Systemic autoinflammatory diseases: Clinical state of the art

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Abstract (138 words)

Systemic auto-inflammatory diseases (SAIDs) are defined as disorders of innate immunity. They were initially defined in opposition to autoimmune diseases due to the lack of involvement of the adaptive immune system and circulating autoantibodies. The 4 historical monogenic diseases are familial Mediterranean fever (associated with *MEFV* mutations), cryopyrinopathies (*NLRP3* mutations), tumor necrosis factor receptor-associated periodic syndrome (*TNFRSF1A* mutations) and mevalonate kinase deficiency (*MVK* mutations). In the last 10 years, more than 50 new monogenic SAIDs have been discovered thanks to advances in genetics. Diagnosis is largely based on personal and family history and detailed analysis of signs and symptoms associated with febrile attacks, in the setting of elevated inflammatory markers. Increasingly efficient techniques of genetic analysis can contribute to refining the diagnosis. This review is a guide for the clinician in suspecting and establishing a diagnosis of SAID.

Introduction

Definition

Systemic auto-inflammatory diseases (SAIDs) are defined according to the International Society of Auto-Inflammatory Diseases as abnormal activation of innate immunity in the absence of infection or autoimmunity(1). Some of the most well-known SAIDs are monogenic, the most common one being familial Mediterranean fever (FMF), while others have a more ill-defined pathophysiology, such as Still's disease or Schnitzler syndrome(2–4). The framework of FMF has been constantly evolving in recent years thanks to advances in genetics and the discovery of new diseases associated with mutations in genes involved in innate immunity(5). Nevertheless, although approximately 60 genes have been associated with a monogenic SAID, it is still difficult in clinical practice to predict if a genetic analysis will detect a pathogenic mutation based only on the clinical phenotype and medical history(4,5). Furthermore, a significant minority of patients are eventually labelled as "unclassified systemic auto-inflammatory disease" or USAID(6).

Main pathophysiological pathways (figure 1)

The pathophysiology of SAIDs is being progressively unraveled as new monogenic diseases are being discovered each year(7). SAIDs are generally caused by a disorder of innate immunity leading to inflammation via multiple effectors.(4,5) In Figure 1, we propose 7 main mechanisms for these diseases.

The most studied and most involved pathway to date is the one of "inflammasomopathies" (top of Figure 1). Associated SAIDs are called as such, since they are caused by excessive and inappropriate activation of inflammasomes (2). In decreasing order of frequency, affected inflammasomes are pyrin, NLRP3, NLRC4 and NLRP1(2). FMF is associated with mutations in the *MEFV* gene encoding pyrin, while cryopyrinopathies are associated with germinal or somatic mutations in the *NLRP3* gene coding for the NLRP3 protein(2). In inflammasomopathies, activation of the final pathway results in excessive production of interleukins (IL)-1, -6 and -18, mainly via the action of caspase 1(2).

In Tumor necrosis factor receptor-associated periodic syndrome or TRAPS, there is an excessive production of reactive oxygen derivatives in the endoplasmic reticulum, ultimately leading to the production of proinflammatory cytokines (8). In case of mutation in the genes coding for IL-1 and IL-36 receptor antagonists, two very rare auto-inflammatory diseases characterized by pustular skin eruptions may occur(9).

We chose to group together several defects downstream of the TNFR1 receptor. One defect involves the protein ubiquitination pathway, leading to activation of the NF-KB pathway. Another involves the RIPK1/caspase 8 pathway, which culminates in apoptosis and necroptosis(10,11). When the A20 protein is mutated, it can induce an autosomal dominant disease called A20 haploinsufficiency, which was first reported in 2015(12). It presents with a wide spectrum of clinical manifestations, with oral and genital ulcers as its hallmark feature(13).

The pathophysiology of ADA2 deficiency, an autosomal recessive disease discovered in 2014, is not yet fully elucidated(14,15). It involves an excess of proinflammatory macrophages to the detriment of anti-inflammatory macrophages, resulting in inflammation of vessel walls. The cerebral vasculature is a frequent site of involvement, and is determinant of its prognosis(16,17).

Interferonopathies are a group of several diseases that lead to uncontrolled signalling via the interferon (IFN) pathway(18,19). Systemic inflammation is generally mild compared to inflammasomopathies (20). Monogenic forms of interferonopathies are rare. They usually begin in childhood and are sometimes associated with autoimmunity. Their treatment is not well established(18,21).

Actinopathies involve a newly discovered pathway. They are caused by mutations in genes encoding proteins that are involved in intracellular actin skeletal assembly and dynamics(22,23). While some actinopathies are associated with primary immune deficiency, others are characterized by autoinflammatory features(22,23). Recently described genes associated with autoinflammatory manifestations and cytopenia are *ARPC1B, WDR1* and *CDC42*(24–30).

1. When to suspect SAID

SAIDs are a distinct group of diseases that are characterized by either periodic or chronic systemic inflammation secondary to errors in the regulation of the innate inflammatory response(1,6). Owing to their genetic nature, most of these disorders have an early onset, ranging from the first hours to the first decade of life; only a limited number of patients develop symptoms during adulthood(7). However, as most of these disorders are extremely rare and comprise a wide clinical spectrum of manifestations, diagnosis is often delayed (6,31).

Roughly speaking, we can identify three clinical situations in which SAIDs should be suspected:

- Some SAIDs are characterized by recurrent flares of systemic inflammation presenting abruptly with fever, dramatic elevation in acute phase reactants, and a variety of clinical manifestations such as rash, serositis (peritonitis, pleuritis, pericarditis, and arthritis), and lymphadenopathy(32). These flares are usually separated by symptom-free intervals of variable duration. They can be triggered by factors often readily identified by the patient such as stress, sleep deprivation, and antigenic stimulation including vaccination and viremia.

- Other SAIDs present with a more chronic course, with systemic inflammation as its core feature. In these cases, dermatological manifestations such as a pseudo-urticarial rash and granulomatous dermatitis can provide clues to the diagnosis(33). The presence of chronic sterile pyogenic abscesses affecting skin, joints and bones are also very suggestive.

- More recently discovered diseases straddle the interface between autoinflammation and immunodeficiency, in which systemic inflammation is associated with a variable degree of immunodeficiency(34). Although their clinical presentation is not stereotyped, family history is often positive, and symptoms tend to respond poorly to standard of care.

Specificities in children:

The recurrence of stereotyped clinical symptoms is probably one of the major features pointing to SAIDs. As in adults, positive family history, presence of consanguinity, and very early onset of disease are all important clues(35). In any case, comprehensive history-taking and repeated clinical examinations remain the best guarantee for correct diagnosis of these complex and rare diseases.

Specificities in adults

In adults, suspecting SAIDs can be difficult because they are less well known and taught than autoimmune diseases. Moreover, historical SAIDs such as FMF, cryopyrinopathies and TRAPS were initially described in the context of a positive family history, such that suspecting SAIDs in a sporadic case is not intuitive at first glance. In general, SAIDs should be suspected when a patient presents with manifestations affecting the mucocutaneous, gastrointestinal, and/or musculoskeletal system(s), as well as systemic inflammation as shown by an elevated C-reactive protein and/or neutrophilic leukocytosis(35). Depending on the clinical context, infection, neoplasia, hematological diseases, and classic autoimmune diseases should be

excluded. Another situation, which is fortunately rarer, is the discovery of AA amyloidosis in a relatively young subject with recurrent fevers in the absence of an alternative cause. Except for adult onset Still's disease, a disease evolution of at least 6 months with the presence on 3 different occasions of elevated inflammatory markers is required before considering SAIDs(36). In all cases, it is necessary to properly question the patient regarding his personal history, going back all the way to his childhood by consulting his health record if available and/or questioning his parents in order to determine the age of onset and main clinical features of his disease(35). Similar signs and symptoms should also be sought in family members for SAIDs with dominant transmission, while consanguinity between parents should be assessed for SAIDs with recessive transmission (37).

Specificities for the rheumatologist

In a rheumatology practice, several clinical features can point towards SAIDs. As mentioned beforehand, recurrent, stereotyped episodes of serositis involving the synovium, pericardium, pleura, and/or peritoneum are a frequent clinical presentation of SAIDs. Although SAIDs can resemble well-known autoimmune diseases, a positive family history, the presence of consanguinity, and early onset of disease are all hints supporting an autoinflammatory pathogenesis. In such cases, atypical features, absence of autoimmunity, and acute inflammatory flares rather than a chronic evolution should further raise suspicion. Finally, an unsatisfactory response to standard of care is not uncommon in SAIDs, given that the latter are mainly driven by IL-1, IL-6, and tumor necrosis factor (TNF). As a result, they may be refractory to disease-modifying anti-rheumatic drugs (DMARDs) as well as certain biologic drugs. Alternatively, inflammatory episodes may spontaneously resolve, only to recur in the same exact fashion.

2- What are the most frequent monogenic SAIDs for clinicians to be familiar with in 2020?

Familial Mediterranean fever

Despite its striking pattern of symptoms, FMF was only first described as a distinct entity in the second part of the 20th century (37). The first generation of investigators dealt with the definition and characterization of its inflammatory attacks and main complication—that is, AA amyloidosis. Starting in 1972, the second generation studied the effect of colchicine on both

inflammatory attacks and amyloidosis (38). In 1992, the gene associated with FMF was mapped to the short arm of chromosome 16, and then cloned in 1997(39,40). It was called *MEFV* for MEditerranean FeVer. FMF is certainly the most common hereditary SAID. It affects populations of Mediterranean descent: Arabs from the East and West, Armenians, Turks, non-Ashkenazi Jews, Druzes, Lebanese, Italians, and Greeks. Among non-Ashkenazi Jews and Turks, the prevalence of *MEFV* heterozygotes exceeds 20%, which explains the pseudodominant mode of inheritance observed in these populations (41).

Clinical picture

Onset of disease occurs before 5 years old in two-thirds of patients. Fever, which is the hallmark feature, is typically associated with signs of acute serosal inflammation: peritonitis (95%), pleuritis (45%), orchitis (3%) and pericarditis (1%); large joints are also affected in more than 50% of patients—mainly knees, hips and ankles(42,43). The most common skin lesion is erysipelas-like erythema of the lower limbs (25%). Usually, a single serosal site is affected during an attack, which may last from a few hours to 3 or 4 days. Attacks resolve spontaneously, with no periodicity in their recurrence. Their frequency varies considerably from one patient to another and from one period of life to another in a same patient. Some factors can trigger attacks, especially stress, viral illnesses in infancy, and even drugs such as metaraminol and cisplatin. Prodromes of FMF attacks are frequent. They may include discomfort at the impending site of involvement, as well as various constitutional, emotional, and physical complaints such as irritability, dizziness, increased appetite, and altered taste sensation.

Except for amyloidosis, chronic manifestations of the disease such as encapsulating peritonitis and chronic destructive arthritis affecting hips and knees are rare. Splenomegaly, usually without clinical repercussion, may also be seen in a subgroup of patients with suboptimal control of inflammation.

Diagnosis

Diagnosis of FMF relies on clinical arguments and is supported by genetic testing (44). In a typical form of FMF, the diagnosis is often obvious. In the appropriate clinical context, the presence of two pathogenic mutations on different alleles (homozygosity or compound heterozygosity) confirms the diagnosis. When only one mutation is present, the diagnosis is not established, but should not be excluded if the clinical presentation is typical. Indeed, although 5 specific mutations represent more than 85% of all mutations, some rare or yet unknown mutations exist (http://fmf.igh.cnrs.fr/infevers/) (45). It is also likely that some heterozygous

patients may have attenuated clinical signs. According to this theory, in large cohorts of patients with periodic fever syndrome, it was noted that the frequency of typical FMF symptoms decreases from patients carrying two high penetrance mutations to patients with a single low penetrance mutation. The development of clinical signs in heterozygotes is probably due to the presence of still unknown modifying factors such as additional molecular defect(s) and/or environmental factors (46–48).

Other disease related to MEFV

A rare dominant autoinflammatory disease characterized by neutrophilic dermatosis was recently discovered and associated with mutations in exon 2 of *MEFV*. It was called PAAND for *Pyrin Associated Auto-inflammation with Neutrophilic Dermatosis*. Patients display recurrent episodes of fever with arthromyalgia and neutrophilic dermatosis beginning early in life (49). Neutrophilic dermatosis include pustular acne, suppurative hidradenitis, pyoderma gangrenosum and neutrophilic panniculitis (50).

Other inflammasomopathies

Cryopyrinopathies (Cryopyrin-associated periodic syndrome or CAPS), or NLRP3-associated autoinflammatory disease (NRLP3-AID) according to the new nomenclature(1):

Three independently defined clinical entities, Muckle-Wells syndrome, Familial cold autoinflammatory syndrome (FCAS) and Chronic infantile neurological, cutaneous, and articular (CINCA) syndrome, were eventually grouped together as cryopyrinopathies or CAPS. They are all associated with mutations in the *NLRP3* gene, and present with cold-induced urticaria as their hallmark feature (51–55). Muckle-Wells syndrome refers to the association of urticaria and sensorineural hearing loss, which may be complicated by AA amyloidosis (55,56). Inflammatory attacks also include signs of ocular inflammation, fever, headache, and less commonly arthritis. FCAS is characterized by a delay in onset of symptoms (minutes to hours) following cold exposure. Symptoms are short-lived and include fever, arthritis, headache, and conjunctivitis, in addition to urticaria. CINCA syndrome presents in the first days of life with a triad of neurological, cutaneous, and articular inflammation. The latter manifests clinically as neurological lesions, chronic meningitis, a diffuse non-pruritic urticarial rash, as well as a progressive deforming arthropathy, particularly of the knee. A characteristic facial dysmorphia, with frontal bossing and saddle-nose deformity, may be observed.

While Muckle-Wells syndrome and FCAS are most commonly transmitted in an autosomal dominant mode, CINCA syndrome is more frequently sporadic. Somatic mutations have been identified in patients with no mutations on genetic analysis by Sanger sequencing, particularly in CINCA syndrome. A recent review estimated that somatic mutations are associated with 0.5 to 19% of cases of CAPS (57,58). Nowadays, in case of strong suspicion for CAPS, geneticists suggest that the *NLRP3* gene should be analyzed by next-generation sequencing (NGS) instead of Sanger sequencing(57), as the latter is not sensitive for somatic mutations.

Treatment of CAPS is based on IL-1 inhibitors, which have shown spectacular efficacy in patients presenting all 3 phenotypes. However, central nervous system damage and deafness are often irreversible despite therapy, especially if there is a long delay between onset of symptoms and diagnosis(52,59).

Mevalonate kinase deficiency

Mevalonate kinase deficiency (MKD), formerly known as hyperIg D syndrome (HIDS), was first described in 1984. The presence of an original biochemical marker, elevation of serum immunoglobulin D (IgD), contributed to the identification of this rare hereditary disease of autosomal recessive transmission (60–62). The clinical aspects were well described by Drenth et al in a series of 50 patients of mainly Dutch and French origin (63). They were subsequently confirmed in two series of respectively 103 and 50 patients (64,65). The disease begins in childhood. Inflammatory attacks generally last 7 days and may relapse every 4 to 8 weeks. Fever, which often exceeds 39°C, is often accompanied by focal signs in 2/3 to 3/4 of cases: abdominal pain, diarrhoea, vomiting, arthralgia, and sometimes arthritis. Mucocutaneous manifestations are frequent and very diverse, including erythematous macules, urticarial lesions, and oral ulcers. Relatively specific signs are hepatosplenomegaly and the presence of painful cervical adenopathy in 94% of cases (63,65,66). There are no clinical signs of inflammation between attacks, and the disease is very rarely complicated by AA amyloidosis (67). While individualization of this disease was partly based on the presence of elevated serum IgD level, both during and in-between attacks, this biomarker is not very specific for MKD as it has also been reported in FMF and TRAPS (68). If MKD is suspected, measurement of urinary mevalonic acid during an inflammatory attack is a reliable diagnostic tool, and should nowadays be used in preference to serum IgD assays (69).

The mutated gene in MKD, *MVK,* encodes an enzyme of the cholesterol pathway, mevalonate kinase, whose partial deficiency is responsible for the MKD phenotype. On the other hand,

complete deficiency of mevalonate kinase causes a more severe pediatric disease called mevalonic aciduria. While children with mevalonic aciduria present inflammatory attacks similar to MKD, they also develop growth retardation, dysmorphia, and severe neurological disorders.

The mechanisms of inflammation associated with MKD involve the IL-1 pathway (70,71). Common anti-inflammatory drugs such as corticosteroids, colchicine and non-steroidal anti-inflammatory drugs (NSAID) are generally not very efficient in MKD. Recent studies have demonstrated the efficacy of IL-1 inhibitors, particularly canakinumab (59,72,73).

PSTPIP1-associated autoinflammatory diseases

Diseases related to *PSTPIP1* mutations are called PAID for *PSTPIP1-associated autoinflammatory diseases* (74,75). The *PSTPIP1* gene encodes an adaptive protein called CD2-BP1 (CD2-binding protein 1). CD2-BP1 can bind to the pyrin inflammasome, participates in the organization of cytoskeletal structures, and influences the cellular dynamics of innate immunity cells (74). Patients with PAID display recurrent febrile attacks with cutaneous and articular inflammation. The first described and most frequent subtype of PAID is PAPA (Pyogenic Arthritis, Pyoderma gangrenosum and Acne) syndrome. It combines recurrent arthritis with neutrophilic dermatosis in more than 75% of cases. Skin lesions include severe cystic acne in more than 50% of cases, pyoderma gangrenosum in 33% of cases, oral ulcers, aseptic abscesses and pustules, psoriasis, and suppurated hidradenitis (76).

NRLC4-associated autoinflammatory disease (NLRC4-AID)

Recurrent fevers linked to mutations of *NLRC4* were first described in 2014. To date, about 30 cases have been described. While 75% are associated with autosomal dominant transmission (77–79), the remaining cases are caused by de novo mutations. Two different phenotypes have been described:

-A severe phenotype (NLRC4-AID phenotype 1) with neonatal onset and a high mortality rate (40%), presenting with high fevers, macrophage activation syndrome (90%), severe enterocolitis (80%), and a non-specific skin eruption (70%).

-A mild phenotype (NLRC4-AID phenotype 2) with onset in childhood, a cutaneous tropism with urticaria and erythematous nodules, arthromyalgia, and conjunctivitis. To date, it has not been associated with vital organ involvement, growth retardation or mortality.

In both phenotypes, IL-18 is always markedly elevated when assayed both during and in-between attacks. Treatment has not been well established(77,79).

NLRP12-associated autoinflammatory disease

Recurrent fevers linked to *NLRP12* mutations were first reported in 2008 in two Caribbean twins suffering from arthralgia, periodic fever and cold-induced urticaria, with spontaneous amendment of disease during adolescence (80). Since the first description, several cases have been reported with considerable clinical heterogeneity, including mild immunodeficiency. The majority were associated with *NLRP12* polymorphisms or variants of uncertain significance. This disease remains rare. To date, organ failure, amyloidosis and disease-related mortality has not been reported. Overall, it remains uncertain whether *NLRP12* mutations are truly associated with an autoinflammatory syndrome.

TRAPS syndrome

A dominant mode of inheritance is observed in a syndrome defined by the acronym TRAPS, which refers to the protein affected by the mutation associated with this disease: TNF receptor superfamily type 1A (TNFRSF1A) (81). While TRAPS was initially described in subjects of Irish ancestry, as emphasized by its original name Familial Hibernian fever, mutations in *TNFRSF1A* have now been identified in many populations, including Afro-Americans, Japanese and patients of Mediterranean ancestry (82)

Clinical picture

TRAPS attacks last longer than those of FMF, generally more than 5 days and up to 3 weeks, although attacks shorter than 5 days have been reported(83). Abdominal pain, often simulating an acute surgical abdomen, is present in almost all patients. Nearly 3/4 of cases develop skin manifestations, including urticaria-like lesions, plaques and patches. The most distinctive lesion consists in erythematous, edematous, warm and tender plaques of various sizes with hazy edges (pseudo-cellulitis). It usually affects the upper and lower limbs but can also be found on the chest. Painful migrating myalgia is another specific manifestation that may herald onset of attacks. Chest pain, scrotal pain, arthritis, orbital edema and conjunctivitis are other yet rarer signs. Renal amyloidosis is the main and most feared complication of TRAPS(67). Increased level of inflammatory markers during symptom-free intervals may identify patients at greatest risk of developing this complication.

Deficiency in adenosine deaminase 2

Deficiency in adenosine deaminase 2 (DADA2) is an autosomal recessive autoinflammatory disease associated with loss-of-function mutations in the *ADA2* gene (14,15). It was first described in 2014 in patients with early-onset small- and medium-vessel vasculitis mimicking polyarteritis nodosa (PAN) (14,15). Since then, approximately 170 cases have been reported in the literature, thus expanding the clinical spectrum(17).The majority of patients present before the age of 10 years with an inflammatory vascular phenotype, a hematological phenotype affecting any cell lineage, and/or an immunological phenotype ranging from immunodeficiency to lymphoproliferation (84–86). Of note, only a minority of patients present during adulthood(15,87).While the vascular phenotype is the most frequent, it can be distinguished from classic PAN by its early onset, positive family history, intermittent fever with increased inflammatory markers, prominent central neurologic manifestations including ischemic and hemorrhagic stroke, and concomitant hematological and/or immunological manifestations (84,85,88). Similar to PAN, the skin is frequently involved, with livedo reticularis and/or racemosa being most commonly observed(84). Skin biopsies often reveal non-granulomatous necrotizing vasculitis or small-vessel vasculitis(14,15).To date, a genotype-phenotype correlation has not been firmly established(85,89). Screening for DADA2 can be easily done through measurement of the serum activity of ADA2, available at low cost in a few selected laboratories(86).Adequate diagnosis is crucial, as anti-TNF is the current mainstay of treatment for the most common inflammatory phenotype(88,90). To date, only two patients have developed AA amyloidosis as a complication of this disease (14,91,92).

Diseases involving pathways downstream TNF1 Receptor

A20 haploinsufficicency (HA20)
A20 protein acts both as a ubiquitin ligase (E3) by adding ubiquitin chains to RIPK1, thus directing it for proteolysis in the proteasome, and as a de-ubiquitinase by removing ubiquitin chains from tumor necrosis factor receptor (TNFR) associated factor 6 (TRAF6) leading to destabilization of the TNFR1. It therefore acts as a negative regulator of the NF-kB pathway(93). A20 is encoded by the tumor necrosis factor alpha-induced protein 3 gene (TNFAIP) on chromosome 6, which can carry dominant loss-of-function mutations that were first described in 2015(12,93). These mutations result in a syndrome combining recurrent fever with bipolar aphtosis, ocular inflammation, gastrointestinal symptoms, arthromyalgia, and cutaneous lesions such as axillary abscess and folliculitis. Interestingly, about a third of patients display autoimmune features, especially antinuclear antibodies (ANA) and thyroid-specific

antibodies. In some patients, humoral immune deficiency has been described, requiring immunoglobulin replacement therapy. To date, more than 60 patients of cosmopolitan distribution have been reported, with a predominance of Japanese origin. Nearly all of them developed symptoms during childhood(13,94). To the best of our knowledge, there is no case of AA amyloidosis secondary to HA20.

RIPK1 mutations

RIPK1 (receptor-interacting serine/threonine kinase 1) is a key mediator of cell death and of inflammatory pathways. It is an intracellular protein located downstream of TNFR1. Five very recent publications described two phenotypes linked to *RIPK1* mutations and involving recurrent fever starting very early in life:

- The first phenotype is severe and transmitted in an autosomal recessive mode. It was described in 13 patients from consanguineous families, who developed an inflammatory bowel disease-like syndrome with marked systemic inflammation requiring hematopoietic stem cell transplantation.

- The second phenotype is milder and transmitted in an autosomal dominant mode. Twelve patients presented with chronic systemic inflammation, fever and lymphadenopathies, with no vital organ involvement. They all responded promptly to tocilizumab. Interestingly, they carried a mutation located at position 324 of the *RIPK1* gene, which affects the protein cleavage site by caspase 8, thus resulting in overactivation of RIPK1. The authors proposed the acronym CRIA for *Cleavage-resistant RIPK1-induced autoinflammatory syndrome* (95–98).

OTULIN and *LUBAC* component mutations both cause extremely rare diseases that begin and are diagnosed in very early childhood(93). They will not be further discussed.

Type I interferonopathies

Type I interferonopathies (Type I IFNs) refer to mendelian autoinflammatory disorders characterized by high type 1 IFN response gene signature in peripheral blood cells (19).
IFN-alpha and –beta are secreted after pattern recognition of self-derived nucleic acids. They then interact in an autocrine and paracrine manner with specific receptors (IFNAR), with subsequent activation of the endonuclear JAK-STAT pathway and induction of hundreds of genes called ISGs (IFN-stimulated genes). Excessive production of type 1 IFN can result from

inappropriate stimulation of the type 1 IFN response pathway or from its defective negative regulation. In some diseases, the molecular pathway involved in IFN stimulation remains unknown (18,99).

To date, the most common type I IFNs are Aicardi Goutières Syndrome (AGS), SAVI (STING-associated vasculopathy, infantile-onset), CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy) now referred to as PRAAS (proteasome-associated autoinflammatory syndrome), Singleton-Merten syndrome (SMS), Spondyloenchondrodysplasia with immune dysregulation (SPENCD), X-linked reticulate pigmentary disorder (XLRPD), USP 18 deficiency (ubiquitin-specific peptidase 18, Pseudo-TORCH syndrome) and COPA syndrome. In general, symptoms develop during infancy. Clues to type I IFNs are the presence of intracranial calcifications, peculiar skin lesions (lipodystrophy, cold-induced acral vasculitis, and lupus-like lesions), and presence of autoimmunity, namely ANA.

AGS is the prototypic interferonopathy. There are 7 genes associated with this syndrome (TREX1 (AGS1), RNASEH2B (AGS2), RNASEH2C (AGS3) RNASEH2A (AGS4), SAMHD1 (AGS5), ADAR1 (AGS6), and IFIH1 (AGS7)). It mainly affects the brain and skin. The classic neurologic phenotype is characterized by early-onset encephalopathy, with a loss of previously acquired skills, spastic paraparesis, or a spastic dystonic syndrome. Variable penetrance partially explains its wide clinical spectrum. Additional neurologic features include glaucoma, chilblains, and systemic lupus erythematosus-like manifestations. Most patients develop symptoms during the first year of life, but it can be congenital or with a delayed onset. SAVI is caused by an autosomal dominant gain-of-function mutation of the viral sensor STING encoded by *TMEM173*. Main features of this disease are cold-induced acral vasculitis and interstitial pneumonia (99). CANDLE or PRAAS is caused by loss-of-function mutation in genes encoding the proteasome complexes. Ubiquitinylated products accumulate as the proteasome is unable to degrade them. Patients present with fever, lipodystrophy, neutrophilic panniculitis, intravascular calcifications, and arthritis. Symptoms usually develop very early in infancy. SMS is characterized by dental dysplasia, glaucoma, psoriasis, aortic calcification, and skeletal abnormalities with tendon rupture and arthropathy. COPA syndrome is inherited in an autosomal dominant mode with mutation affecting the *COPA* gene. Symptoms occur early in life and are characterized by polyarticular arthritis, progressive lung disease with alveolar haemorrhage, and renal involvement with frequent positivity of auto-antibodies (namely ANA) and rheumatoid factor (101).

Actinopathies

Several mutations have been discovered in genes involved in the actin cytoskeleton. These diseases are currently called actinopathies. Immune cell remodeling is implicated in the pathogenesis of hematological/auto-inflammatory diseases, underlining the importance of the actin cytoskeleton in modulating inflammatory responses. Some of the following diseases are associated with an autoinflammatory phenotype.

SAID associated with *ARPC1B* mutations is an autosomal recessive cosmopolitan disease described to date in 14 patients and beginning in the first months of life. Patients display growth retardation with skin rash, recurrent infections, gastrointestinal bleeding, enterocolitis and hepatosplenomegaly. Allergic phenomena are common. Arthritis can be observed in a quarter of cases, while macrophage activation syndrome is rarer. Biologically, thrombocytopenia, eosinophilia and elevated IgE level are commonly reported. There is no autoimmunity. Allogenic stem cell transplantation is currently being considered as a curative therapeutic option (24).

The *CDC42* gene encodes the "control protein 42 homolog" which belongs to the Rho GTPase family and regulates numerous intracellular signaling pathways including cell polarization and migration. In 2019, two teams reported a total of 8 different unrelated and non-consanguineous patients with de novo mutations of the *CDC42* gene and very early onset autoinflammatory disease(26,27). They proposed the acronym NOCARH syndrome for *Neonatal onset of cytopenia, autoinflammation, rash, and hemophagocytosis*. Affected children presented with pancytopenia with dyshematopoiesis, fever, skin rash, hepatosplenomegaly, and systemic inflammation. While cytopenia was present in all cases (100% anemia, 50% thrombocytopenia), macrophage activation syndrome developed in half of them. The amino acid substitution that causes the disease leads to abnormalities in the functioning of CDC42, leading to disruption of hematopoiesis, immune function, and inflammatory response(26,27). To date, 3 patients with NOCARH syndrome have died.

WDR1 is a negative regulator of F actin expressed ubiquitously in the body. Twelve patients from 7 families have been described with mutation in *WDR1*(29,30,102). This autosomal recessive monogenic disease is at the border between auto-inflammation and neutrophil deficiency. The patients all present with an autoinflammatory phenotype with recurrent fever, oral ulcers, and severe recurrent infections. Almost half developed thrombocytopenia, 25% presented diarrhea, and 17% had hepatosplenomegaly. Attempted treatments include intravenous immunoglobulins, antibiotics and, if possible, allogenic stem cell transplantation.

3- The most common polygenic diseases

Non-monogenic SAIDs may be referred to as "inclined" AIDs when they do not meet the criteria for the diseases mentioned above but meet the general clinical and biological criteria for autoinflammatory diseases. These diseases are characterized by episodes of recurrent fever with systemic inflammation and clinical auto-inflammatory features, with no underlying genetic cause identified to date. Some non-Mendelian inflammatory diseases have pathophysiological, genetic, clinical, and/or histological similarities with hereditary autoinflammatory syndromes, but appear to have a multifactorial origin.

The systemic form of juvenile idiopathic arthritis and adult onset Still's disease

The systemic form of juvenile idiopathic arthritis (sJIA) is considered as an auto-inflammatory disease (103). According to the classification of the International League of Associations for Rheumatology, sJIA is defined as a fever of minimum 2-week duration, preceding or accompanying arthritis of at least 6-week duration and beginning before the age of 16 years. It should be accompanied by one or more of the following signs: evanescent rash, lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis. The exact etiology of sJIA remains uncertain but is characterized by deregulation of the innate immunity. Adult onset Still's disease is a heterogeneous entity characterized by 4 cardinal features: marked fever, evanescent rash, arthralgia or arthritis, and neutrophilic leukocytosis in the absence of rheumatoid factor and ANA(103). Like sJIA, this definition positions the disease on the autoinflammatory spectrum, even though the underlying molecular and cellular mechanisms have not yet been fully elucidated. The management of both diseases is aimed at achieving remission of systemic and articular manifestations, as well as preventing complications such as joint destruction and AA amyloidosis. Treatment is based on NSAID in mild disease forms, and on corticosteroids, methotrexate, anti-IL1 and anti-IL6 biotherapies in severe forms, including in cases of joint damage.

Schnitzler syndrome was defined by L. Schnitzler in 1972 as the association of adult onset urticaria and monoclonal gammopathy of the IgG or IgM subtype. It presents with a neutrophilic urticarial dermatosis that is clinically and histologically very similar to the one observed in CAPS, but with no monogenic defect detected(104).

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

With this acronym are often classified patients presenting with periodic fever attacks like those seen in monogenic periodic fevers, but lacking mutations in known autoinflammatory genes (*MEFV*, *MVK*, *TNFRS1A*). Although some anecdotic familial cases of PFAPA have been reported, a genetic basis has not been identified. There is also no ethnic predilection.

PFAPA was first described by Marshall et al in 1987 (105). The disease usually develops before 5 years of age. It is characterized by fever spikes of abrupt onset lasting 3–6 days; the latter recur regularly every 2–6 weeks, although an explanation for its clockwork periodicity is lacking. They are usually heralded by chills. Some older children complain of general malaise and myalgia during attacks. The aphthous lesions observed in PFAPA are small, localized to labial gingival tissues, and rapidly self-remitting. Cervical lymph nodes are commonly enlarged and tender. Acute phase reactants and neutrophils are elevated during attacks, and then normalize during symptom-free intervals. The disease has a benign course and tends to remit spontaneously with time (106).

The diagnosis of PFAPA is generally based on several variables (dramatic onset of attacks, lack of response to antibiotics, repetitive presence of cardinal symptoms, and prompt response to steroids). However, to date, different attempts to develop reliable diagnostic criteria have failed(31,107,108). Moreover, the recently described heterogeneous group of USAID, described as recurrent inflammation not corresponding to the clinical picture of any well-defined SAID or without pathogenic mutation causing a known hereditary SAID, seems to display characteristics similar to PFAPA syndrome (6). Therefore, the relevance of positioning PFAPA as a distinct entity than USAID in patients with non-monogenic periodic fevers is debatable (109).

4- Which genetic analyses are available in SAID, when to undertake one, and how to select the most appropriate one?

Genetic diagnosis: methods

Historically, monogenic diseases were genetically tested by Sanger sequencing, the reference method. This approach was time-consuming, since each exon of the gene had to be individually amplified and sequenced. As result, the genes were sequentially screened, and the diagnostic process could take years. Nevertheless, this method remains cheap and fast. It is a good choice when there is a strong clinical suspicion (e.g. FMF in an Armenian patient), or when a functional

test has proven a metabolic disorder (e.g. increased mevalonic aciduria, decreased ADA2 enzymatic activity). The downside of Sanger sequencing is its poor performance in detecting somatic mosaicism, copy number variations (CNV), and structural variants (Figure 5). Next-generation sequencing (NGS) encompasses several techniques using massive parallel sequencing, such as panel sequencing, whole exome sequencing (WES) and whole genome sequencing (WGS). NGS panel sequencing is now largely used in routine diagnosis. This approach allows the analysis of phenotypic panels involving tens to hundreds of genes. Diseases with genetic heterogeneity, such as familial cold urticaria which can be caused by mutations in *NLRP3*, *NLRP12*, *NLRC4* and *PLCG2,* are particularly suited to this method. Furthermore, when the read depth is sufficient, it can detect CNV and low-level mosaicism. Given that some SAIDs are associated with genetic mosaicism, the panel approach is preferred when those are suspected. Technically-speaking, WES is considered as a big gene panel. The main limitation of this method is caused by the possibly low read depth in certain genomic regions. Some variants can be missed, and the detection of CNV and mosaicism is suboptimal. WGS is different from WES as it involves amplification and enrichment steps, allowing a much more homogeneous coverage of the genome. Although the risks of missing some variants are low, the detection of mosaicism depends on the read depth, which is usually lower than in a panel. On the other hand, structural variants and CNV are best detected by using WGS. Compared to panel sequencing, the main advantage of WES and WGS is the possibility to re-analyse data in the future, when new genes have been discovered.

Germinal mutations and somatic mutations

Germinal mutations are inherited from one parent (or both) and appear in sequencing as heterozygous or homozygous. Somatic mutations are post-zygotic events that occur either early in the embryonic development or later in life. As a result, 2 cell populations coexist. The new mutation ratio can vary from 0.5% to 50%, depending on the analysed tissue. Disease-causing somatic mosaicism events have been described in *NLRP3*, *TNFRSF1A*, and *MVK* (57). Deep sequencing, such as panel sequencing with a good read depth, is mandatory to detect low-level mosaicism.

Diagnostic strategy

The genetic diagnostic strategies vary from a country to another, depending on access to next-generation sequencers and bioinformatic resources in the laboratories (Figure 6). Sanger sequencing should be used especially when there is a strong clinical suspicion, such as FMF in

patients from Mediterranean ancestry, or MKD in those with documented mevalonic aciduria. Sanger sequencing for *ADA2* is appropriate when a rapid result is needed in order to initiate treatment, with the downside of potentially missing CNV which may be responsible for DADA2 (110). Quantitative polymerase chain reaction can be useful to complete *ADA2* sequencing. Panel sequencing have a better diagnostic yield than Sanger, especially when the indication is validated in an expert multidisciplinary meeting in light of the non-specificity of autoinflammatory symptoms such as fever and arthritis(111). WES is best suited to the identification of alternate diagnoses (autoimmunity or immunodeficiency overlaps) or the search of new SAID genes.

5- What are the principles of treatment of SAID?

Colchicine

Daily colchicine is an effective treatment for preventing recurrence of attacks and occurrence of amyloidosis in FMF (38). In adults, the usual starting dose of colchicine is 1 mg/day. If disease activity is not controlled, either because of recurrence of attacks or persistent elevation of inflammatory parameters, the dose of colchicine should be increased by 0.5 mg/day every 3–6 months up to a maximum of 2.5 mg/day (112,113). Diarrhea due to colchicine is rare and can be managed by dividing the dose into two or restricting lactose intake (114).

Although colchicine intoxication remains a serious concern, long-term daily colchicine is relatively safe, including during pregnancy. Rarer acute adverse effects include myopathy, rhabdomyolysis and myelosuppression (115). Colchicine neuromyopathy may occur with chronic daily use, particularly in patients whose dose has not been appropriately adjusted for renal function. Of note, fatalities during therapeutic colchicine use have only been reported in cases of chronic renal insufficiency with unadjusted doses of colchicine, intravenous administration, and inappropriate combination with CYP3A4 inhibitors (116,117).

In FMF, true non-responders to colchicine are rare; most of them actually correspond to non-compliant patients. Because of the excellent response rate observed in FMF, colchicine has been tried as maintenance therapy in various other recurrent fever syndromes. Unfortunately, its effectiveness in SAIDs other than FMF is much more modest; only some patients with USAID seem to benefit to some extent (59,118).

Biotherapies

Anti-IL-1

Biologic drugs are the cornerstone of therapy for autoinflammatory diseases using a treat-to-target approach. As explained above, IL-1 is the leading proinflammatory cytokine involved in most inflammasomopathies. Anti-IL-1 (anakinra, canakinumab and rilonacept) have shown remarkable efficacy in these diseases. Anakinra has been approved for treatment of CAPS since 2001(52,55,59). Canakinumab is currently approved for CAPS, sJIA, TRAPS, MKD, as well as FMF in case of resistance or contraindication to colchicine. Its approval in TRAPS, FMF, and MKD is based on the positive results of the randomized controlled trial CLUSTER (72). Both anakinra and canakinumab are administered subcutaneously. While anakinra is given daily due to his short half-life, canakinumab has the advantage of being given every 4-8 weeks. Anti-IL1 can also be used as a diagnostic and therapeutic tool in USAID. Overall, they have a good safety profile, and cutaneous local injection-site reactions are usually self-limiting after a few weeks.

Anti-IL-6

Tocilizumab, a humanized monoclonal antibody against IL6-R, is FDA-approved for JIA. It is administered subcutaneously every 1-2 weeks or intravenously every month. Anti-IL-6 are often used as second or third-line agents in most autoinflammatory diseases(59).

TNF inhibitors

Five TNF inhibitors are currently approved by the FDA for the treatment of several inflammatory conditions. They are the mainstay of treatment in DADA2 patients, in which they efficiently control fever and vasculopathy and prevent strokes (16,90). A trial of etanercept in TRAPS showed some efficacy in decreasing symptoms and acute-phase reactants; however, most patients discontinued the drug due to insufficient or declining efficacy after a few years(59).

JAK inhibitors

The JAK/STAT pathway mediates the effect of many molecules including ILs, IFNs, growth hormones, and many more(119). In interferonopathies, JAK inhibition has led to promising results. Sanchez *et al* reported clinical improvement and significant reduction in corticosteroid by administering baricitinib to 18 patients with CANDLE, SAVI, and other interferonopathies

(120). Major adverse events were upper respiratory tract infections, gastroenteritis, and BK viruria and viremia.

Conclusions

More and more new monogenic SAIDs are being described every year, thus expanding the clinical spectrum of these disorders of innate immunity. Advances in genetics are important and allow a progressively better understanding of the pathophysiology of these diseases. Nevertheless, pathogenic mutations are not detected in all patients with a clinical and biological presentation compatible with SAIDs. The rheumatologist has an important role to play in suspecting SAID when faced with a young patient presenting an inflammatory syndrome and systemic manifestations without autoimmunity. Comprehensive history-taking is crucial in guiding the diagnosis and genetic analysis, and in selecting the treatment. The patient should then be closely monitored in order to optimize treatment based on the clinical and biological response and disease evolution over time, with periodic surveillance for development of AA amyloidosis.

***Practice points:* How to approach a suspected SAID (figures 2-4 and tables 1-2)**

- First, confirm the presence of inflammation by measuring the C-reactive protein level during at least 3 attacks.

-Second, draw a family tree.

-Third, determine the age of onset (see figure 2) which will point towards an early- versus late-onset SAID.

-Fourth, determine the patient's origin from his 4 grandparents, in order to determine if the patient is at risk for the most common SAID: familial Mediterranean fever.

-Fifth, identify the main signs and symptoms as well as the duration of attacks. Take time to search for and examine any skin lesions; if present, discuss the necessity to perform a skin biopsy.

-In a patient with arthritis and/or arthralgia, fever, and elevated inflammatory markers, attempt to classify his disease in a category of SAID based on associated signs and symptoms in order to guide genetic testing (see figure 4).

The main categories of signs and symptoms are as follows:

-Cutaneous (urticaria, neutrophilic dermatosis, oral ulcers)

-Abdominal

-Thoracic: pleuritis and/or pericarditis

-Neurologic: stroke, deafness, aseptic meningitis, mental retardation

-Macrophage activation syndrome

-Lymphadenopathy

***Research agenda*.**
- *Advances in genetics will allow to better investigate and characterize USAID, which represent a significant proportion of SAIDs.*
- *This may help in the future to individualize treatment for each disease and patient.*

Figures' legends

Figure 1. Simplified representation of the main pathophysiological pathways involved in SAIDs.

Figure 2. Main SAIDs according to age of onset.

Figure 3. Main cutaneous features in SAID

A: Erysipelas-like erythema of the ankle during an attack of familial Mediterranean fever

B: Oral ulcers during a flare of severe cryopyrinopathy (CINCA syndrome)

C: Cold-induced urticaria on the arm of a patient with a cryopyrinopathy (Muckle wells syndrome)

D: Aseptic pustule in PSTPIP1-associated autoinflammatory disease

E: Livedo of feet associated with ADA2 deficiency

F: Chronic urticaria on the arm of a patient with Schnitzler syndrome

Figure 4. Proposition of a simplified algorithm for suspecting SAID based on history and physical examination.

Figure 5: Comparative chart of the sequencing approaches in SAIDs. NGS: Next-generation sequencing; WES: whole exome sequencing; WGS: whole genome sequencing.

Figure 6: The diagnostic algorithm used in Montpellier, France. SAID: systemic autoinflammatory disease.

Table 1. How to approach a patient with SAID and recurrent urticaria

1. Perform a genealogic tree to study the transmission of the disease: sporadic or familial? Dominant or recessive => they are all dominant!

2. Ask for age of onset: at birth? Early in life? In adulthood? Cryopyrinopathies and NLRC4-AID phenotype 1 begin very early in life. Others begin in childhood (NLRC4-AID phenotype 2, PLAID, NLRP12-AID) or even later in life (cryopyrinopathies due to somatic mutations, Schnitzler syndrome)

3. Look for associated symptoms
   - Deafness, eye involvement (conjunctivitis, uveitis), neurological features: suspect a cryopyrinopathy
   - Macrophage activation syndrome: suspect NLRC4-AID phenotype 1 (mostly familial)
   - Immune deficiency and allergies: suspect PLAID
   - Periodic fever or just mild inflammation: suspect NLRP12-AID or NLRC4-AID phenotype 2 (almost always familial)

Table 2. How to approach a patient with SAID and predominant abdominal pain

1. Perform a genealogic tree to study the transmission of the disease: sporadic or familial? Dominant or recessive?

   => the most frequent is FMF and is recessive

2. Ask for the age of onset: at birth? Early in life? In adulthood? => MKD and cryopyrinopathies begin early in life, usually in the first year of life

   => usually HA20 and NLRC4-AID (autosomal dominant), as well as ADA2 deficiency (autosomal recessive) begin in infancy

   => FMF (autosomal recessive) and TRAPS (autosomal dominant) usually begin between 3 to 20 years old

3. Assess duration of attacks

   - A few days (2 to 3 and less than 7 days): always suspect the most frequent SAID, FMF, or less commonly MKD. Both are autosomal recessive.

   - More than 10 days: suspect 2 autosomal dominant diseases: TRAPS and HA20

   - Another rare dominant disease with variable duration of attacks is NLRC4-AID

   - Concerning patients with almost permanent or chronic symptoms, consider ADA2 deficiency if autosomal recessive and cryopyrinopathies if sporadic or autosomal dominant.

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Conflict of interest:

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Abbreviations:

AOSD: adult onset Still's disease

CAPS: cryopyrin-associated periodic syndrome = *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID)

CINCA: Chronic infantile neurological, cutaneous, and articular syndrome

DADA2: ADA2 deficiency

DIRA: Deficiency of the IL-1 receptor antagonist

DITRA: Deficiency of the IL-36 receptor antagonist

DUB: deubiquitinase

FCAS: Familial cold autoinflammatory syndrome

FMF: Familial Mediterranean fever

HA20: A20 haploinsufficiency

LUBAC: Linear ubiquitin chain assembling complex

MKD: mevalonate kinase deficiency

MWS: Muckle Wells syndrome

NAID: *NOD2*-associated autoinflammatory diseases

NGS: Next-generation sequencing

NLRC4-MAS: *NLRC4*-associated macrophage activation syndrome

NLRC4-AID: *NLRC4*-associated autoinflammatory disease

NLRP12-AID: *NLRP12*-associated autoinflammatory disease

PAAND: Pyrin-associated autoinflammation with neutrophilic dermatosis

PAID: *PSTPIP1*-associated autoinflammatory diseases

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome

SAID: systemic autoinflammatory disease

SAVI: STING-associated vasculopathy with onset in infancy

SoJIA: Systemic onset juvenile idiopathic arthritis

TRAPS: Tumor necrosis factor receptor-associated periodic syndrome

USAID: Unclassified systemic autoinflammatory disease

WES: whole exome sequencing

WGS: whole genome sequencing