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QMR Autoinflammatory diseases

Autoinflammatory diseases: state of the art

Authors:

Sophie Georgin-Lavialle[1,2], Antoine Fayand[1], François Rodrigues[1], Claude Bachmeyer[1], Léa Savey[1], Gilles Grateau[1,2].

Affiliations:

[1]Sorbonne Université, AP-HP, Hôpital Tenon, Service de médecine interne, Centre de référence des maladies auto-inflammatoires et des amyloses d'origine inflammatoire (CEREMAIA), F-75020, Paris

[2]INSERM UMRS_933, Hôpital Trousseau, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie (UPMC)-Paris 6, Paris, France

Corresponding author:

Dr Sophie Georgin-Lavialle

Internal medicine department, Tenon hospital, 4 rue de la Chine, 75020 Paris, France

Sorbonne Paris Université, Assistance Publique-Hôpitaux de Paris.

E-Mail: sophie.georgin-lavialle@aphp.fr

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Key points

Monogenic autoinflammatory diseases are characterized by genetic abnormalities encoding proteins involved in innate immunity.

Their main feature is the presence of peripheral blood inflammation in crisis without infection. The best-known autoinflammatory diseases are mediated by interleukin 1 and consist in the 4 following diseases: familial Mediterranean fever, cryopyrinopathies, TNFRSF1A-related intermittent fever, and mevalonate kinase deficiency.

In the last 10 years, many other autoinflammatory diseases have been discovered, especially thanks to the progress in genetics.

The diagnosis of autoinflammatory disease is mainly based on anamnesis, presence of peripheral blood inflammation during attacks and genetic analysis which are more and more sensitive.

QMR Autoinflammatory diseases

Editorial
Gilles Grateau, France

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Per Wekell, Sweden

Abstract

Autoinflammatory diseases are characterized by innate immunity abnormalities. In autoinflammatory diseases (AID), inflammatory blood biomarkers are elevated during crisis without infection and usually without autoantibodies. The first 4 described AID were familial Mediterranean fever, cryopyrin-associated periodic fever syndrome (CAPS) or *NLRP3*-associated autoinflammatory disease (*NRLP3*-AID), mevalonate kinase deficiency (MKD) and *TNFRSF1A*-receptor associated periodic fever syndrome (TRAPS). Since their description 20 years ago, and with the progresses of genetic analysis, many new diseases have been discovered; some with recurrent fever, others with predominant cutaneous symptoms or even immune deficiency. After describing the 4 historical recurrent fevers, some polygenic inflammatory diseases will also be shortly described such as Still disease and periodic fever with adenitis, pharyngitis and aphtous (PFAPA) syndrome. To better explore AID, some key anamnesis features are crucial such as the family tree, the age at onset, crisis length and organs involved in the clinical symptoms. An acute phase response is mandatory in crisis.

1-INTRODUCTION

Since the term autoinflammation was coined, several definitions and therefore classifications of autoinflammatory diseases (AID) have been proposed (1). We will retain here the definition of auto-inflammatory diseases as disease with clinical and biological inflammatory component and linked to an anomaly of innate immunity (2). Many advances in genetics over the past decade have led to the discovery of several new monogenic AID each year. The best-known subgroup because first described is the "hereditary recurrent fevers" subgroup, including 4 historical interleukin (IL)-1 dependent diseases: familial Mediterranean fever (FMF), the most frequent AID, cryopyrinopathies which form a spectrum of diseases related to *NLRP3* mutations (*NRLP3*-associated autoinflammatory disease or *NLRP3*-AID), mevalonate kinase deficiency (MKD) and TRAPS syndrome (Tumor Necrosis Factor type 1A Receptor-Associated Periodic fever Syndrome) (1,3).

Interestingly, genetic discoveries in recent years have shown that some monogenic diseases have a different clinical expression depending on the site of the mutation in the gene; indeed, the clinical spectrum of the diseases associated to mutations of the following genes *MEFV*, *NLRC4*, *NOD2*, *PSTPiP1* has been extended (4–8). Another advance in genetics is the discovery of patients displaying somatic mutations of genes associated with AID either when the disease occurs late in life or if it occurs early in life but among these patients, only a fraction of cells is mutated (9–14). This article aims to summarize the main AID, their pathophysiology and the treatment's principles, and to propose a diagnostic approach.

2-MAIN PATHOPHYSIOLOGICAL PATHWAYS INVOLVED IN AID

The innate immune response has evolved to protect organisms from exogenous and endogenous hazards that threaten, damage or destroy the organism (figure 1). The goal of the immune response is to eliminate or sequester the source of the disturbance and restore tissue function and homeostasis. Innate immune system uses a limited number of receptors recognizing exogenous and endogenous molecular units; when the pathway is activated it leads to the production of proinflammatory cytokines and chemokines to recruit immune cells into tissues and coordinate tissue defense. To avoid inappropriate and damaging responses, there are many regulatory mechanisms. Autoinflammatory diseases are caused by abnormalities that can occur at each stage of the immune response and its regulation.

Some of the autoinflammatory diseases are due to an exaggerated detection of extracellular and intracellular danger signals. The best examples are inflammasomopathies due to a genetic

abnormality of a component of a cytosolic receptor responsible for facilitated or permanent production of pro-inflammatory cytokines (15). Inflammasomes are protein platforms, which in response to danger signals will recruit caspase 1, capable of cleaving pro-Il-1β and pro-IL-18, and result in secretion of IL-1 and IL-18 pro-inflammatory cytokines. Inflammasomopathies are diseases associated with mutations of inflammasomes: pyrin (FMF, PAAND), NLRP3 (CAPS), NLRC4, NLRP12; in these diseases, the role of interleukin-1 is major (15).

Ubiquitination is the process which leads to the specific and regulated binding of one or more ubiquitin molecules to a target protein. The main function of this post-translational modification are the recognition and destruction of the protein thus labeled by the proteolytic complex of the proteasome. Ubiquitination involves enzymes called ligases E1, E2 and E3. This highly dynamic process is reversible: this so called deubiquitination is the process by which Ubiquitin chains are removed from substrates modified by a class of enzymes known as deubiquitinases (DUB) (16,17). There are about 100 proteases with DUB activity including the proteins A20 and OTULIN, which function as negative regulator of NF-kB signaling; the linear assembly complex of the linear ubiquitin chain (LUBAC) - is a set of proteins: HOIP, HOIL-1 and SHARPIN which, together with the E3 ligase, helps to maintain the stability of membrane receptors including the TNF 1 (TNFR1) receptor, TLR and IL-1R (16,17). After stimulation with pro-inflammatory signals, LUBAC is recruited to attach linear Ub chains to target substrates: thus, in the event of an anomaly of one of the constituent proteins of LUBAC, this reduces its stability in the cells. Since immune responses must be regulated to avoid chronic inflammation, LUBAC activity is counter-regulated by such as OTULIN and A20. OTULIN hydrolyses the linear Ub chains, which reduces activation of the NF-kB and A20 pathway, can direct proteins to the proteasome (16,17). Recently, deregulation in the ubiquitin pathway has been reported in patients with auto-inflammatory diseases: abnormalities associated with defects in the linear assembly of the ubiquitin chain (LUBAC), and abnormalities associated with defects in protein deubiquitination: A20 deficiency (HA20) and otulinopenia (ORAS) (16,18–25).

Other autoinflammatory diseases are due to insufficient clearance of proteins in the immune system that are no longer needed, proteasome-related diseases, or to an accumulation of poorly-folded proteins in the endoplasmic reticulum responsible for increased secretion of pro-inflammatory cytokines; an example of such a mechanism is TRAPS syndrome (15).

Finally, some autoinflammatory diseases are linked to the inability to regulate cytokine signaling, which will lead to the development of abnormal cytokine loops that amplify and

perpetuate inflammatory responses. A good example of this mechanism is illustrated by DIRA and DITRA, in which the IL-1 and IL-36 signals of cytokine antagonists are absent (15).

In the ADA2 deficiency, there is an imbalance in the balance of pro- and anti-inflammatory macrophages in favour of pro-inflammatory macrophages, which causes inflammation of the vessel walls and the release of pro-inflammatory cytokines, including TNF (26).

In interferonopathies, some mutations induce type I interferons pathway activation leading to increased proinflammatory cytokine secretion(27).

3-DESCRIPTION OF THE MAIN MONOGENIC AUTO-INFLAMMATORY DISEASES (TABLE 1)

3.1. The four « historical » recurrent fevers

Recurrent fevers are characterized by recurrent attacks of systemic inflammation manifested by sudden episodes of fever associated with elevated acute phase proteins and several clinical manifestations affecting mainly the skin and mucosae, muscles and joints, and digestive tract; the most frequent symptoms are cutaneous rashes, serositis (peritonitis, pleuritis, pericarditis), arthromyalgia and lymphadenopathy. Attacks of disease are usually separated by symptom-free intervals of varying duration, characterized by complete wellness, normal growth and normalization of inflammation biomarkers.

3.1.1. Familial Mediterranean fever (FMF)

Familial Mediterranean fever is the most frequent monogenic auto inflammatory disease, which is associated with mutations in *MEFV* gene (28–34). The main symptoms are acute inflammation attacks in serosa leading to recurrent febrile abdominal pain in most cases and the most feared complication is inflammatory amyloidosis (29).

Epidemiology

FMF mainly affects patients originating from Mediterranean countries such as Arabic populations, Armenians, Sephardic Jews, Turks, Lebanese, Italian and Greek (29). In Sephardic Jews and Armenians, the frequency in the general population of heterozygous carriers of a mutation in *MEFV* gene is estimated from 1/4 to 1/6; and the worldwide estimated number of patients is around 100 000(29,31).

Genetics and mechanisms

The association between *MEFV* gene and FMF was discovered in 1997; *MEFV* is a gene of average size, located in chromosome 16, comprising 10 exons, and encoding a protein named pyrin (from the Greek name of fever: pyros) (29). The disease begins in 80 to 90% of cases before the age of 20 years and has a recessive autosomal transmission; *MEFV* is expressed

only in circulating neutrophils and to a lesser degree in monocytes; the most frequent pathogenic *MEFV* mutations stand in exon 10, especially the M694V (29,31).

Inflammatory attacks of FMF

Acute attacks are characteristic of the disease, and as indicated by its name, fever is almost constant during attacks; it is rarely isolated, and frequently there are signs of acute inflammation of serosa, in decreasing order of frequency peritoneum, pleura, testicular vaginal and pericardium. Acute abdominal attack is often impressive and in the presence of a first attack, suspicion of acute appendicitis or peritonitis can lead to emergency surgery. Other organs frequently affected are joints, skin, especially in the form of a erysipelas-like erythema of the lower limbs (figure 2.A), and muscles with myalgias; most often only one organ is affected during an inflammatory attack and the peritoneum is the main target (31,33,35).

Acute attack lasts from a few hours to 72 hours, usually 2-3 days, and resolves spontaneously, sometimes leaving the patient tired for a few more days. Attacks are recurrent without any regularity and with a very variable frequency from one subject to another and from one period of life to another for a given subject. Patients have no clinical signs when they are not experiencing attacks. However, some manifestations of the disease can extend beyond the usual 72 hours, such as acute arthritis and protracted myalgias that can last several weeks. Clinical inflammation or its sequelae can have a chronic repercussion, especially joint involvement such as coxitis, much more rarely occurs chronic ascites by chronic peritoneal inflammation. Patients homozygous for the *MEFV* M694V mutation usually display a more severe clinical form. Some diseases are more frequently associated with FMF such as Ig A vasculitis, hidrosadenitis suppurativa and a special HLAB27 negative spondyloarthritis, most often axial (29). Clinical inflammatory attack is accompanied by the usual peripheral blood inflammation abnormalities: neutrophilic polynucleosis, elevation of acute phase response proteins including C reactive protein (CRP) and serum amyloid associated (SAA) (29,31).

AA Amyloidosis secondary to FMF

AA or inflammatory amyloidosis, kidney is the main organ involved; amyloid nephropathy was the leading lethal cause in patients with FMF, before the era of colchicine (36,37). Other organs preferentially affected are the digestive tract and thyroid; heart involvement is very rare in this type of amyloidosis. Genetic and/or environmental factors are involved in the development of amyloidosis in FMF. Several studies strongly suggest that amyloidosis occurs preferentially in association with homozygous *MEFV* M694V mutation. Among the candidate genes playing a role in modifying the expression of the disease are the genes encoding the SAA protein derived from the AA protein forming amyloid deposits in inflammatory

amyloidosis (=AA amyloidosis). In humans, it has been shown that some polymorphisms in *SAA1.1* variant significantly increases the risk of amyloidosis during FMF compared to other genotypes at the *SAA1* loci (31,38). Rarely some patients without clinical symptoms of the disease can be diagnosed at the stage of AA amyloidosis, which is considered as a, FMF Phenotype II, which could be explained by the existence of subclinical inflammation during FMF, as revealed by the systematic measurement of markers of inflammation between acute attacks (39).

Diagnosis

The diagnosis of FMF is based on a combination of clinical arguments and genetic diagnosis (28,29,31). There are neither specific clinical signs of FMF, nor specific marker of inflammation available in a routine diagnosis. Therefore, the diagnosis of FMF may be a diagnosis of exclusion of other diseases, depending on the clinical signs observed, which is however based on elements of certainty. Several sets of criteria have been proposed to help in the diagnosis of FMF. They are almost all based on a variable composition of the following elements: 1) presence of the most common clinical signs, 2) presence of AA amyloidosis, 3) familial character, 4) efficacy of colchicine, 5) exclusion of another well-defined disease (28,31). The discovery of the *MEFV* gene and mutations responsible for FMF provides a definite diagnostic aid, with the preliminary difficulty of defining when a DNA sequence variation becomes a pathogenic mutation. In the presence of suggestive clinical signs, the detection of 2 mutations in *MEFV* (homozygosity or composite heterozygosity) confirms the diagnosis of FMF (31). The diagnosis of FMF can also be made in subjects belonging to populations at risk and who have recent signs, with little inflammatory attack, not always fulfilling the criteria sets. Genetic analysis makes it possible to start treatment at an early stage. In the presence of at most one mutation, the diagnosis neither can be stated, nor be excluded since it is possible that not all mutations responsible for FMF are yet known. It is now established, as with other recessive diseases, that some individuals who are heterozygous for a mutation in the *MEFV* gene may have clinical signs requiring colchicine treatment. It is possible that in this case the clinical signs may diminish or even disappear in adulthood (40–42). Finally, and very rarely, in some non-Mediterranean family's certain variants of the *MEFV* gene are associated with an inflammatory dominant disease (43–46).

Treatment

There is no real treatment for acute inflammatory attack except classical antalgics (29,31). The main treatment is preventive, and colchicine is efficient to prevent both attacks and AA amyloidosis development. The dosage in adults begins at 1 mg/day which is often enough to

prevent attacks, but higher doses are sometimes required, until 2.5 mg/day. Treatment with colchicine may be continued during pregnancy and lactation (47–51). Once amyloidosis is established, colchicine treatment may stabilize renal impairment, even when nephrotic syndrome exists (36,52). Rarely, patients can be resistant to colchicine, and experts have tried to definite colchicino-resistant patients. Among those patients or in case of colchicine major side effects, interleukin-1 inhibitors have recently proved their efficiency but should be prescribed after expert advice, as those expensive biologics need to be use reasonably (29,31).

3.1.2. Cryopyrinopathies (Cryopyrin Associated Periodic Syndrome-CAPS) or *NLRP3*-associated Auto-Inflammatory Disease (*NRLP3*-AID) in new nomenclature

Three clinical entities previously defined independently were finally genetically grouped because there were all associated with *NLRP3* mutation: Muckle Wells syndrome, Family Cold Autoinflammatory Syndrome (FCAS) and CINCA syndrome (chronic, infantile, articular, neurological, cutaneous and articular) under the name of cryopyrinopathies or CAPS (cryopyrin associated periodic syndrome); the common feature is cold-induced urticaria (figure 2.B) (53,54). Muckle-Wells syndrome refers to the association of urticaria, predominantly renal amyloidosis and sensorineural hearing loss, transmitted in the autosomal dominant mode. Clinical inflammatory attacks include, in addition to urticaria defining the disease), signs of eye inflammation, and less often arthritis. FCAS is characterized by delayed onset (several minutes to hours) by environmental exposure to cold. Hives attacks are associated with other signs: fever, arthritis and conjunctivitis, The CINCA syndrome is a disease which is expressed from the first days of life, and which is defined essentially by a triad: cutaneous, neurological and articular. Skin signs include diffuse, non-pruritic urticarial erythema, neurological damage, chronic meningitis, and progressive joint arthropathy, especially of the knees, which can be severely deformed. This triad is associated with a characteristic facial dysmorphia (53).

Mutations of *NLRP3* have been discovered in subjects with these 3 phenotypes where the most specific clinical symptom in chronic urticaria and peripheral inflammation. Somatic mutations have been found among patients without mutation by Sanger genetic analysis, especially in CINCA syndrome (12,55); a recent review reports on 64 patients with somatic mutations and suggests that those can be found from 0.5 to 19% of patients with a clinical phenotype of cryopyrinopathy (56). Nowadays, geneticists suggest looking for NLRP3 mutations by next generation sequencing when there is a high suspicion of cryopyrinopathy even when the disease began in adulthood (56).

The treatment is based on interleukin-1 inhibitors which have shown dramatic efficacy in patients with all 3 phenotypes, with a restriction for central nervous system involvement and deafness, especially if the delay between the beginning of symptoms and the diagnosis is long (57–60).

3.1.3. Intermittent hereditary TNF-1A receptor-related intermittent hereditary fever (TRAPS)

TRAPS is a very rare disease and probably represents a large proportion of hereditary autosomal dominant transmission fevers of patients displaying abdominal pain with inflammation during more than one week among patients from all origins (61). The symptoms of inflammatory attacks are in some cases richer: fever and abdominal pain can be accompanied by myalgia, muscle stiffness, conjunctivitis, arthralgia, chest pain, testicular pain and two signs that are probably most specific to this variety of hereditary fever - periorbital edema and cutaneous rash. The most typical cutaneous signs are very painful pseudocellulitis affecting the upper as well as lower limbs, migrating from the root to the extremity of the limb during attack and which is monocyte inflammatory fasciitis. Other skin signs that are polymorphic and less typical of TRAPS exist in more than 50% of patients. AA amyloidosis can complicate the course of this chronic inflammatory disease in some families (61).

The gene responsible for TRAPS syndrome encodes for the TNF type 1A receptor. Most mutations concern the cysteins underlying the spatial structure of the extracellular part of TNFRSFA1, which reinforces the suspicion of their pathogenicity. The mechanisms of the disease are not yet fully understood. Initially described in families of Irish and Scottish origin, this disease exists in all populations (61,62). The diagnosis, based on the clinical data described above, must be confirmed by genomic DNA analysis for *TNFRSF1A* mutations (63).

Treatment with colchicine has no proven effect on preventing inflammatory attacks, nor does it appear to prevent the occurrence of amyloidosis; corticosteroids, on the other hand, have a definite effect and reduce the severity and duration of inflammatory attacks which can last several weeks and in some cases be infraclinical (60). Recently interleukin 1 inhibitors use during crisis or as attack prophylaxis has shown its efficacy; therefore, anakinra and/or canakinumab can be used in this indication (64,65).

3.1.4. Mevalonate kinase deficiency (MKD)

Mevalonate kinase deficiency (MKD), formerly called Hyperimmunoglobulinemia D syndrome (HIDS) was firstly described in 1984; the presence of an original biochemical marker, the elevation of serum IgD, allowed the individualization of this hereditary autosomal recessive transmission condition (66). The clinical aspects were well described in a series of 50 patients by Drenth *et al*, essentially of Dutch and French origins and confirmed on a series of 103 and on a series of 50 described by Bader-Meunier *et al* (67,68). The disease usually begins in childhood. Inflammatory attacks typically last 7 days and can relapse every 4 to 8 weeks, with fever reaching at least 39°C, accompanied by focal signs in 2/3 to 3/4 of cases: abdominal pain, diarrhea, vomiting, arthralgia or oligoarthralgia and sometimes arthritis. Skin or mucosal manifestations are frequent and very various including erythematous macules, urticarial lesions and sometimes mouth ulcers (figure 2.C). Relatively specific compared to the 2 previous varieties of fevers, are hepatosplenomegaly and especially the presence of painful cervical adenomegalies in 94% of cases (66,69). There are no clinical signs of inflammation between attacks and the disease is very rarely complicated by AA amyloidosis (66,69). The individualization of this condition was based on the existence, both during and between attacks of a high level of serum IgD, but high level of serum immunoglobulin D is probably not highly specific and may also occur in FMF and TRAPS (70). The *MVK* gene, mutated in this disease, codes for an enzyme of the cholesterol pathway, mevalonate kinase, whose partial deficiency underlies the phenotype of MKD and the complete deficiency is the cause of a pediatric disease: mevalonic aciduria. Children with this disease also have inflammatory attacks typical with hyperimmunoglobulin D syndrome, growth retardation, dysmorphia and severe neurological disorders. The intimate mechanisms of inflammation associated with this metabolic disorder involves the interleukin-1 pathway (15,71). To date, mevalonaturia is mainly used among children and the serum IgD assay is not very specific and therefore rarely used (70).

The usual anti-inflammatory drugs, corticosteroids, colchicine, non-steroidal anti-inflammatory drugs, are generally not very active on this variety of inflammation (66). Recent studies showed the efficacy of IL-1 inhibitors, especially canakinumab with a continuous treatment (65,72,73).

3.2. ADA2 deficiency (DADA2) (figure 3)

First described simultaneously by two teams in 2014, deficiency in adenosine deaminase 2 (DADA2) is a rare autoinflammatory disorder characterized by three cardinal types of manifestations: inflammatory vascular manifestations, hematologic manifestations and, to a

lesser extent, immunodeficiency (74,75). Case reports since 2014 have continuously widened the clinical spectrum of the disease, with great variation of clinical presentation even among related patients (26,76).

DADA2 is an autosomal recessive disease, whose cause has been highlighted by a whole exome sequencing genetic approach: it results from loss-of-function mutation of *ADA2* (also called *CECR1*, standing for Cat Eye syndrome Chromosome Region candidate 1). *ADA2* gene is mapped to the q arm of chromosome 22 (22q11.1) and includes 13 exons; the gene encodes the adenosine deaminase 2, a dimeric enzyme mainly expressed by myeloid cells which is involved in the purine metabolism (26,76). To date, more than 60 disease-causing mutations have been reported with poor genotype-phenotype correlation; most of them being novel mutations, only found within one single patient or family; however, most common variants seem to be more frequent in certain population: p.G47R in Georgian Jewish and Turkish individuals, p.R169Q in Dutch population and p.T360A in Italian patients (76–78).

Pathogenesis of DADA2 is still mysterious despite ADA2's enzymatic activity; ADA2 has been shown to have a substantially lower affinity for its substrate (adenosine and 2'-deoxyadenosine) than ADA1 in physiological conditions; thereby ADA1 rather than ADA2 accounts for almost all of adenosine deamination and it is likely that the catalytic defect of ADA2 is not responsible for the clinical manifestations – although patients displaying a collapsed ADA2 activity could have a more severe phenotype (77,79). Main physiopathogenic hypothesis is a shift of the macrophage balance toward a pro-inflammatory M1 polarization rather than an anti-inflammatory M2 polarization leading to endothelial disruption (75). Indeed, ADA2 has previously been showed to have a growth-factor activity and accounts of an ADA2-dependent T cell proliferation and monocyte-macrophage differentiation/proliferation which could be deficient in DADA2 patients(80). The role of type I interferon has also been hypothesized according to several observation, though not investigated yet (81–83).

DADA2 diagnosis is based on the identification of one pathogenic variant of *ADA2* at the homozygous state or two compound heterozygous pathogenic variants of *ADA2*; serum ADA2 activity is another useful tool, which is constantly low in DADA2 patients (84).

Clinical presentation varies widely between patients, even within the same family; first symptoms usually occur during early childhood, mainly before 10 years old and 25% before one year old; however late diagnosis can be done as the oldest patient reported to date was 59 yo at the time of the diagnosis(26,76,85). DADA2 equally affects both genders worldwide (26,76). First articles on DADA2 described the inflammatory-vascular phenotype of the

disease, which is by far the most frequently reported: it consists of a vasculitis of medium- and small-sized arteries fulfilling periarteritis nodosa criteria (PReS or EULAR criteria) in one third of patients (74,75). As in most other autoinflammatory diseases, fever and inflammatory syndrome wax and wane along with vasculitis symptoms –neurological and cutaneous symptoms being the most common; ischemic strokes account for majority of neurological manifestations of DADA2 with typical MRI findings consistent with acute or chronic small-vessels ischemia of the deep brain nuclei and/or the brain stem; involvement of medium-sized vessels is less frequent: to date only one patient with intracranial aneurysm and 3 with intracranial stenosis or irregularity has been reported; transient ischemic attacks are also frequently described; hemorrhagic strokes have also been reported, although an uncertain proportion of them could be explained by antiplatelet or anticoagulant therapies given for previous ischemic strokes (26,76,78). Skin vasculopathy, present in 75% of patients, is characterized by a livedoid rash and rarely distal necrosis; in some cases – but not all – skin biopsy shows a non-granulomatous necrotizing vasculitis suggestive of cutaneous PAN and also nonspecific leukocytoclasic vasculitis and panniculitis have also been observed in others; other less frequent cutaneous/mucosal manifestations include non-specifi skin rashes and mouth ulcers (76). Vasculitis can also affect other organs, such as the gastro-intestinal tract, kidney or liver (26,76,78).

Anti-TNF therapies are now the cornerstone of the treatment of the vascular phenotype of DADA2; it controls inflammatory symptoms of vasculitis and prevents strokes whereas classical immunosuppressive therapies have shown disappointing results (75,76). Of note, antiplatelet or anticoagulant therapies for ischemic strokes are considered at risk of hemorrhagic transformation and there is no consensus on their indication, unlike other causes of ischemic stroke(75,76).

DADA2 is associated with a mild immunodeficiency linked to compromised B cell compartment, resembling to common variable immunodeficiency (CVID): approximately 25% of DADA2 patients suffer from hypogammaglobulinaemia (IgM being the most affected) and 20% experience recurrent infections (86,87). Considering the humoral immunodeficiency, the most commonly infections affect the lower and upper respiratory tracts; however, herpes virus infections, consisting mainly of recurrent herpes simplex outbreaks, are also reported; though T cell compartment is normal; Thus, immunodeficiency is almost never an isolated symptom of DADA2 in a single patient (86,87). Treatment of immunodeficiency is based on intravenous immunoglobulin supplementation in case of recurrent infections (86,88). Interestingly, correction of IgM defect was reported in a few

patients treated with ant-TNF therapies (86). Finally, allogenic hematopoietic stem cells transplantation (HSCT) may be an alternative in severe cases (89).

Hematological disease is the third cardinal manifestation: mild cytopenia, especially anemia and leukopenia are frequent (26,78). Regarding severe hematological phenotypes, pure red cell aplasia is the most described and affects about 5% of patients; severe neutropenia has also been described; The only effective treatment of those severe hematological phenotypes is HSCT (76,89).

Recently a case mimicking Castleman disease has been reported and the patient was successfully treated with tocilizumab (76,90).

3.3.- Other monogenic AID

3.3.1. Diseases with urticaria as a main feature

In this type of AID, systemic inflammation is dominated by a characteristic urticarial rash occasionally associated with other variable clinical manifestations. CAPS are the most emblematic AID of this group, but other pathological conditions such as NLRP12 or NLRC4 deficiency are entities with close clinical presentations. The latter condition may also be associated with severe episodes of macrophage activation syndrome.

Diseases related to NLRC4 mutations

Recurrent fevers linked to mutations of *NLRC4* were first described in 2014 among 3 families (91–93). In two families, phenotype consisted in a neonatal association of macrophage activation syndrome and early onset inflammatory bowel disease; the third family presented with an autosomal dominant cold urticaria without hematological or digestive involvement. To date, 28 cases have since been described, 75% of which being familial with an autosomal dominant transmission, 25% being caused by de novo mutations, probably because of the severity of one particular phenotype(94–96). Two different phenotypes seem to differentiate among case reports: a first group of patients have very early onset of disease (mean 1.8 months after birth), high fever with macrophage activation syndrome (90%), severe enterocolitis (80%) and an unspecific cutaneous rash (70%) leading to very high mortality rate (40%); a second phenotype suffers from a milder disease with later onset (mean 39 months). Tropism is cutaneous with urticaria or erythematous nodes, articular frequent (arthromyalgias) and ocular (conjunctivitis or sicca syndrome). There is neither reported vital organ involvement, nor mortality nor growth retardation (94,96). Interestingly, interleukin-18 was always markedly elevated when assayed, for both phenotypes and even between attacks. Treatment is not yet codified: used for severe patients of the first phenotype, glucocorticoids,

anakinra and ciclosporin provided complete remission in only one third of cases, whereas TNF-alpha inhibitors or vedolizumab were not efficient; anti-interleukin 18 and anti-IFN gamma agents gave interesting results in life-threatening situations (92). In the second phenotype, abstention or symptomatic treatment with NSAIDs was often preferred, while two paradoxical reactions to anakinra which worsening of arthritis and induced a Crohn disease, were described out of three trials (94).

Periodic fever associated with NLRP 12 mutations

Recurrent fevers linked to mutations of *NLRP12* 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 (97). Since the first description, 36 cases have been reported with considerable clinical heterogeneity between authors. Regarding genetics, most cases are related to *NLRP12* polymorphisms or VUS, rendering adequate characterization of the disease even more difficult; for instance, a Chinese review of the literature with no critical analysis of case reports analyzed 29 patients considered as having a *NLRP12*-related disease (98). Only 30% of 29 patients displayed a history of elevated acute phase reactant or CRP during crises; fifty percent of cases were sporadic, and only 6 patients presented variants with undetectable frequency in the general population; the remaining 23 patients were diagnosed based on polymorphisms or variants of undetermined significance(98). The authors also included 9 patients from a *De Pieri* et al. letter who had no diagnosed *NLRP12*-associated periodic fever (99). Meanwhile, a Russian team screened *NLRP12* variants in 246 children suffering from periodic fevers with 86% of common variable immunodeficiency diagnostic: 15 patients with *NLRP12* variants were retained as having an autoinflammatory disease linked to NLRP12; they presented a very low frequency of urticaria, arthralgia and cold sensitivity, respectively 13%, 20% and 20%, but 60% of recurrent infections (100). Recurrent infections in *NLRP12* related disease are only reported by this author: out of the 18 identified *NLRP12* variants in this article, twelve had a detectable frequency in the general population (99). Considering all 36 declared cases in the literature, there is neither report of organ failure, nor amyloidosis nor disease-related mortality; altogether, the actual published data seems both insufficient in quantity and quality to currently affirm with certainty that *NLRP12* mutations can produce genuine autoinflammatory syndromes (97–100).

3.3.2. Diseases with recurrent fever as a main feature

Recurrent fever associated with TNFRSF11A mutations.

A French team reported three patients with hereditary recurrent fever and a mutation of the *TNFRSF11A* gene, a gene known to regulate fever in rodents (101). This mutation was associated with increased secretion of several inflammatory cytokines and altered the biological effects of the receptor on NF-κB signalling. This entity was clinically very close to TRAPS syndrome, with prolonged fevers, and is associated with mutations in a gene of the same family, *TNFRSF11A* (101).

Recurrent fever and polyarthritis with LACC1/FAMIN mutations.

A mutation of the *LACC1/FAMIN* gene has been found to date among 15 patients, all from consanguineous marriages with systemic forms of idiopathic juvenile arthritis from Saudi Arabia (n=13) or Lebanon (n=2); the transmission was autosomal recessive (102,103). This gene encodes the laccase enzyme, which belongs to the multi-brass oxidase family that contains other enzymes such as ceruleoplasmin. All patients displayed symmetrical polyarthritis in both small and large joints with fever and inflammatory syndrome beginning between 12 and 36 months of life. Other clinical signs included maculopapular rash (n=13), organomegaly (n=7), deep adenomegalies (n=2); any patients developed macrophage activation syndrome (102,103).

3.3.3. Diseases with sterile skin /joint / bone inflammation as a main feature

Other autoinflammatory diseases are dominated by sterile inflammation of joints, bones and skin. This category contains many different rare diseases. The most frequent are those associated with *NOD2/CARD15* mutations, of which nearly 150 mutations are described to date.

Diseases associated with NOD2 mutations

Blau syndrome: this is a dominant autosomal disease linked to function gain mutations of *CARD15/NOD2* gene, which most typical presentation is a triad with joint, cutaneous and ocular involvement (104). It is named “Blau syndrome” in familial forms and early onset sarcoidosis in sporadic forms. Regarding rheumatological lesions, more than 90% of patients have symmetrical polyarthritis with synovitis and tenosynovitis, mainly affecting the extremities: hands with an involvement of proximal interphalangeal joints, which can lead to camptodactily, wrists, ankles and knees. Cutaneous lesions consist of a maculo-micro-papular erythematous and eczema-like rash, beginning in the first year of life, which may mimic atopy or vulgar ichthyosis; a skin biopsy will show granuloma without necrosis. Ophthalmological involvement is responsible for granulomatous uveitis very serious in 80% of patients. Other

rarer injuries include: a knotty rash, cranial nerve damage (104). Interestingly, a case of Blau syndrome with a somatic mutation gain of NOD2 function has recently been published (14).

Other NAID disease, for *NOD2*-associated autoinflammatory diseases: in 2011, Yao et al described a new category of auto inflammatory disease called NAID for *NOD2*-associated autoinflammatory disease (or more recently Yao syndrome) which is associated with variants of *NOD2* IV58+158 or R702W (105–107). It is a sporadic entity affecting Caucasians with a feminine predominance (70%) and diagnosed at a mean age of 35 years old; Patients display recurrent episodes featuring erythematous or macular plaques of the trunk in most cases, non-erosive oligo or polyarthritis in almost 80% of cases with fairly characteristic swelling of the distal extremities, gastrointestinal symptoms such as abdominal pain and diarrhea, and recurrent fever with general symptoms such as fatigue and weight loss; sometimes serositis are noted (105,106). However, it is important to remain cautious about this entity, which merely associates sporadic cases of non-specific phenotypes with genetic variants of undetermined significance to date.

Diseases associated with PSTPIP1 mutations

Diseases related to *PSTPIP1* mutations are called PAID for *PSTPIP1*-associated autoinflammatory diseases (6,108) . To date, more than 27 different mutations have been described in the *PSTPIP1* gene, which encodes a protein called CD2-BP1 (CD2-binding protein 1), an adaptive protein that can bind to inflammasome pyrin; this protein is involved in the organization of cytoskeletal structures and has an impact on the cellular dynamics of innate immunity cells, the release of IL-1 and modulation of T cells activation (6). Patients experience recurrent inflammatory attacks with systemic signs such as fever, inflammatory skin and joint lesions; In fact, as in cryopyrinopathies, it is a spectrum of diseases, the most frequent and firstly described was PAPA (Pyogenic Arthritis, Pyoderma gangrenosum and Acne syndrome). Since then, several different clinical entities associated with different mutations of this gene have been identified, the most serious being PAMI syndrome (PSTPiP1-Associated Myeloid-related-protein. In PAMI, there is an increase in the synthesis of a pro-inflammatory alarmin: MRP8/14 (myeloid-related-protein) protein, also known as calprotectin or S100A8/A9 protein which seems interesting to measure in peripheral blood of patients with PAID-compatible clinical phenotype in order to guide the sequencing of *PSTPiP1* when high (6).

PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum and Acne syndrome). This syndrome is the most common disease associated with *PSTPiP1* mutations and combines

recurrent arthritis with neutrophilic disease in more than 75% of cases and cutaneous lesions: severe cystic acne in more than 50% of cases, pyoderma gangrenosum in 33% of cases, mouth ulcers, aseptic abscesses, aseptic pustules, sometimes psoriasis or even suppurated hidradenitis (109).

PAMI syndrome (*PSTPiP1*-Associated Myeloid-related-proteinemia Inflammatory syndrome. It is clinically associated with aseptic arthritis in more than 55% of cases, pyoderma gangrenosum in almost half of cases, ulcerated and/or necrotic lesions in 30% of cases, acne and/or pustular rash in 20-25% of cases (6). Signs specific to this entity include hepatosplenomegaly in almost 90% of cases, polyadenopathy in 40% of cases and pancytopenia (almost constant neutropenia, very frequent anemia, thrombocytopenia in half of the cases) (6,108). Nephropathy may occur with renal impairment in 20%; growth retardation or mental retardation. Rarely cerebral vasculitis may develop (6). Biologically, the main characteristics, almost 90% of cases, are an extremely high serum calprotectin level (MRP8/14) and hyperzincemia , both being a much simpler and faster way to diagnose PAMI syndrome than genetics (6,108). These patients have a good response to anti-interleukin-1 biologics such as anakinra.

PAPASH syndrome (Pyoderma gangrenosum, Acne and Hidradenitis Suppurativa) was given for the combination of aseptic arthritis, pyoderma gangrenosum, acne and suppurated hidradenitis. This entity is close to features encountered among patients with nicastrin mutations (*NCSTN*) and/or mutations in *MEFV* exon 2 (see *infra*) (110).

PAPA-like syndrome (Pyogenic Arthritis, Pyoderma gangrenosum and Acne-like syndrome) combines arthralgia of acne and pyoderma gangrenosum, mouth ulcers and anemia (111).

PAC syndrome (Pyoderma gangrenosum, Acne and ulcerative Colitis) combines ulcerated colitis and severe acne, recurrent skin ulcerations, severe pustular rash with sometimes pyoderma gangrenosum (112).

Auto-inflammatory syndrome with neutrophilic dermatosis associated with MEFV exon 2 mutations (PAAND=periodic auto-inflammation with neutrophilic dermatosis).

It is a dominant autosomal syndrome discovered initially in 2016 in a large Belgian family with recurrent episodes of fever with arthromyalgia and neutrophilic dermatosis beginning early in life (4). Mutations *MEFV* in the p.S242R position (exon 2) have been found in a different domain from the classical FMF mutations. It was then confirmed in two other patients, one French and one Lebanese (4). A very recent publication has demonstrated *MEFV* mutation in exon 2, codon p.E244S, in a family of Spanish origin with three affected members

(5). They had pustular acne, suppurative hidradenitis, pyoderma gangrenosum and neutrophilic panniculitis. These two publications show that the spectrum of diseases linked to *MEFV* mutations is not limited to the classic familial Mediterranean fever of recessive transmission since, in the case of exon 2 mutation, patients of non-Mediterranean origin have a dominant transmitted disease with neutrophilic dermatoses in the foreground and may even mimic suppurative hidradenitis (4,5,27).

Majeed's Syndrome (LPIN2 mutations)

It is an autosomal recessive disease, described in a few predominantly Bedouin families, which combines recurrent multifocal chronic osteomyelitis, recurring fevers every 2 to 4 weeks lasting during 3 to 4 days or more, neutrophilic dermatosis, especially Sweet's syndrome or aseptic skin pustulosis or even psoriasis and congenital anemia. Most often the diagnosis is made in childhood with associated growth retardation, but a few cases have been described in adolescents/young adults. Mutations of the *LPIN2* gene have been reported in these patients (113,114).

DIRA: Inflammatory disease associated with mutations of the IL-1 receptor antagonist or DIRA (deficiency of the interleukin one receptor antagonist).

Recessive mutations of the IL-1 receptor antagonist have been found in some children with highly inflammatory neonatal disease associated with pustules resembling pustular psoriasis, multifocal aseptic osteomyelitis with periostitis. Patients display no or mild fever but have significant elevation of the biological markers of inflammation. The disease is autosomal recessive and highly susceptible to anakinra inhibition of interleukin-1(115) .

DITRA: Inflammatory disease associated with mutations of the IL-36 receptor antagonist or DITRA (deficiency of the interleukin thirty-six receptor antagonist).

It is an autosomal recessive disease described in 2011 in Tunisian families. Patients with generalized pustular psoriasis who started mostly in childhood. All of them had a diffuse erythematous, squamous, rapidly erythematous rash, progressing with relapses and accompanied by high fever associated with an inflammatory syndrome. These patients are at risk of sepsis and anakinra has been partially effective in some patients (116). More recently ustekinumab may have a complete efficacy on general signs and skin rash (117).

NAIAD: Auto inflammatory syndrome with arthritis and dyskeratosis associated with NLRP1 mutations (NAIAD).

This new entity described in 2017 in 2 families is autosomal recessive or dominant according to mutations (118). The onset is early in life, during the first six months: clinical presentation is rich with polymorphic mucosal and skin damage such as papillary or filiform hyperkeratosis, pseudo-phrynoderma, HPV negative condylomas, extended candidiasis; polyarthritis predominant in the knees, ankles, wrists and hands, with abnormalities in bone growth, and unexplained recurrent fever often associated with dysimmunity. NLRP1 inflammasome activating mutations are responsible for interleukin-1 hypersecretion and a decrease in CD27+ memory B cells, and anti-TNF or anti-IL-1 therapy has been shown to be effective(118). Other mutations of *NRLP1* have been described with a different clinical phenotype (15).

CAMPS: Pytiriasis rubra pilaris syndrome associated with CARD14 mutations

This dominant autosomal disease has recently been described in families with pityriasis rubra pilaris (119,120). The disease begins before the age of 3 years and is characterized by extensive erythematous and sometimes scaly coalescent extensive plaques containing islets of healthy skin associated with follicular papules and palmoplantar keratoderma but without psoriasis-like lesions (119,120). The mutations of the CARD14 gene encode a protein mainly expressed on keratinocytes and capable of activating the NF-KB pathway Histologically, there is a parakeratosis, or orthokeratosis, acanthosis and mononucleated dermal infiltrate (119).

Hidradenitis suppurativa associated with nicastrin mutations (NCSTN)

In 2011 Liu described cases of suppurativa hidradenitis associated with mutations of the *NCSTN* gene (121). Nicastrin is a transmembrane protease type glycoprotein acting as a gamma-secretase (121). Since then, several teams have reported families with a dominant autosomal transmission of suppurativa hidradenitis in several countries such as China, France and Iran (122–124). Depending on the families affected presenting with only recurrent aseptic abscesses of the large folds (axillar, inguinal, perineal, and anorectal) or associated with pyoderma gangrenosum and acne; this disease is therefore a differential diagnosis of diseases associated with *PSTPiP1* mutations (PAID) and *MEFV* exon-2 mutations (PAAND) (4,5,124,125).

3.3.4. Ubiquitinopathies

In addition to the well-known autoinflammatory interleukin1 (IL-1) and interferon pathways, the range of possibilities widens with the description of negative regulation defects of the NF-κB pathway. The NF-κB pathway initiated upon contact of a ligand with tumor necrosis factor receptor 1 (TNFR1) plays a critical role in the initiation of the inflammatory process since it produces major cytokines such as IL-1, interleukin 6 and TNF; its downregulation is essential for stopping the inflammatory process and depends on the level of ubiquitination of TNFR1-associated proteins and other intermediate compounds. A20 and OTULIN are proteins that modify ubiquitination and their defect can induce the NF-κB pathway activation with excessive production of proinflammatory cytokines (16,126).

HA20 haploinsufficiency (table 2).

The initial description by Zhou *et al*, reported 16 patients with HA20 and clinical features more detailed in a recent publication by the same team (18,19). The patients come from 7 families including 5/7 multiplexes with a dominant transmission. In these initial patients, the disease began early in life with some similarities with Behçet's disease due to the presence of bipolar aphthae in most patients as well as ocular inflammation (19). It was distinguished by the presence of febrile attacks in most cases and always associated with biological inflammation during attacks which are not usual in Behçet's disease with systemic inflammation observed only during attacks of serositis, vasculitis and digestive involvment and rare in Asian populations. Fifty-one patients have yet been reported in the literature within 3 years, mostly women (60%), and more frequently from Japan (60% of all cases) but the disease can affect worldwide. The main features are the dominant autosomal transmission, the early age at onset, in the first year of life, and the oral aphtae lesions in 88% of cases even though genital aphtae ulcers can also occur in 68% of cases. Recurrent fever and digestive symptoms, such as bloody diarrhea are frequent during attacks. Cutaneous lesions are various (45%) and arthromyalgia observed in 1/3 patients. One third of patients displayed autoantibodies especially antinuclear and thyroid-specifi antibodies (16,19,127).

All patients described required treatments ranging from colchicine alone (effective in 8 patients) to combinations of corticosteroids and immunosuppressants (methotrexate, azathioprine, thalidomide, cyclophosphamide, tofacitinib). Overall corticosteroids were effective but with high levels of corticosteroid dependence responsible for major side effects. The biotherapies used were anakinra, tocilizumab, and anti-TNF and were considered to influence systemic inflammation. Intraveinous immunoglobuline replacement therapies have

been used in the few patients with associated humoral immune deficiency; in patients with HA20 a personalized therapeutic approach should rely in part on detected cytokine levels since there is probably a large phenotypic variability which complicates the establishment of standardized management (18,126,127).

ORAS: otulinopenia or ORAS (OTULIN-related autoinflammatory syndrome) by mutations of OTULIN.

A new recurrent hereditary fever has been discovered in connection with mutations of a gene called *OTULIN* that encodes a deubiquitinase (20,25). Two teams reported a total of four mutations of this gene in eight patients from four consanguinous families of different origins (English, Turkish and Pakistani). It is an autosomal recessive transmission disease characterized by severe neonatal systemic inflammatory manifestations consisting of prolonged fevers, joint swelling, severe diarrhea with growth delay. The attacks are long and do not resolve without treatment (20,25). On the skin level, various rashes have been described including erythema, pustules, subcutaneous nodules, panniculitis and lipodystrophy. Fever usually lasts for about two weeks. Serum total immunoglobulin levels is discreetly elevated and sometimes there are anti-smooth muscle antibodies. Five of 6 patients with ORAS reported in the literature were treated initially with anti-TNF drugs; with the last one received corticosteroids and anakinra (20,25,126,128).

3.4. Interferonopathies

It is a heterogeneous group of diseases characterized by increased expression of interferons (IFN) type 1 that can lead to the secretion of proinflammatory cytokines by innate immune cells. These diseases are mainly diagnosed in paediatrics and have phenotypic similarities and skin signs of chilblain lupus or livedo present in the first few months of life and neurological manifestations (from asymptomatic cerebral calcifications to encephalopathies) (129,130).

A disease called SAVI, known as STING-associated vasculopathy with onset in infancy, belonging to interferonopathies, has been described in patients with severe skin vasculopathy with possible ulcers and interstitial lung disease wich can progress to early pulmonary fibrosis and systemic inflammation; This dominant autosomal disease is associated with gain-of-function gain mutations of *TMEM173* encoding a protein called STING (130–132). Lung damage is severe and is the main cause of death and may require lung transplantation (130).

3.5. MAI with immune deficiency

3.5.1. Deficits in *HOIL1* and *HOIP*

Mutations of *HOIL-1* (or *RBCK1*), a subunit of the LUBAC complex which ubiquitins intracytoplasmic proteins before addressing them to the proteasome, have been described by a French team. This syndrome associates recurrent fever, inflammatory colitis, hepatosplenomegaly, adenomegalies, recurrent pyogenic infections and severe B immune deficiency (decrease in switched B lymphocytes), but no autoimmunity. There is cardiac amylopectinosis (23).

Mutations of *HOIP* (or *RNF31*), another subunit of the LUBAC complex which ubiquitinates intracytoplasmic proteins before addressing them to the proteasome, have been described by the same French team; this syndrome combines a recurrent fever with arthralgia, diarrhea, splenomegaly, subclinical amylopectinosis and lymphangiectasis, no autoimmunity, hypogammaglobulinemia and T-cell abnormalities (133).

3.5.2. Diseases associated with *PLCG2* mutations (PLAID and APLAID)

Two dominant autosomal diseases associated with different mutations of the same gene, *PLCgamma*2, are responsible for autoinflammation associated with immune deficiency and immune deregulation: PLAID and APLAID.

The PLAID ("*PLCG2*-associated Antibody-deficiency and Immune Dysregulation") was described in 27 patients from three American families in 2012: all had environmental cold urticaria with a positive ice cube sign (100%), an immune deficiency close to a common variable immunodeficiency (CVID) with recurrent ENT and pulmonary infections (75%), the presence of anti-nuclear antibodies or autoimmune disease including thyroid disease in 56%; seven patients had granulomas on skin biopsy examination (134). This disease is on the verge of autoinflammation (low level) and dysimmunity (low level).

APLAID (false sense mutations with function gain), initially described in a family, is therefore rarer. It means "Autoinflammatory *PLCG2*-associated Antibody-deficiency and Immune Dysregulation". It combines the presence of bullous and/or oozing skin lesions (without cold urticaria), enterocolitis, ocular inflammation (ulceration/erosion, which can lead to intraocular hypertension and cataracts), non-specific interstitial lung disease, arthralgia and moderate immunuodeficiency with recurrent sino-pulmonary infections due to low serum levels of IgM and IgA. These PLCgamma abnormalities modify the intracellular metabolism of calcium, activating the inflammasome NLRP3(135).

3.5.3. PFIT for periodic fever with immunodeficiency and thrombocytopenia (*WDR1* mutation).

It is an autosomal recessive disease described for the first time in 2017 in Pakistani twins from inbreeding parents (136). From birth, it combines recurrent fever, mouth ulcers and perianal canker sores, severe opportunistic infections with encapsulated bacterium or fungus and thrombocytopenia with small-sized platelets (136). The disease is linked to mutations in the *WDR1* gene, whose loss of function leads to the accumulation of actin molecules that activate pyrin, responsible for interleukin-18 hypersecretion. Disturbance of the cytoskeleton leads to dysfunction of T cells, antigen-presenting cells and megakaryocytes, such as in Wiskott-Aldrich syndrome (136). The only effective therapy to date appears to be bone marrow allografting, corticosteroids and biotherapies being only partially effective and increasing the risk for infection (136).

3.5.4. TRNT1 mutations in SIFD syndrome

Mutations of the *TRNT1* gene associated with a syndrome associating: immune-deficit sideroblastic anemia, recurrent fever and delayed development (SIFD for Sideroblastic anemia with B-cell Immunodeficiency, periodic Fevers and Developmental delay, *TRNT1* mutations) (137). The cases mainly concern young children of all ethnic origins who present with severe (microcytic) anemia (7g/dL), recurrent fever, attacks of major digestive symptoms such as diarrhea, various neurological signs (epilepsy, deafness, mental retardation), as well as nephrocalcinosis and panhypogammaglobulinemia, with absence of total B lymphocytes. Only one adult has been reported to date due to high morbidity/mortality rates. The *TRNT1* gene encodes an RNA polymerase necessary for cytosolic maturation and transfer of RNAt to mitochondria (137,138).

3.5.5 Other rare AID with immunodeficiency

ADA2 deficiency is frequently associated with hypogammaglobulinemia and is described above in section 3.4 (26,76). More recently patients with *TNFAIP3* mutation (described in section 3.2.4.1) and *NOD2* variations (described in section 3.2.3.1) have been reported with immune deficiency (18,128,139).

Mutations in *NFKB1* and *NFKB*2 were associated in some cases with autoinflammatory features and primary immunodeficiencies which could mimic Behçet's disease or common variable immunododeficiency with or without alopecia and viral infections such as EBV infection (140,141) .

3.6. H syndrome

H syndrome is an autosomal recessive genodermatosis firstly described by Molho-Pessach *et al* in 2008 (142). It is associated with mutations in *SLC29A3* gene which encodes the human equilibrative nucleoside transporter 3 (hENT3) (143). The name of H syndrome was chosen to represent the most frequent features: cutaneous Hyperpigmentation and Hypertrichosis, Hepatosplenomegaly, Hearing loss, Heart anomalies, Hypogonadism, low Height, Hyperglycemia/insulin dependant diabetes mellitus and Hallux valgus/flexion contractures. Cutaneous hyperpigmentation and progressive sclerodermatous induration, typically affecting the medial thighs are pathognomonic. Other systemic features are reported as well as, exophthalmos or eyelid swelling, lymphadenopathy, gastro intestinal symptoms such as chronic diarrhea, pancreatic dysfunction, skeletal abnormalities(142,144). Histological examination of skin lesions or lymphadenopathy shows marked fibrosis and infiltration by small histiocytes expressing CD68; perivascular infiltrates composed of lymphocytes, plasma cells, and mast cells accompanied by hemosiderin deposition [24]. It can mimic Rosai-Dorfman disease with CD60+ S100+ CD1a- histiocytes infiltration and emperipolesis (145,146). It belongs to the R group of the revised classification of histiocytoses and related neoplasms by the Histiocyte Society [26]. Chronic inflammation is a classic biological feature and some patients display recurrent fever. It can be severe and often refractory to conventional immunosuppressive drugs or blockade of interleukin-1 and tumor necrosis-α and a few reports suggesting efficacy of tocilizumab have been published (147,148).

4-NON-MONOGENIC AID.

Non-monogenic AID can be called "unclassified" MAI when they do not meet the criteria for the diseases mentioned above but have the general clinical-biological criteria for autoinflammatory diseases. These diseases are characterized by episodes of recurrent fever with biological inflammatory syndrome and clinical features of the auto-inflammatory type, without any genetic cause being identified to date. Some non-Mendelian inflammatory diseases have clinical, histological, pathophysiological or genetic similarities with inherited autoinflammatory syndromes, but appear to have a multifactorial origin.

4.1. Schnitzler's syndrome

Schnitzler's syndrome, defined by the association of adult acquired urticaria and monoclonal IgG or IgM by L. Schnitzler in 1972, shares with cryopyrinopathies a clinically and

histologically very similar rash (neutrophilic urticaria) (149). A Dutch team reported the presence of NLRP3 somatic mutations restricted to the myeloid line in patients with Schnitzler's syndrome but they were not confirmed in a larger population (150,151).

4.2. The systemic form of juvenile idiopathic arthritis and Still's disease in adults

The systemic form of juvenile idiopathic arthritis (FS-AJI) is classified as an idiopathic juvenile arthritis but is a auto-inflammatory disease (152). According to the International League of Rheumatology Associations classification, the definition of FS-IAJI is a fever of at least two weeks duration preceding or accompanying arthritis of unknown origin, of at least six weeks duration, which begins before the age of 16 years; accompanied by at least one of the following signs: fugitive rash (figure 2.D), adenopathy, hepatomegaly and/or splenomegaly, serositis. The exact etiology of FS-AJI is currently imperfectly known but is characterized by a deregulation of innate immunity.

Adult onset Still's disease is undoubtedly a heterogeneous entity characterized by the association of 4 clinical-biological cardinal elements: marked fever, evanescent skin rash, arthralgia or arthritis, and neutrophilic polynuclear hyperleukocytosis in the absence of rheumatoid factor or antinuclear antibodies (153). Thus defined, Still's disease was an autoinflammatory disease before the hour, although the molecular and cellular mechanisms underlying it have not yet been fully elucidated.

The management of these two entities aims to obtain the remission of systemic and articular manifestations and prevent complications such as joint destruction, inflammatory amyloidosis. Treatment is based on non-steroidal anti-inflammatory drugs (NSAIDs) in mild and in severe forms corticosteroids, methotrexate and anti-IL1 and anti-IL6 biotherapies, especially in cases of joint damage (154).

4.3. Aseptic abscess syndrome

It is defined by the existence of diffuse tissue abscesses with neutrophils, predominantly in intra-abdominal organs, and more rarely extra-abdominal (lung, brain, skin); it may be associated with Crohn's disease or relapsing polychondritis, or even with pyoderma gangrenosum, or be isolated; there is sometimes identical personal of familial history (155,156).

4.4. PFAPA syndrome

PFAPA syndrome is the leading cause of recurrent fever in pediatrics; the acronym PFAPA stands for "periodic fever aphtous stomatitis pharyngitis adenitis" (157). This syndrome combines recurrent fever of very regular frequency about once a month with pharyngitis,

mouth ulcers (figure 2.C), cervical adenopathy, sometimes headache, and abdominal pain for 3 to 6 days. Single-dose steroids are very effective. The prognosis is good: usually clinical signs disappear in adolescence, but adult cases have already been described (157,158).

5-DIAGNOSTIC CHECK-LIST FOR AID (TABLE 3)

Table 3 proposes a plan to guide the clinician suspecting an AID. Some specific features suggesting on or another AID are indicated in the third column. The plan of a AID's semiological analysis to orientate itself towards this or that category and guide a possible genetic analysis.

5.1. Family history

Draw the family tree and collect the country or region of origin of his grandparents. The objectives are to look for Mediterranean area origin and see if each generation is affected, ssuggesting dominant autosomal transmission or, on the contrary, horizontal transmission suggesting recessive heredity; just like inbreeding unions orientating towards a recessive trait. Cases of death due to kidney failure (dialysis patients) as well as other inflammatory diseases possibly more frequent in families with AID (inflammatory disease of the digestive tract, psoriasis, spondylitis etc.) will also be investigated.

5.2. Personal history

Ask for the age at onset (beginning of symptoms) and the duration of attacks in days : The age at which the first symptoms began is very important to evoke a Mendelian AID. For example, in the most severe phenotypes of cryopyrinopathies, urticaria is often present in the first few days of life; in the case of mevalonate kinase deficiency, febrile seizures and digestive disorders often begin in the first year of life. More likely to be referred to as Somatic Mutagenic AID if symptoms are atypical (mitigated) or begin after age 40 yo. Similarly, the duration of relapses is interesting to collect: when the crisis lasts more than 7 days, one thinks more of a TRAPS syndrome (or more rarely of the deficiency in mevalonate kinase), than of a familial Mediterranean fever (figure 4).

5.3. Clinical symptoms in crisis (figure 5 and table 1).

Recurrent fevers are usually accompanied by stereotyped clinical signs, with the three systems most commonly involved being the cutaneous/mucosal, digestive tract and musculoskeletal systems. Table 1 summarizes the main outcomes that need to be addressed as a matter of priority for an AID.

Cutaneous features (figure 2)

*T*he most suggestive skin lesiosn are urticaria, mouth ulcers and or bipolar aphtae, erythema, pustules, livedo, lipodystrophy of the face or limbs, frostbite, livedo, purpura. Any suspicious lesion must be biopsied in search of a specific histological lesion (neutrophilic filtrate, vasculitis, granulomas...). The patients should if possible take pictures of their lesions when attacks occur at home and send them to their physician by email or cellular phones or present them during the consultation.

Articular

The interrogation looks for myalgia, arthralgia and will specify their location. The clinical examination will look for arthritis, synovitis and arguments for sacroilitis, spondyloarthritis.

The main serous membrane localizations are the peritoneum responsible for abdominal pain, the pleura, responsible for chest pain and less frequently the pericardium, synovial and the tunica vaginalis.

Digestive tract

Apart from abdominal pain of aseptic peritonitis, cramp-like pain can be secondary to deep adenomegalies; diarrhea is sometimes found at the end of the FMF crisis but is above all reminiscent of inflammatory colitis (MKD, or other AID with MICI). In case of surgery, the surgical report must be retrieved.

Neurological

Interrogation and clinical examination look for headache, chronic aseptic meningitis, stroke, paraparesis

Ophthalmic

Interrogation and clinical examination look for uveitis, conjunctivitis, scleritis, episcleritis, glaucoma.

ORL

Interrogation and clinical examination look for sensorineural deafness, chondrite, cervical adenomegalies

Immuno/hematological

Interrogation and clinical examination look for hepatosplenomegaly, peripheral adenomegalies, repeated bacterial infections or opportunistic infections suggesting immune deficiency, signs consistent with cytopenia (pallor, purpura)

5.4. Blood test to detect inflammatory markers in crisis

The presence of an acute phase response in crisis must be objectively assessed by measuring CRP, search for a hyperleukocytosis with a predominance of neutrophilic polynuclears in the bloodstream and sometimes erythrocyte sedimentation rate in children. The patient should be given a blood test prescription for attacks, and three evidence of CRP elevation (three different attacks) for at least 6 months must be gathered to consider AID as possible. In addition, it is also interesting to have the result of CRP level during the non-crisis time to check their normal rate. Except in interferonopathies, CRP levels are always elevated in crisis of AID.

5.5. Check for diagnostic criteria

Some diseases are defined by diagnostic criteria such as FMF, diseases associated with NOD2 or NAID mutations, Schnitzler's syndrome, Still's disease and cryopyrinopathies [14-19]. For the 4 historical recurrent fevers (FMF, TRAPS, CAPS, MKD, there is a website which allows the clinician to be directed towards one of the 4 diseases with an online algorithm (link: http://printo.it/eurofeer/scoreCriteria.asp) developed by the pediatrician's from Eurofever working group (63). It can be useful in daily practice to guide a request for targeted DNA analysis.

6-MAIN TREATMENT STRATEGIES

Daily colchicine remains the reference and preventive treatment for FMF attacks. Compliance must be verified in the event of inefficiency. For CAPS, anti-IL-1 is the reference treatment and provides a complete control of inflammatory manifestations in more than 90% of cases. In other rare monogenic AIDs dependent on interleukin-1, treatment is not always codified. Overall in inflammasomopathies, anti-IL-1 drugs are tempted first, then if ineffective, should be discussed anti-IL-6 or anti-TNF drugs, the latter being very effective in ADA2 deficiency (76). In ubiquitinopathies, anti-IL-1 agents have been used, sometimes successfully and in the event of failure of anti-TNF agents. About the rare diseases combining immunodeficiency and autoinflammation, their treatment is not codified, it is necessary to act in priority on the most clinically severe auto inflammatory symptoms by a biotherapy and to discuss a supplementation by polyvalent immunoglobulin on the other hand, or even bone marrow allograft in some very severe cases. In general, the treatment of these very rare diseases must be discussed/decided in a multidisciplinary consultation meeting with experts who are used to treat these patients.

7-CONCLUSIONS

Analysis clinical signs during relapses is very important for the precise diagnosis of an auto-inflammatory disease (AID). More and more effective treatments for inflammatory manifestations are available to relieve patients and prevent the development of secondary amyloidosis (AA amyloidosis), the chronic complication of these inflammatory diseases. Since the discovery of the familial Mediterranean fever gene 20 years ago, great progress has been made in genetics to better dismember these rare diseases of innate immunity. Interestingly, the same gene may be responsible for a varied spectrum of more or less severe clinical phenotypes such as cryopyrinopathies and diseases associated with *MEFV* mutations; and for some newly discovered diseases, the phenotypic spectrum is certainly not yet completely known: such as the *ADA2* deficiency. Indeed, in that disease, initially described in 2014, other features were recently reported with patients displaying immunodeficiency or even erythroblastopenia or a Castleman-like disease (76,90)! Thus, this is a new field of systemic diseases in adult and pediatric internal medicine, which will lead to interesting opportunities in clinical, pathophysiological and genetic discoveries for the next coming years.

Conflicts of interest:

The authors state that they have no conflict of interest in relation to this manuscript. The following authors declare that they have received occasional fees as consultants or assistance in attending congresses of Novartis and SOBI laboratories: SGL, GG.

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Tables.

Table 1. Orientation of AID from clinical, biological or histological main features.

Table 2. Main characteristics of HA20 with autoinflammatory features from literature.

Table 3. A diagnostic-check-list for AID.

Figures legends

Figure 1. Main known pathophysiological pathways in monogenic autoinflammatory diseases.

Panel A. In the first described and most known monogenic autoinflammatory diseases, there is an excessive production of pro-inflammatory cytokines (especially interleukins 1, 6, 18 and TNFα) by pyrin or NLRP3 inflammasomes. In mevalonate kinase deficiency the activation of the pathway also results in stimulation of pyrin. The danger signal can also come from a failure of protein folding as in the mutations of *TNFRSF1A* (TRAPS syndrome) which leads to increased secretion of oxygenated radicals (ROS) and thus activate inflammasomes. Recently discovered autoinflammatory diseases involve other inflammasomes such as NLRP1 or NLRC4-NAIP. The inflammasome activation can also come from an imbalance of endogenous antagonists in the rare mutations of *IL1RN* (DIRA syndrome) or *IL36RN* (DITRA syndrome).

Panel B. In *ADA2* deficiency, there is an imbalance in the balance of macrophages M1/M2 with an excess of pro-inflammatory macrophages and vasculitis.

Panel C. Diseases that result in stimulation of NF-KB pathway are either related to gain of function of activators (*NOD2* mutations) or loss of function of inhibitors such as the LUBAC, OTULIN and HA20 ubiquitin-ligases.

Panel D. Interferonopathies have several entities where mutations induce overexpression of the interferon gene. In those diseases there is an excess of interferon and pro-inflammatory cytokines.

Figure 2. Most frequent cutaneous and mucosal lesions in AID.

Panel A: Erysipelas-like erythema in the ankle of a patient during an attack of familial Mediterranean fever.

Panel B: Urticaria in a patient with cryopyrinopathy.

Panel C: Oral aphtae in a patient with mevalonate kinase deficiency.

Panel D: fugitive erythematous lesion in a patient with adult onset Still's disease.

Figure 3. Main features of DADA2

This figure compiles the most important elements to know on DADA2. On panel A are represented the main clinical features, in red the most frequent and most specific compared to other AID. On panel B: a family tree showing typical autosomal recessive transmission – with consanguineous parents – which is the most frequent type of transmission in DADA2. On panel C are represented strokes that usually appear early in life. On panel D is represented an hypogammaglobulinemia, since immunodeficiency mimicking common variable immunodeficiency is one of de cardinal manifestations of DADA2. On panel E is represented a cutaneous livedo, a frequent clinical feature of the diseases as well as abdominal pain (panel F) and arthromyalgia (panel G).

Figure 4. Main chronological features of AID.

The main chronological features that can help to guide the diagnosis to one AID or another are represented on this figure. On panel A is represented the usual attack length in familial Mediterranean fever (2-4 days); on panel B is represented the specificity of PFAPA with very often the same interval of days between 2 attacks; On panel C is represented this long attack length of TRAPS between 7 and 21 days; On the panel D is represented Still disease with usually very long attack from 15 to 30 days, and even more when not treated. It emphasizes the importance of asking of attack length and the interval between 2 crises.

Figure 5. Main clinical features of the most frequent AID.

The main features during crisis of the four historical monogenic AID are represented on 4 panels: A for familial Mediterranean fever; B for *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID); C for TNFRSF1A receptor associated periodic syndrome; D for mevalonate kinase deficiency. For each disease the main symptoms are written in red and the frequency of amyloidosis is written at the bottom of each subject.

Abbreviations:

APLAID: Autoinflammation and PLCg2-associated Antibody deficiency and Immune Dysregulation

CAMPS: CARD14-mediated pustular psoriasis= *CARD14*-associated psoriasis

CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome

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

CINCA: Chronic infantile neurological, cutaneous and articular syndrome

DIRA: Deficiency of the IL-1 receptor antagonist

DITRA: Deficiency of the IL-36 receptor antagonist

DUB: deubiquitinase

FCAS: Familial cold autoinflammatory syndrome

FCAS2: Familial cold autoinflammatory syndrome 2 (*NLRP12*-associated autoinflammatory disease).

FMF: Familial Mediterranean fever

HA20: A20 haploinsufficiency

LUBAC: Linear ubiquitin chain assembling complex

MKD: mevalonate kinase deficiency

MWS: Muckle Wells syndrome

NAIAD: *NLRP1*-associated autoinflammation with arthritis and dyskeratosis

NAID: *NOD2*-associated autoinflammatory diseases

NLRC4-MAS: *NLRC4* associated macrophage activation syndrome

ORAS: Otulin related autoinflammatory syndrome

PAAND: Pyrin-associated autoinflammation with neutrophilic dermatosis

PAID: PSTPIP1-associated autoinflammatory diseases

PAMI: PSTPiP1-Associated Myeloid-related-proteinemia Inflammatory syndrome

PAPA: syndrome pyogenic arthritis, pyoderma gangrenosum and acne

PAPASH: PSTPiP1-associated Pyoderma gangrenosum, Acne and Hidradenitis Suppurativa

PAC: Pyoderma gangrenosum, Acne and ulcerative Colitis

PFAPA: Periodic Fever Aphtous Stomatitis Pharyngitis Adenitis

PFIT: Periodic Fever with Immunodeficiency and Thrombocytopenia

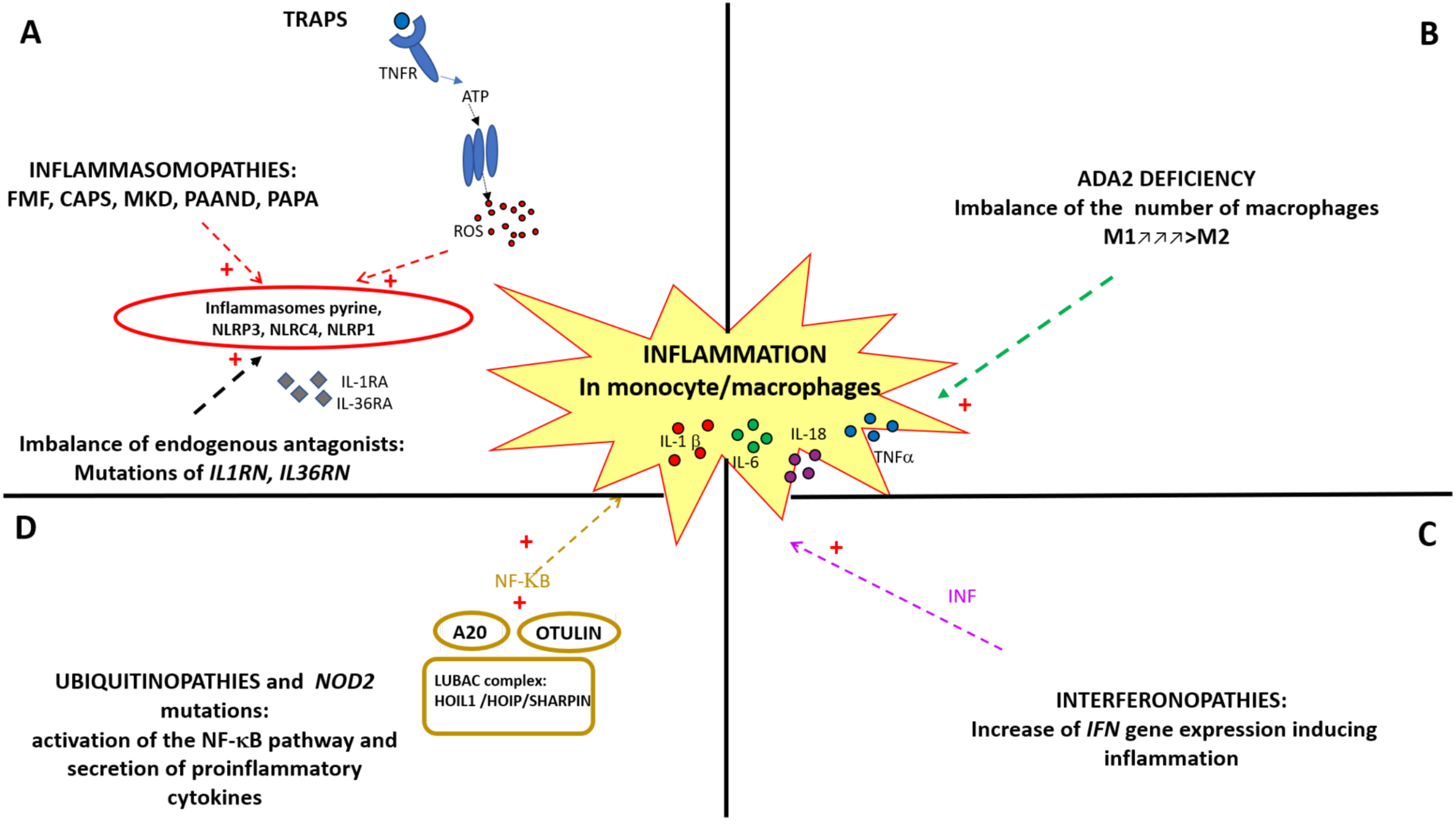
PLAID: PLCg2-associated Antibody deficiency and Immune Dysregulation

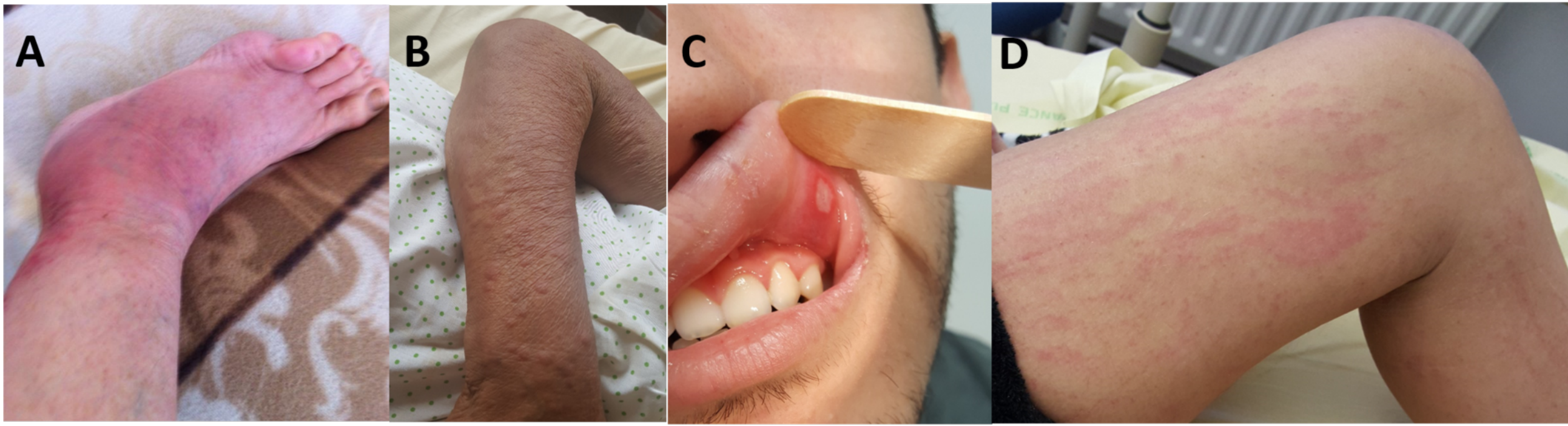
SAVI: STING-associated vasculopathy with onset in infancy

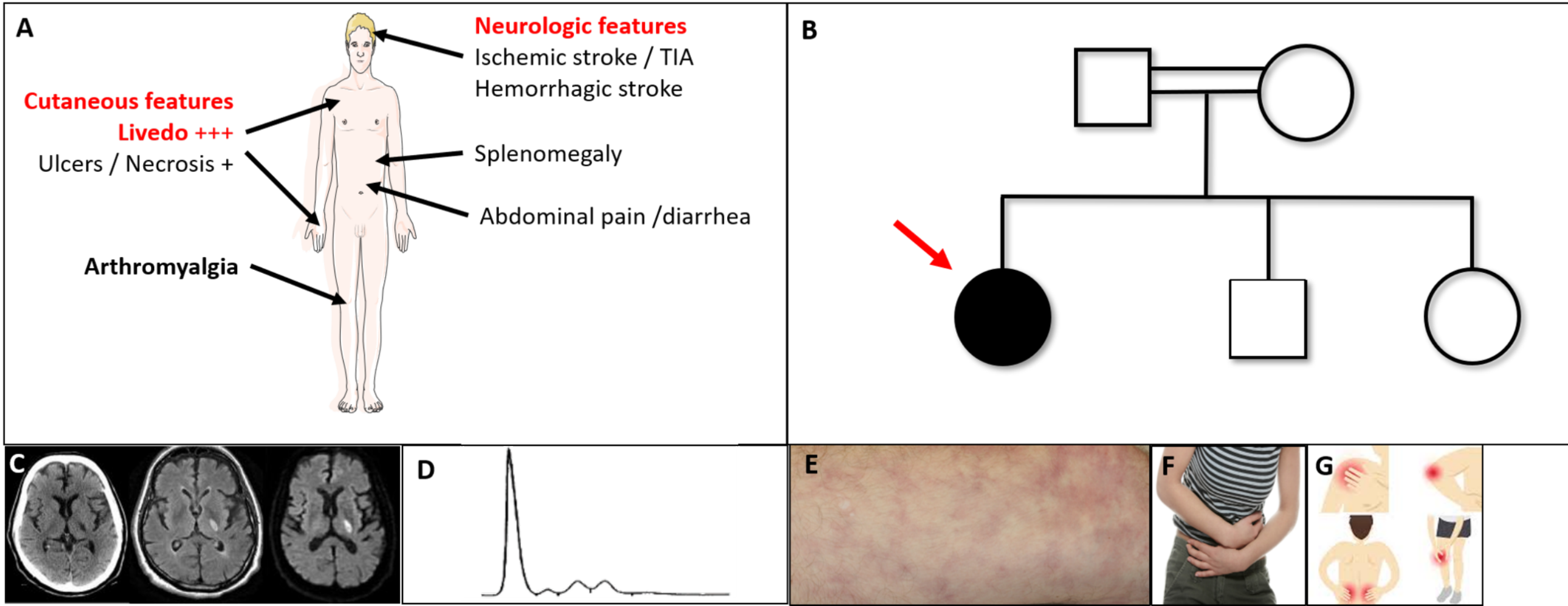
SIFD: Sideroblastic anemia with B-cell Immunodeficiency, periodic Fevers and Developmental delay

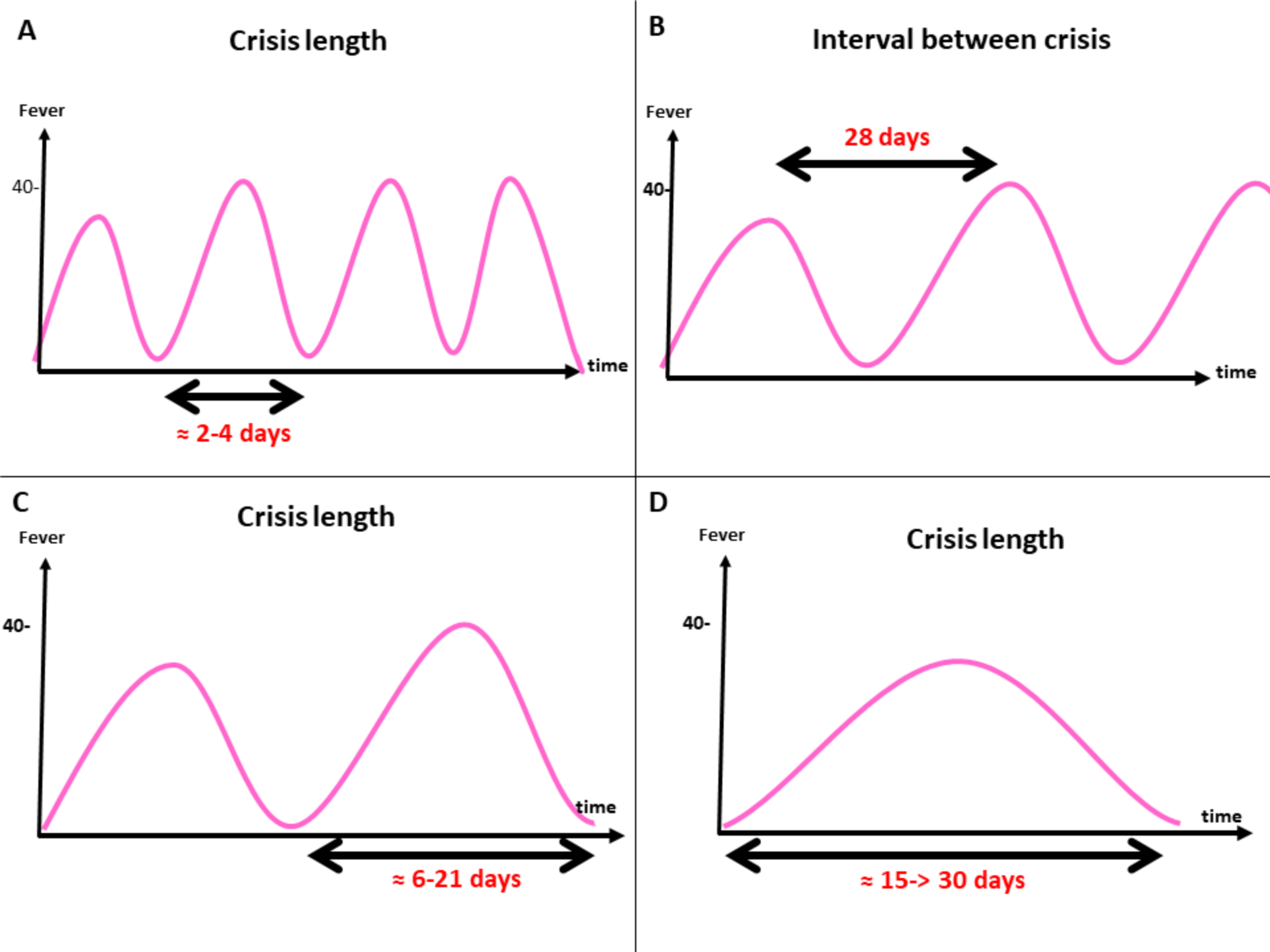
TNFRSF11A: TNF11α–Receptor associated periodic syndrome

TRAPS: TNF-Receptor associated periodic syndrome


A
TRAPS
TNFR
ATP
ROS
INFLAMMASOMOPATHIES:
FMF, CAPS, MKD, PAAND, PAPA
+
+
Inflammasomes pyrine,
NLRP3, NLRC4, NLRP1
+
IL-1RA
IL-36RA
Imbalance of endogenous antagonists:
Mutations of IL1RN, IL36RN
B
ADA2 DEFICIENCY
Imbalance of the number of macrophages
M1↗↗↗>M2
+
INFLAMMATION
In monocyte/macrophages
IL-1 β
IL-6
IL-18
TNFα
D
+
NF-KB
+
A20
OTULIN
LUBAC complex:
HOIL1 /HOIP/SHARPIN
UBIQUITINOPATHIES and NOD2
mutations:
activation of the NF-κB pathway and
secretion of proinflammatory
cytokines
C
+
INF
INTERFERONOPATHIES:
Increase of IFN gene expression inducing
inflammation


A
B
C
D


A
Neurologic features
Ischemic stroke / TIA
Hemorrhagic stroke
Cutaneous features
Livedo +++
Ulcers / Necrosis +
Splenomegaly
Abdominal pain /diarrhea
Arthromyalgia
B
C
D
E
F
G


A
Crisis length
Fever
40-
time
≈ 2-4 days
B
Interval between crisis
Fever
28 days
40-
time
C
Crisis length
Fever
40-
time
≈ 6-21 days
D
Crisis length
Fever
40-
time
≈ 15-> 30 days

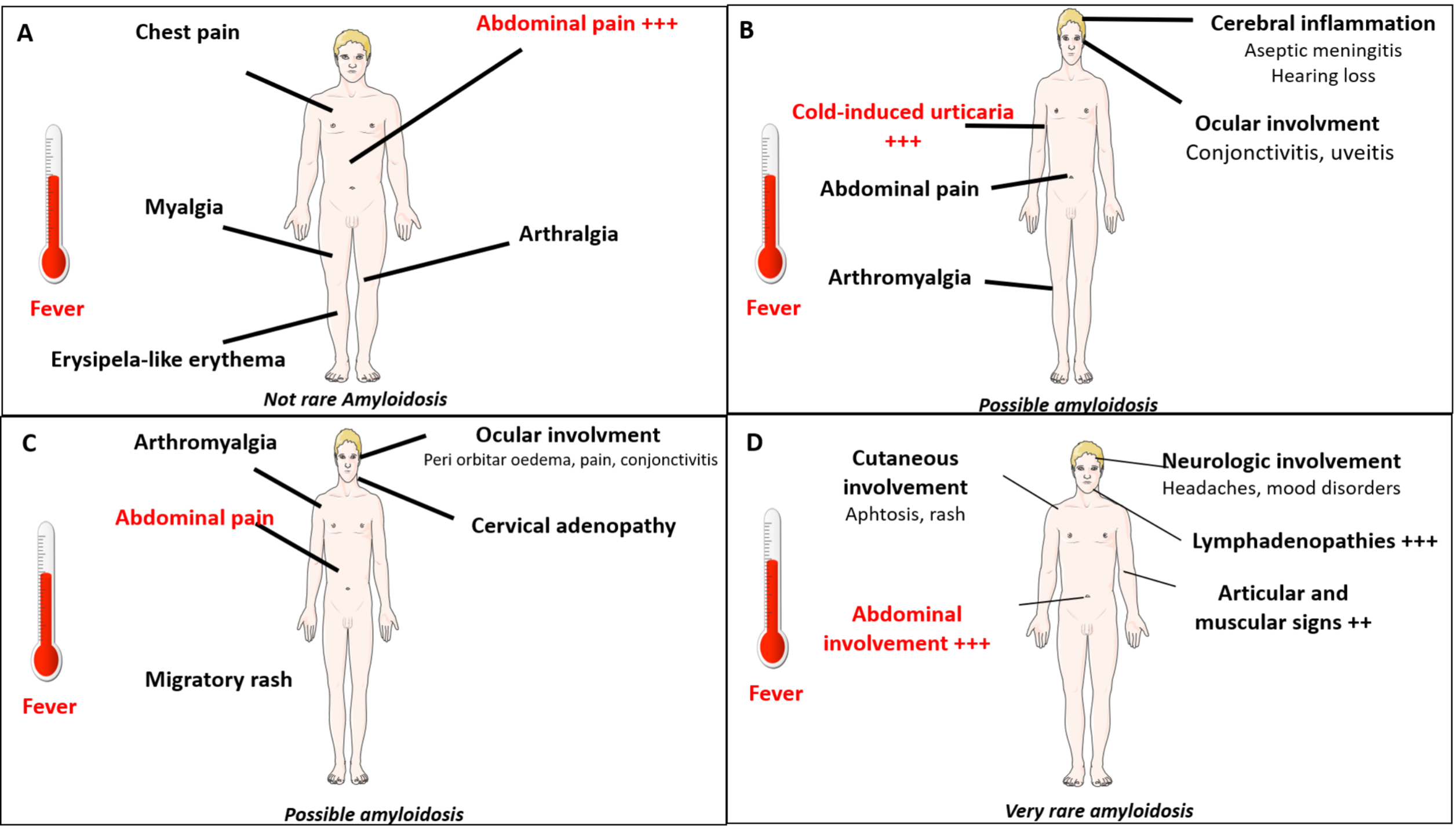

A
Chest pain
Abdominal pain +++
Myalgia
Arthralgia
Fever
Erysipela-like erythema
Not rare Amyloidosis
B
Cerebral inflammation
Aseptic meningitis
Hearing loss
Cold-induced urticaria +++
Ocular involvment
Conjonctivitis, uveitis
Abdominal pain
Arthromyalgia
Fever
Possible amyloidosis
C
Arthromyalgia
Ocular involvment
Peri orbitar oedema, pain, conjonctivitis
Abdominal pain
Cervical adenopathy
Fever
Migratory rash
Possible amyloidosis
D
Cutaneous involvement
Aphtosis, rash
Neurologic involvement
Headaches, mood disorders
Lymphadenopathies +++
Articular and muscular signs ++
Abdominal involvement +++
Fever
Very rare amyloidosis

Table 1. Orientation of AID from clinical, biological or histological main features.

Main clinical, biological or histological features	Presence in the four historical hereditary recurrent fevers	Presence in other AID
Main cutaneous or mucosal features		
Urticaria	*NLRP3-associated autoinflammatory disease (NLRP3-AID)* *MVK*	*NLRP12-associated autoinflammatory disease (NLRP12-AID)* *NLRC4* PLAID (*PLC-gamma2*) Schnitzler's syndrome
Neutrophilic dermatosis	TRAPS (*TNFRSF1A*)	PAAND (*MEFV*) DIRA (*IL-1 RN*) DITRA (*IL-36 RN*) *PAPA* Syndrome *(PSTPiP1)* ORAS Syndrome (*OTULIN*) Majeed Syndrome *(LPIN2)* Proteasome associated diseases= CANDLE (*PSMB8*) Aseptic abcesses syndrome
Aphtous ulcer	MKD *(MVK)* CAPS *(NLRP3)*	Familial cold urticaria with *NLRP12* mutations *(NLRP12)* Majeed Syndrome *(LPN2)* A20 haploinsufficiency *(TNFAIP3)* NOD2 associated autoinflammatory diseases (*NOD2*) PFAPA PAPA-like *(PSTPiP1)*
Erythema	FMF (*MEFV*) TRAPS (*TNFRSF1A*) Familial cold urticaria with *NLRP12* mutations *(NLRP12)*	NLRC4-MAS (*NLRC4)* TNRF11A- receptor associated periodic syndrome (*TNFR11A)* Systemic juvenile arthritis (*LACC1*) Adult and children onset Still disease
Pustulosis and/or psoriasis Pityriasis rubra pilar		PAAND (*MEFV* exon 2) DIRA (*IL-1 RN*) DITRA (*IL-36 RN*) PAPA et PAMI (*PSTPiP1*) CAMPS *(CARD14)*
Acne, sterile abcess Pyoderma gangrenosum, And/or hidradenitis suppurativa		PAAND (*MEFV* exon 2) PAID (*PSTPiP1*) Nicastrine associated diseases (*NCSTN*) Aseptic abcesses syndrome
Eczema, atopic dermatosis		NAID (*NOD2*) Blau Syndrome (*NOD2*)
Livedo	0	Interferonopathies ADA2 deficiency (*ADA2*)
Lipodystrophy		Proteasome-associated autoinflammatory syndrome (PRAAS)
Hyperpigmentation and hypertrichosis		H syndrome (*SLC29A3*)
Digestive features		
	FMF (*MEFV*) *MVK* *NLRP3* TRAPS (*TNFRSF1A*)	NLRC4-MAS (*NRLC4*) Ubiquitinopathies (*A20, Otulin*)
Neurological features		
Chronic recurrent meningitis	CAPS (CINCA, MWS) *NLRP3* MKD *(MVK)*	*NLRC4*
Strokes		Interferonopathies SFID (*TRNT1*) ADA2 deficiency (*ADA2*)
Hematological or immunological abnormalities		
Immunodeficiency	0	PLAID (*PLC-gamma2*) Ubiquitinopathies (*HOIL-1*) SFID (*TRNT1*) ADA2 deficiency (*ADA2*) PFIT (*WDR1*)
Cytopenia	0	PFIT (*WDR1*) SFID (*TRNT1*) NLRC4-MAS Majeed Syndrome (*LPIN2)*
Autoantibodies	0	Ubiquitinopathies (*A20, ORAS*) NAIAD (*NLRP1*) PLAID (*PLC-gamma2*) Interferonopathies ADA2 deficiency (*ADA2*)
Monoclonal immunoglobulin	0	Schnitzler's syndrome
Histological features		
Granuloma	0	Blau syndrome (*NOD2*) ADA2 deficiency (*ADA2*) PLAID et APLAID (*PLC-gamma2*) ORAS Syndrome (*OTULIN*)
Vasculitis	FMF (*MEFV*)	PAAND (*MEFV*) A20 haploinsufficiency (*TNFAiP3*) ORAS (*OTULIN*) PAPA (*PSTPiP1*) ADA2 deficiency (*ADA2*) SAVI Syndrome (*TMEM173*)

Table 2. Main characteristics of HA20 with autoinflammatory features from literature.

Characteristics	Details	Frequency (%)
Epidemiology	Geographic origin **:** - Japan - Europe - Turkey Sex ratio : women	 60% 30% 10% 68.6%
Age at onset	Minimum 2 months Maximum 20 years	92% in childhood
Crisis length	Between 3 to 14 days. Sometimes persistent symptoms	
Crisis recurrences	Between 1 to 12/year	
Main clinical symptoms	Buccal aphtae ulcer	88%
	Recurrent fever	78%
	Genital aphtae ulcer	68%
	Digestive features (pain/diarrhea)	57%
	Cutaneous lesions	45%
	Arthromyalgia	31%
	Ocular symptoms	10%
	Cardiovascular features	8%
	Immunodeficiency	6%
	Central nervous system features	4%
Autoantibodies	(n=17) especially: - antithyroidis (n=8) - antinuclear(n=4)	33%
Efficient treatments	- Colchicine (n=8) - Infliximab (n=6) - Anakinra (n=2) and adalimumab (n=2)	15.7% 11.7% 8%

Table 3. A diagnostic-check-list for AID.

Elements to investigate	Details to check	Most famous elements that usually orientate toward one of the most frequent AID
1-Familial history	Mediterranean origin	FMF
	Dominant transmission	CAPS, TRAPS, HA20
	Recessive transmission	MKD, DADA2
	Sporadic case	PFAPA, Still disease
2-Personal history	Age at onset - early (birth or during the firsts years) - during or after childhood	CAPS, MKD, DADA2
	Duration of crisis	FMF: 2 to 4 days MKD: 5 to 8 days TRAPS: 7 to 21 days Still disease: 15 to more than 30 days
3-Clinical symptoms	Digestive (abdominal pain)	FMF, TRAPS, MKD
	Cutaneous (urticaria, erythema, aphtae, livedo)	urticaria: CAPS
	Rheumatic: arthromyalgia	livedo: DADA2
	Neurological (meningitis)	bipolar aphtous: HA20
	Ocular (conjunctivitis, uveitis)	Still disease, TRAPS
	ENT (hearing loss)	CAPS CAPS
	Recurrent infections	CAPS DADA2
4-Peripheral inflammation	CRP level and neutrophil cell count elevation during attacks Normal rate after attack resolution	All AID (except interferonopathies)
5-Existence of diagnostic criteria	Only in some AID	FMF CAPS NOD2 AID Schnitzler disease Still disease