DADA2 is an autosomal recessive disease caused by loss-of-function mutations in *ADA2*, formerly named cat eye syndrome chromosome region, candidate 1, which result in a monogenic vasculitis syndrome [7]. The majority of patients present in childhood, but occasionally diagnosis is delayed until adulthood due to low disease activity, prolonged disease-free intervals, or symptoms being attributed to other immune-mediated inflammatory disorders. Multi-system involvement is common and the phenotypic manifestations of DADA2 are still expanding.

Vasculopathy of small- and medium-sized arteries is the major hallmark of DADA2. The central nervous system and skin are most commonly involved, yet the gastrointestinal system, the renal system, and coronary arteries may also be affected [59]. Neurologic manifestations are caused by lacunar strokes. They may have a very early onset. Hemorrhagic strokes mostly occur at the site of a previous lacunar infarct and may be worsened by the use of an anti-thrombotic or anticoagulation treatment initiated for earlier stroke [7]. There may also be spinal cord or peripheral nervous system ischemia, resulting in bilateral extremity involvement or mononeuritis multiplex, respectively. Cutaneous manifestations are present in over 75% of patients. Livedo racemosa is a common symptom, usually observed in the extremities. Other dermatologic manifestations include cutaneous arteritis, leukocytoclastic vasculitis, subcutaneous nodules, Raynaud phenomenon, and digital ischemia [59]. Gastrointestinal manifestations are present in 33% of patients, ranging from abdominal pain and liver test abnormalities to severe complications such as intestinal necrosis and bowel perforation or stenosis. Hypertension, sometimes refractory, is present in 21% of patients. Other possible manifestations include arthralgia, myalgia, arthritis, lymphoproliferation as manifested by hepatosplenomegaly or enlarged lymph nodes, renal artery stenosis, and testicular symptoms [59].

Fever with increased inflammatory parameters is reported in 50% of patients. In addition, immunologic and hematologic manifestations are often prominent in DADA2. Hypogammaglobulinemia is present in over 20%, and patients were often diagnosed with common variable immunodeficiency in the past [59,60]. Other immunologic features include neutropenia, CD4 lymphopenia, and decreased memory B cells [60]. Anemia, thrombocytopenia, or even pancytopenia are present in a minority of patients, yet hematologic manifestations may be the initial presenting symptom of DADA2 [59]. These abnormalities can explain the infectious susceptibility seen in this patient group as 20% of patients had recurrent sinopulmonary infection.

TNF-α inhibition is the mainstay of treatment and is successful in controlling fever episodes, vasculopathy, strokes [61]. In contrast to routine care for stroke patients, it is recommended to discontinue antithrombotic and anticoagulant agents as hemorrhagic stroke is a potential complication. B-cell depletion using rituximab has been reported with variable success for controlling cytopenia, and immunoglobulin substitution, antibiotics, and antiviral treatment may be beneficial in case of documented hypogammaglobulinemia with clinical immunodeficiency. Guided by the severity of the phenotype and the lack of response to treatment with TNF-α inhibitors, hematopoietic stem cell transplantation has been reported to control immunological,

hematological, and vascular manifestations as a more definitive treatment [62].

5.1.7. Type 1 interferonopathies

Type 1 interferonopathies comprise a group of disorders caused by dysregulated interferon-mediated immune responses. Most type 1 interferonopathies are early-onset inflammatory syndromes [63]. More recently, an increasing number of adult-onset cases are being described.

Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL) is an adult-onset interferonopathy caused by heterozygous frameshift mutations in the C-terminus of *TREX1* and encompasses three conditions, including cerebroretinal vasculopathy, hereditary vascular retinopathy, and hereditary endotheliopathy with retinopathy, nephropathy and stroke. Symptoms may include central nerve system degeneration, stroke, motor impairment, cognitive decline, loss of vision, Raynaud phenomenon, glomerular dysfunction, and micronodular cirrhosis. Death occurs in most patients 5–10 years after disease onset [64,65].

Aicardi-Goutières syndrome (AGS) was originally described as a progressive brain disease with early onset mimicking in utero viral infection [66]. Since then, a range of genetic mutations associated with AGS have been reported and the phenotype has expanded significantly [67]. The presentation may range from severe neonatal forms to later-onset forms with considerable intrafamilial and interfamilial variability. An adult patient has been reported to present with *RNASEH2B*-related Raynaud phenomenon and digital ischemia associated with arthralgia and myalgia [68]. Other adult patients may have been misdiagnosed with cerebral palsy in childhood, with a seemingly static disease course from infancy, in whom the presence of chilblains may be an important clue leading to the diagnosis of AGS [69].

Janus kinase (JAK)-inhibition, and more specifically inhibition of JAK1 and JAK2, has become the mainstay of treatment of Aicardi–Goutières syndrome and other type I interferonopathies [70–72]. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. The measurement of neurologic improvement remains complex, but baricitinib treatment may improve neurologic function, even in patients with severe and long-standing disease [72].

5.1.8. Vacuoles, E1 enzyme, X-linked, autoinflammatory somatic syndrome (VEXAS)

VEXAS is caused by acquired inactivating mutations in UBA1, a gene encoding the ubiquitin-activating enzyme 1. This disorder is a late-onset, X-linked, treatment-refractory autoinflammatory syndrome with associated hematologic abnormalities. The median age at disease onset is 64 years [73].

The majority of patients have recurrent fevers, pulmonary involvement, dermatologic manifestations (including neutrophilic dermatoses and cutaneous vasculitis), macrocytic anemia, hematopoietic dyspoiesis, and bone marrow vacuolization restricted to myeloid and erythroid precursor cells. All patients have highly elevated levels of acute-phase reactants and had no response to multiple disease-modifying antirheumatic drugs except for corticosteroids, often administered in high doses. Of the 25 patients reported, 40% died from disease-related causes, including respiratory failure or progressive anemia, or complications related to treatment [73].

5.2. Complex autoinflammatory disease

5.2.1. Adult onset Still disease (AOSD)

AOSD is considered a polygenic disease. It was originally described as an adult-onset form of pediatric Still's disease, characterized by arthritis, fever, lymphadenopathy, organomegaly and pericarditis, better known today as systemic juvenile idiopathic arthritis [74,75]. AOSD and systemic juvenile idiopathic arthritis are commonly considered to be part of a disease continuum. The pathogenesis of AOSD remains to be fully elucidated, but evidence supports the role of both genetic risk factors and environmental triggers, which together result in excessive inflammation (IL-1β, IL-6, and IL-18) mediated by the innate immune system [76–78].

AOSD is commonly characterized by the tetrad of spiking fever, rash, sore throat, and arthritis. Nonetheless, the clinical presentation is heterogeneous in disease manifestations, severity, and course. Fever is the hallmark of AOSD and is present in virtually all patients [79,80]. Classically, fever has an abrupt onset and a high spiking pattern (over 39 °C), with several daily spikes [81]. The typical rash in AOSD is a salmon pink erythema, often appearing together with fever on the trunk and proximal limbs. Other cutaneous manifestations, including urticaria, eczematous lesions, and acne-like lesions, are also observed [82,83]. A sore throat may be present in up to 92% of cases [79].

Arthritis in AOSD is polyarticular in nature, with a predilection for large joints. It may be destructive, ultimately leading to ankylosis [79,84,85]. Myalgia is common during flares. Serositis is often present but rarely prominent and may involve pericardium, pleura, or peritoneum [79,80]. Generalized lymphadenopathy and hepatosplenomegaly are other features that can occur during episodes of disease activity [86]. Macrophage activation syndrome is an important complication of AOSD and is the major cause of death [87].

AOSD may manifests as a single flare easily controlled by NSAIDs or a short course of corticosteroids. In case of early signs of corticosteroid dependency, methotrexate should be considered timely for a corticosteroid-sparing effect. In patients with refractory AOSD and predominant systemic features, IL-1 inhibition is preferred considering the significantly higher efficacy for systemic symptoms compared to articular manifestations. In patients with an articular form of refractory AOSD, IL-6 inhibitors or TNF-α inhibitors are preferred treatment options [88].

5.2.2. Idiopathic recurrent pericarditis (IRP)

Recurrent pericarditis is defined as a relapse of pericarditis following a symptom-free interval of at least four weeks, corresponding to the usual duration of treatment in most non-complicated cases of acute pericarditis. In chronic pericarditis, symptoms persist during more than three months without a symptom-free interval of four weeks [89]. The frequency of recurrence varies between 20 and 30% after the first episode of acute pericarditis and between 20 and 50% after the first relapse [89].

In 80% of adult patients, recurrent pericarditis is considered idiopathic because a specific etiology cannot be identified [90]. The pathophysiology is complex and may involve inadequate clearance of infection and autoreactive antibodies against pericardial antigens. The spectacular effect of IL-1 inhibition as well as the occurrence of recurrent episodes of pericarditis in several monogenic autoinflammatory disorders are evidence of a role of the innate immune system. This led to the belief that the mechanism of recurrence in idiopathic recurrent pericarditis is the result of autoinflammatory processes, while the etiology of the initial eliciting factors may vary widely, including (viral) infections and autoimmune disorders.

The most frequent manifestations of patients with recurrent pericarditis include chest pain (100%), pleuritic pain (36%), fever (30%), elevation of liver enzymes (8%), and peritonitis (5%) [91,92]. Typically, chest pain is improved by leaning forward and worsened by lying supine. Usually, objective signs of pericardial inflammation are present, such as a pericardial friction rub or effusion and compatible ECG changes. Symptoms and signs are often less pronounced in recurrent episodes, especially during treatment. Imazio et al. defined a recurrence of pericarditis by recurrent pain and ≥ 1 of the following signs: fever, pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, elevations in white blood cell count, or C-reactive protein or erythrocyte sedimentation rate [93].

Colchicine is the mainstay of treatment in IRP. In case of refractory symptoms, low-dose corticosteroids are often associated. In patients with corticosteroid dependence, classic DMARDs, such as azathioprine

or methotrexate, should be used for their corticosteroid-sparing effect [94]. Anakinra, an IL-1 inhibitor, is very effective in the treatment of IRP, but usually reserved for very refractory cases [95]. Pericardiectomy can be considered as a last option in case of failure of IL-1 inhibition, but residual chest pain may persist [96].

5.2.3. Schnitzler syndrome

Schnitzler syndrome was first described in 1972 by Liliane Schnitzler as a constellation of clinical symptoms associated with a monoclonal gammopathy [97]. The median age of onset is 55 years and there is a slight predominance among males [98]. The pathophysiology of Schnitzler syndrome remains to be elucidated. Clinical and biological features largely overlap with the CAPS, a monogenic autoinflammatory syndrome caused by activating mutations in the NLRP3 gene, suggesting an autoinflammatory nature of this disorder. Somatic mosaicism of NLRP3 mutations in the myeloid lineage was reported in a few patients, but is unclear if these cases should rather be considered as mosaics of CAPS [99]. Increased production of IL-1β and IL-6 by lipopolysaccharide-stimulated peripheral blood mononuclear cells was reported, and suggest increased inflammasome activity [100]. The role of the paraprotein in the pathogenesis remains unclear.

Schnitzler syndrome is characterized by recurrent fever, urticarial rash, bone and/or joint pain, and presence of a paraprotein. At onset, the clinical findings of Schnitzler syndrome may be less specific and involve isolated recurrent fever, bone and/or joint pain, or weight loss [98]. According to the Strasbourg criteria, the presence of urticarial rash is mandatory in all patients. It is usually reported as the first presenting symptom, and may precede the other symptoms by several years [101]. Although the extent may differ greatly, it is predominantly present on the trunk and limbs. Lesions may persist less than 24 to 48 h.

Recurrent fever is present in 72% of cases, and usually occurs simultaneously with the rash. Up to 40% of patients report join or bone pain, predominantly in the lower limbs, but frank arthritis is rare. Lymphadenopathy is present in 25% of patients, and splenomegaly or hepatomegaly may also be observed. Less frequently, patients may also report weight loss and symptoms of neuropathy [101]. By definition, a monoclonal gammopathy is present in all patients with Schnitzler syndrome. The IgMκ paraprotein is the most prevalent antibody, observed in over 80% of patients. However, the number of patients with Schnitzler syndrome who have a monoclonal IgG paraprotein may be underestimated, considering earlier classification criteria required an IgM paraprotein for diagnosis.

Many immunosuppressive drugs have been used in Schnitzler syndrome, but most of these drugs had only limited to no efficacy [16]. Continuous IL-1 inhibition is highly effective in patients with Schnitzler syndrome [102,103]. In the small number of patients who do not have a good clinical response to IL-1 inhibition, IL-6 blockade may be an effective alternative [104].

5.2.4. Periodic fever with aphthous stomatitis pharyngitis and adenitis (PFAPA)

PFAPA was first described in 1987 as a periodic syndrome occurring every 4 to 6 weeks with episodes of fever, aphthous stomatitis, pharyngitis, and cervical adenitis with spontaneous resolution after 3 to 6 days [105]. PFAPA is generally regarded as an autoinflammatory disorder of the pediatric population with onset within the first 5 years of life. However, multiple studies have reported on adult cases of PFAPA [106–108].

The periodic nature of episodes is the most characteristic feature of PFAPA. Most studies report recurrence every 2 to 8 weeks in pediatric patients. Rigante et al. reported a mean frequency of PFAPA flares of 11.6 per year (every 4.5 weeks) and a mean duration of flares of 6.2 days [108]. Fever episodes were significantly longer among adults, while the characteristic clockwork recurrence is less frequently observed in adult patients compared to children.

Exudative pharyngitis is present in 77% of adult patients, which is significantly less common than in children. Cervical adenitis is present in 73% of patients and is usually bilateral, tender, and nonsuppurative. Aphthous stomatitis is present in half of the patients [108]. The characteristic triad of aphthous stomatitis, pharyngitis, and adenitis is present in only 41% of adult patients with PFAPA, but a combination of 2 of these symptoms may be observed in approximately 60% [107]. Accompanying symptoms such as arthralgia, myalgia, fatigue, headache, ocular signs, and skin rash are more frequent in adults [108].

Treatment approaches for the adult population have been largely derived from those for pediatric patients. In many patients, a single dose of corticosteroids at the onset of fever will result in complete resolution of symptoms, with lower prednisolone doses (0.5 mg/kg/day) being as effective as the higher dose regimen (2 mg/kg/day) [109]. In some patients, colchicine may be effective in increasing the interval between episodes [110]. In case of very frequent episodes, IL-1 inhibitors are a good therapeutic option. High-quality evidence for tonsillectomy in adults is lacking [111].

5.2.5. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome (SAPHO)

Initial reports described an association between cutaneous manifestations, in particular severe acne, palmoplantar pustulosis, and hidradenitis suppurativa, with certain osteoarticular manifestations like aseptic osteitis or peripheral synovitis. Before a French group proposed SAPHO as a unifying concept, over 50 designations have been used to report this constellation of symptoms, including sternocostoclavicular hyperostosis, acne-associated spondyloarthropathy, or chronic recurrent multifocal osteomyelitis [112].

The osteoarticular involvement is generally insidious in onset. The anterior chest wall is affected in up to 90% of patients. Sacroiliitis may be seen in up to 52% of patients with SAPHO syndrome. The spine is involved in 30% of patients, with the thoracic spine most frequently affected. In contrast to children, the long bones are affected in only 10% of patients. Arthritis may be present in the articulations adjacent to bone lesions. Synovitis in peripheral joints distant from the sites of bone involvement is seen in 30% of adults [113].

The cutaneous manifestations in SAPHO are neutrophilic dermatoses. They may present simultaneously with, earlier, or later than the osteoarticular symptoms. In 70% of patients with cutaneous lesions, skin involvement occurs within an interval of 2 years before or after the onset of osteoarticular symptoms [114]. At least 15% of adults will never experience cutaneous manifestations, whereas others may exhibit multiple different ones. Palmoplantar pustulosis is the most common dermatologic manifestation, affecting up to 60% of patients [115,116]. Severe acne affects approximately 25% of patients with SAPHO [112,115]. Hidradenitis suppurativa is present in 5% of patients [117]. Other rare cutaneous manifestations of the SAPHO syndrome include pyoderma gangrenosum and Sweet's syndrome [113].

SAPHO is associated with inflammatory bowel disease and up to 7.5% of patients may develop Crohn's disease or ulcerative colitis [118]. Systemic manifestations are common, including low-grade fever and moderate elevations of inflammatory parameters [113].

NSAIDs can be used for pain during the diagnostic phase. Corticosteroids, bisphosphonates, and DMARDs such as methotrexate have variable degrees of efficacy. Antibiotics should be used in case of culture-positive bone biopsies. TNF-α inhibition and IL-1 inhibition show good clinical efficacy in persistent disease [119].

6. Clinical approach of adults with suspected SAID

The diagnosis of SAID is often associated with a significant delay, especially in the adult population. In a cohort of 32 adult patients with autoinflammatory disorders, Hernández-Rodríguez et al. reported a mean delay of 12 years (range 0 to 47 years) after onset of symptoms [120]. Thus, a high index of suspicion remains crucial and SAIDs should be suspected in patients presenting with unexplained recurrent or

persistent fever episodes or inflammation associated with mucocutaneous manifestations, serositis, lymphadenopathy, vasculopathy, or musculoskeletal symptoms.

The diagnosis of monogenic SAIDs relies on genetic analysis and identification of a pathogenic mutation. It is pivotal to understand that adult patients may also present with a monogenic SAID, as can be seen in individuals with disease-onset dating back to childhood or patients with a delayed disease-onset due to low-penetrance genetic variants [20]. Hernández-Rodríguez et al. reported a final diagnosis of monogenic SAIDs in 19% of adult patients with genetic testing for suspected autoinflammatory disease [121]. Moreover, somatic mosaicism is increasingly being recognized and may represent in some cases an adult-onset, possibly acquired disease counterpart of an early-onset germline monogenic SAID.

The diagnosis of complex SAIDs is primarily based on a thorough knowledge of the clinical phenotype and, if available, the fulfillment of specific diagnostic criteria such as the Yamaguchi criteria for adult onset Still disease or the Strasbourg criteria for Schnitzler syndrome [101,122]. However, adults with manifestations suggestive of SAIDs may not fit the features of one of the currently known disorders and they may lack a pathogenic variant in genes currently associated with autoinflammatory disease. In patients with undifferentiated SAIDs, continued observance is recommended as the development of new symptoms and signs may lead to a final diagnosis. In addition, new pathogenic mutations and autoinflammatory syndromes may be identified. Furthermore, the presence of clinical and biochemical similarities with known SAIDs may influence therapeutic considerations in these patients.

The clinical approach to autoinflammatory syndromes is based on complete history taking and physical examination (Table 1). Even in monogenic SAIDs, a comprehensive clinical approach is required for a proper interpretation of genetic testing. The age of onset of SAIDs may vary significantly. Although many SAIDs are characterized by an early disease-onset in infancy or childhood, including CAPS, HIDS, type I interferonopathies, and granulomatous autoinflammatory disorders, others usually manifest in adolescence or adulthood, such as Schnitzler syndrome and idiopathic recurrent pericarditis. Ethnicity may also be helpful in establishing the diagnosis. FMF is primarily reported in people of Eastern Mediterranean ancestry. MKD, MWS, and TRAPS are more prevalent in the European population. Nonetheless, the majority of SAID can be found in patients of nearly all genetic backgrounds and geographical regions. A thorough knowledge of the clinical phenotype of SAID is crucial in the assessment of these disorders (Fig. 3). Early referral of patients with clinical features suggestive of SAID may significantly reduce the diagnostic delay. In addition, a low threshold for genetic testing in adults with an unexplained symptom complex, to exclude known monogenic causes, may be warranted given the increased availability and lower cost of next generation sequencing.

7. Conclusion

SAID encompass an expanding group of rare conditions characterized by clinical and biological inflammation and mediated by dysfunction of the innate immune system. Diagnosis is often established in childhood, but a growing number of adult patients are being recognized with autoinflammatory disorders, including adult-onset disease. Despite the recent advances in genetic testing, the diagnosis of autoinflammatory disease is often based on a thorough knowledge of the clinical phenotype. Becoming acquainted with the clinical features of these rare disorders may assist in developing a high index of suspicion for autoinflammatory disease in patients presenting with unexplained fever episodes or inflammation associated with mucocutaneous manifestations, serositis, lymphadenopathy, vasculopathy, or musculoskeletal symptoms.

Table 1
Clinical differentiation of autoinflammatory disorders in adults.

Typical age of onset	Monogenic SAID	Complex SAID
Childhood	CAPS (NOMID – FCAS), NLRP12, AGS, HIDS	PFAPA
Adulthood	RVCL	AOSD, Schnitzler syndrome, IRP, SAPHO
Variable	FMF, CAPS (MWS), TRAPS, HA20, DADA2	–
Disease attack duration		
≤3 days	FMF, CAPS, NLRP12	–
>3 days	PAAND, TRAPS, MKD	PFAPA
Chronic	HA20, DADA2, Interferonopathies	AOSD, IRP, Schnitzler syndrome
Attack-free intervals		
≤4–6 weeks	HIDS	PFAPA
>6 weeks	TRAPS	–
Unpredictable	All others	All others
System involvement		
Cardiorespiratory		
Pleuropericarditis	FMF, TRAPS	AOSD, IRP
Pulmonary involvement	VEXAS	–
CNS		
Hearing loss	CAPS, NLRP12	–
Recurrent meningitis	FMF, CAPS, HIDS	–
Stroke/vasculopathy	HA20, DADA2, AGS	–
Gastrointestinal		
Abdominal pain	HIDS, HA20, DADA2	PFAPA
Peritonitis	FMF, TRAPS	IRP
Diarrhea	TRAPS, HIDS, HA20	–
Lymphoproliferation		
Lymphadenopathy	NLRP12, HIDS	AOSD (+MAS), PFAPA
Splenomegaly	FMF, TRAPS, HIDS	AOSD (+MAS)
Tonsilitis	TRAPS, HIDS	PFAPA
Mucocutaneous		
livedo/chilblains	DADA2, Interferonopathies	–
maculopapular/plaque	FMF, TRAPS, HIDS	AOSD
oral ulcerations	HIDS, HA20, DADA2, NLRP12	–
urticarial-like rash	CAPS, NLRP12, HIDS	AOSD, Schnitzler syndrome
vasculitis	FMF, HIDS, DADA2, PAAND, VEXAS	–
Musculoskeletal		
Arthritis	FMF, CAPS, TRAPS, HIDS, HA20, DADA2	AOSD
Inflammatory bone disease	–	Schnitzler syndrome, SAPHO
Severe myalgia	FMF, TRAPS	–
Ophthalmologic		
Conjunctivitis	CAPS, TRAPS, HIDS	–
Uveitis	CAPS, HA20	–
Treatment response		
Anti-TNF	FMF, TRAPS (*), DADA2 (*)	SAPHO
Anti-IL-1	FMF, TRAPS, CAPS, HIDS	AOSD, Schnitzler syndrome, IRP, PFAPA
Anti-IL-6	–	AOSD, Schnitzler syndrome
JAK inhibitor	Interferonopathies	–

Abbreviations: *, etanercept; AGS, Aicardi-Goutières syndrome; AOSD, adult onset Still's disease; CAPS, cryopyrin-associated periodic syndrome; DADA2, deficiency of adenosine deaminase 2; HA20, haploinsufficiency A20; HIDS, hyperimmunoglobulin D syndrome; FMF, familial Mediterranean fever; IRP, idiopathic recurrent pericarditis; MAS, macrophage activation syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and adenitis; RVCL, retinal vasculopathy with cerebral leukodystrophy; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; TRAPS, TNF-receptor associated periodic syndrome; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory somatic syndrome.

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