Diagnostic and therapeutic algorithms for monogenic autoinflammatory diseases presenting with recurrent fevers among adults

Marion Delplanque, Antoine Fayand, Guilaine Boursier, Gilles Grateau, Léa Savey, Sophie Georgin-Lavialle

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Authors: Marion Delplanque[1,*], Antoine Fayand[1,*], Guilaine Boursier[2,*], Gilles Grateau[1, *], Léa Savey[1, *], Sophie Georgin-Lavialle [1,*].

Affiliations:
1 : Sorbonne University, AP-HP, Tenon hospital, internal medicine department, 4 rue de la Chine, 75020 Paris, France
* : National reference center for autoinflammatory diseases and AA amyloidosis (CEREMAIA)
2: Department of molecular Genetics and cytogenomics, Rare and Auto Inflammatory Diseases Unit, CHU Montpellier, University of Montpellier, Montpellier, France

Corresponding author:
Pr Sophie Georgin-Lavialle, MD, PhD
Sorbonne University, AP-HP, Tenon hospital, internal medicine department, 4 rue de la Chine, 75020 Paris, France
E-Mail: sophie.georgin-lavialle@aphp.fr
Tel: 00 33 156016077
Fax: 0033156017146

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Abstract (167 words)

Autoinflammatory diseases (AID) are defined as disorders of innate immunity. They were initially defined in contrast to autoimmune diseases because of the lack of involvement of the adaptive immune system and circulating autoantibodies. The 4 monogenic AIDs first described are called the "historical" AIDs and include: Familial Mediterranean Fever (associated with *MEFV* mutations), cryopyrinopathies (associated with *NLRP3* mutations), Tumor Necrosis Factor Receptor-associated Periodic Syndrome (associated with *TNFRSF1A* mutations) and Mevalonate Kinase Deficiency (associated with *MVK* mutations). In the last 10 years, more than 50 new monogenic AIDs have been discovered due to genetic advances. The most important discovery for adult patients is VEXAS syndrome associated with somatic *UBA1* mutations leading to an autoinflammatory disease affecting mostly elderly men. Diagnosis of monogenic AIDs is based on personal and family history and detailed analysis of symptoms associated with febrile attacks, in the context of elevated peripheral inflammatory markers. This review proposes a practical approach of the diagnosis of the main monogenic AIDs among adult patients to guide the clinician.

Key words: autoinflammation, monogenic autoinflammatory disease, recurrent fever, familial Mediterranean fever, VEXAS syndrome.

Introduction

Autoinflammatory diseases (AIDs) are defined as abnormal activation of innate immunity in the absence of infection or autoimmunity (1,2). They are characterized by periodic or chronic systemic inflammation secondary to mutations in genes encoding proteins involved in the regulation of the innate immune response. AID can be divided in two main categories: monogenic diseases and polygenic AID such as Adult onset Still's disease or Schnitzler syndrome. Polygenic AID are usually defined with diagnosis criteria and will not be discussed in this work. The most frequent monogenic AID is familial Mediterranean fever (FMF) (3). The number of AIDs has been steadily increasing in recent years due to advances in genetics (4,5). However, although approximately 60 genes have been associated with AIDs, it is still difficult in clinical practice to predict whether a genetic analysis will detect a pathogenic mutation based solely on a patient's clinical phenotype and medical history. The term monogenic autoinflammatory diseases is more appropriate than hereditary recurrent fevers because some patients may display continuous / chronic inflammation rather than intermittent flares with fever. We propose here a pragmatic approach for the diagnosis of monogenic AID among adults in 2022.

1-When to suspect?

A diagnosis of monogenic AID is usually suspected in a patient with a systemic inflammatory disease of which the symptoms are not related to an infection, that does not fulfill a set of diagnosis criteria for a specific autoimmune or systemic disease or does not respond to conventional immunosuppressants (6). Fever is a main characteristic for most AID. The three main affected systems are the mucocutaneous system, with skin rash and/or mouth ulcers (Figure 1), the musculoskeletal system with arthromyalgia and/or arthritis, and the digestive system with abdominal pain and diarrhea. Other symptoms can involve the neurological system (headaches, aseptic meningitis, psychiatric disorders, mental retardation), the ENT region (sensorineural deafness), and finally the eye (conjunctivitis, keratitis, uveitis, papilledema). Hepatosplenomegaly and peripheral adenopathy are frequent but non-specific. It should be noted that in some rare diseases, patients can also suffer from recurrent or severe infections related to associated immunodeficiency (7–10)

The inflammatory nature of the disease should be assessed by the existence of a biological inflammatory syndrome, either chronic or intermittent, assessed using simple biological markers such as elevated C reactive protein and polynuclear neutrophil elevation. *In practice,*

it is considered that in an adult, to suspect a monogenic AID, three results of elevated CRP on different occasions during attacks or attack free periods (some patients can be chronically inflammatory between crisis) are required on a period of at least 6 months. Additionally, blood count is often helpful, typically showing neutrophilic leukocytosis especially during attacks. It also frequently reveals anaemia, which is typically microcytic and non-regenerative due to chronic inflammation. Conversely, macrocytosis can be encountered in the VEXAS syndrome (11).

2- In whom to suspect?

Due to their genetic nature, most of these diseases have an early onset, from birth to the first decade of life; only a limited number of patients develop symptoms in adulthood. However, as most of these disorders are very rare and present a wide spectrum of clinical manifestations, their diagnosis is often delayed until adulthood. Also, the description of monogenic AIDs associated with somatic mutations of innate immunity genes, such as VEXAS [Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic] syndrome (11), Cryopyrinopathies, Blau syndrome or NLRC4 inflammasomopathies (12), highlight the importance of being able to suspect them even in adults with sporadic symptoms if the clinical presentation is suggestive. Thus, it is now clear that monogenic AIDs can be encountered at any age of life and precise questioning regarding age at symptoms onset is key for generating early hypotheses.

The history of the patient and his family will allow the establishment of a family tree going back to the four grandparents of the index case. This first documents the origins of the patient and his/her ascendants. It is particularly useful for FMF, which is suspected if at least one grandparent on each side (paternal and maternal) has a Mediterranean origin (mostly Turkish, Armenian, Sefaradic Jewish, Algerian, Tunisian, Moroccan, Egyptian, Lebanese or Syrian origins). Family tree also determines whether the patient is consanguineous in case if his/her parents are relatives, which could point to a recessive disease if the patient is the only one affected or if the siblings are affected but the parents are not *(e.g.* mevalonate kinase deficiency or ADA2 deficiency). If there are several cases in the family with vertical transmission, a dominant disease should be considered (*e.g.* TRAPS syndrome, familial cryopyrinopathies, or A20 haploinsufficiency). In sporadic cases, the age of onset of symptoms may point to a neomutation that occurred in the fetal period (*e.g.* CINCA syndrome) or a somatic mutation acquired during life (*e.g.* VEXAS syndrome).

Finally, a personal history of AA amyloidosis in a patient can be highly suggestive of autoinflammatory disease after having carefully eliminated common pathologies responsible for chronic inflammation such as chronic inflammatory rheumatism and chronic infections (13). If the patient is of Mediterranean origin, FMF should always be considered.

Table 1 proposes an analytical grid summarizing when and in whom to suspect a monogenic AID.

3-When to perform genetic testing?

When a monogenic AID is suspected, the first step is to choose the appropriate genetic diagnosis strategy, depending on the clinical features of the patient. Several techniques are now available, each with its strengths and weaknesses. Target Sanger sequencing remains inexpensive and fast. As it focusses on a single gene or variants hotspots, it should be considered only in situations when the clinical abnormalities are specific enough to make most other monogenic AID unlikely, or when a functional test has already proven a metabolic disorder. Apart from the disadvantage of looking at only one gene at a time, Sanger sequencing has also poor performance in detecting somatic mosaicism and do not detect copy number variants. In practice, we believe that Sanger sequencing is relevant in a limited list of indications: sequencing of *MEFV* exon 10 for FMF, *UBA1* exon 3 screening for VEXAS (two diseases with very specific presentations); *ADA2/CECR1* for DADA2 and *MVK* for MKD (two diseases in which a biochemical assay of enzymatic function is available).

In case of unspecific clinical presentations, suspicion of a disease that can be phenocopied by other monogenic AIDs or negative Sanger testing, AID-related gene panel sequencing can be proposed. This massive-parallel sequencing approach allows the analysis of phenotypic panels involving tens to hundreds of genes and mosaicism detection. Diseases with genetic heterogeneity are particularly suitable for this method. Strategies for genetic diagnosis vary from country to country, depending on access to new generation sequencers and bioinformatics resources in laboratories. Compared to gene panel sequencing, the main advantage of whole exome sequencing and whole genome sequencing is the possibility of reanalyzing the data at a later stage, when new genes have been discovered. A diagnostic algorithm is proposed in Figure 2.

4-Main monogenic autoinflammatory diseases

The most frequent monogenic recurrent fevers in 2022 worldwide are: at first FMF, which is even not a rare disease in Mediterranean countries; cryopyrinopathies, VEXAS syndrome, TRAPS syndrome, mevalonate kinase deficiency, A20 haploinsufficiency, ADA2 deficiency and PSTPIP1 associated AID. The other diseases are very rare, only a few patients in each country such as actinopathies and interferonopathies, especially among adults. We thus chose to provide a description of the most frequent AID and an introduction to the rarest below.

1-Familial Mediterranean fever (FMF)

FMF mainly affects Sephardic Jews, Armenians, Turkish and Maghreb Arabs. It is also frequently represented among Middle East Arabs, Kurds, Druze, Lebanese, Italians, Greeks, and Ashkenazi Jews. Mutations affect the *MEFV* gene (MEditerranean FeVer) encoding pyrin with the main recessive pathogenic mutations on exon 10. Pyrin inflammasome activation induce pro inflammatory cytokines IL-1β and IL-18 release (14). The symptoms usually begin in childhood and consist of recurrent febrile abdominal pain attacks lasting 48-72h; thoracic pain (45%), inflammatory joint involvement affecting predominantly ankles, knees and hip concerns (> 50%); erysipelas like erythema is a specific skin involvement mostly on the ankle or the foot (30%); exertional myalgia (20%). Diagnosis relies on clinical history of recurrent inflammatory attacks and is supported by genetic testing; clinical diagnostic criteria sets are available and new classification criteria have been recently published (4; 5). Inflammatory (AA) amyloidosis is the main chronic complication and the leading cause of mortality in FMF (17).

2-Cryopyrinopathies (CAPS)

Cryopyrinopathies (Cryopyrin-associated periodic syndrome or CAPS), or *NLRP3* mutation-associated autoinflammatory diseases (*NRLP3*-AID) (1) include three dominant clinical entities Muckle-Wells syndrome, familial cold urticaria (FCAS) and chronic infantile neurological, cutaneous and joint syndrome (CINCA) which were characterized by cold-induced urticaria (18). Muckle-Wells syndrome patients display urticaria, chronic inflammation and even recurrent fever, sensorineural deafness, ocular inflammation, headache, arthritis and may be complicated by AA amyloidosis. CINCA syndrome presents at birth and is characterized by central nervous system inflammation (chronic meningitis), skin involvement (a diffuse non-itchy urticarial rash), joint involvement (deforming arthropathy preferentially affecting the knees) and facial dysmorphia characterized by the presence of frontal bumps and nasal saddle deformation. Somatic mutations have been identified in CAPS

patients especially in CINCA syndrome which is more frequently sporadic (12); thus, today, *NLRP3* mutations should be analyzed preferentially by massive-parallel sequencing. AA amyloidosis can complicate all forms of CAPS and can lead to the discovery of the disease.

3-TRAPS

Tumor necrosis factor receptor 1 associated periodic syndrome (TRAPS) is a cosmopolitan autosomal dominant relapsing fever syndrome secondary to mutation of the TNF receptor superfamily protein type 1A encoded by the *TNFRSF1A* gene (19).

TRAPS flares last longer than FMF, ranging from 5 days to 3 weeks. Abdominal pain, often simulating a surgical abdomen, is prominent. Seventy five percent of patients develop skin manifestations in the form of erythematous, edematous, warm placards of various sizes with blurred edges (pseudo cellulitis) on the upper and lower limbs but may also occur on the chest. Migratory myalgia are also specific announcing the beginning of the crises. Chest pain, scrotal pain, arthritis, orbital edema, and conjunctivitis are rarer. AA amyloidosis is the major and most feared complication of TRAPS.

4-MKD

Mevalonate kinase deficiency (MKD), formerly known as hyperIg D syndrome (HIDS), was first described in 1984 (20). The disease begins in childhood with inflammatory attacks usually lasting 7 days and recurrent every 4-8 weeks. The fever, which often exceeds 39°C, is often accompanied by abdominal pain, diarrhea, vomiting, arthralgia, and sometimes arthritis. Cutaneous and mucosal manifestations are frequent and very diverse, such as erythematous macules, urticarial lesions and mouth ulcers. Relatively specific signs are hepatosplenomegaly and the presence of painful cervical adenopathy in 94% of cases. The disease progresses in flare-ups separated by non-inflammatory intervals (21,22). MKD is very rarely complicated by AA amyloidosis. Whereas elevated serum IgD level is not specific of MKD and is not advised in AID, an elevated urinary mevalonic acid level during an inflammatory attack may point to the diagnosis, especially in children. The mutated MKD gene, *MVK*, encodes an enzyme of the cholesterol pathway, mevalonate kinase, whose partial deficiency is responsible for the recessive MKD phenotype. The mechanisms of inflammation associated with MKD involve the IL-1β pathway.

5-DADA2

DADA2 is a complex autosomal recessive AID, linked to loss-of-function variants of *ADA2* which encodes adenosine deaminase 2 (23,24). Although symptoms usually appear before the age of 10, a significant number of patients are currently not diagnosed until adulthood (8). Additionally, rare cases of adult-onset DADA2 have been reported. As a highly polymorphic disease, DADA2 can manifest with a wide variety of symptoms. They result either from an inflammatory vasculopathy mimicking polyarteritis nodosa, a hematologic phenotype mainly consisting of cytopenia of varying severity, or a humoral immunodeficiency ranging from isolated immunoglobulin class deficiency to symptomatic pan-hypogammaglobulinemia. Vasculopathic presentations account for nearly 80% of adult diagnosed DADA2 cases, with livedo racemosa and ischemic strokes being the main manifestations, as in children (8). Strokes, however, appear less frequent than in cases diagnosed in childhood. In addition to livedo, adults may have a more varied skin involvement than children, including chronic ulcers and nodules for example. DADA2 diagnosis rely on genetic testing, either targeted or not depending on the level of clinical suspicion, and the assessment of the ADA2 activity level.

6-Haploinsufficiency A20 (HA20)

The A20 protein is a negative regulator of the NF-kB pathway. Mutations in the *TNFAIP3* gene that encodes A20 lead to a dominant syndrome associating recurrent fever with bipolar aphtous, ocular inflammation, gastrointestinal symptoms, arthromyalgia and folliculitis-like skin lesions(5). To date, more than 140 patients worldwide have been diagnosed, with a slight predominance of Asian origin but it is cosmopolite. Almost all of them developed symptoms in childhood.

7-VEXAS syndrome

A new AID was discovered in 2020 and called VEXAS syndrome. It is associated with somatic mutations in the *UBA1* gene (found on the X chromosome) (3). *UBA1* gene codes for the main E1 enzyme that initiates ubiquitination. The patients, all men over 45 years of age, presented with often fatal inflammation with fevers, cytopenia (including macrocytic anemia) with vacuoles in myeloid and erythroid progenitors on the myelogram when performed. Clinically, patients often present with neutrophilic dermatosis, pulmonary infiltrate, chondritis, vasculitis and thrombosis. It is thus an acquired AID with the acronym VEXAS for: Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic syndrome.

8- PSTPIP1 associated AID

PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1) is a cytoskeletal adaptor protein of which the mutation may lead to various autosomal dominant syndromes that share common pathophysiological mechanisms involving increased production of IL-1β by the pyrin inflammasome. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome

is the first described and the best known. It is clinically characterized by recurrent episodes of fever, severe acne, pyoderma gangrenosum (PG), and arthritis in non-axial joints (knees, ankles, and elbows) (25) beginning in childhood, typically with sterile pauciarticular arthritis as the presenting sign of the disease (25,26).

The joint symptoms tend to decrease around adulthood and cutaneous symptoms become more prominent (25). PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome (PAMI) (27–31)is the second main clinical syndrome. It is characterized by early-onset chronic systemic inflammation, skin lesions, arthralgia/arthritis, hepatosplenomegaly, pancytopenia and failure to thrive (29). A hallmark of the disease is the extreme concomitant increase in serum concentrations of calprotectin and zinc (29).

9- Type I interferonopathies

Type I interferonopathies (type I IFNs) refer to Mendelian autoinflammatory disorders characterized by a high genetic signature of the type 1 IFN response in peripheral blood cells (15). In this group of diseases, inflammation is minimal or absent and patients do not have a fever in the foreground. Excessive type 1 IFN production may result from inappropriate stimulation of the type 1 IFN response pathway or its defective down-regulation. To date, the most common type 1 IFNs are Aicardi Goutières syndrome (AGS), SAVI (STING-associated vasculopathy, infantile), CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature), now called PRAAS (proteasome-associated autoinflammatory syndrome), Singleton-Merten syndrome (SMS), Spondyloenchondrodysplasia with immune dysregulation (SPENCD), X-linked reticular pigment disorder (XLRPD), USP 18 deficiency (ubiquitin-specific peptidase 18, Pseudo-TORCH syndrome) and COPA syndrome (32,33). Symptoms usually develop in early childhood. Signs suggestive of type I IFN are the presence of encephalopathy, intracranial calcifications, skin lesions (lipodystrophy, cold-induced acral vasculitis, and lupus-like lesions), and the presence of autoimmunity, namely ANA.

10- Actinopathies

Several mutations have been discovered in genes involved in the actin cytoskeleton such as *CDC42* and *ARPC1B*; these diseases are currently called actinopathies (34). Immune cell remodeling is involved in the pathogenesis of hematological/autoinflammatory diseases, which underlines the importance of the actin cytoskeleton in the modulation of inflammatory responses. Patients usually display cutaneomucous features and cytopenia. Due to their rarity, especially among adults, we have chosen not to detail them in this chapter.

Table 2 gives a quick overview of main features of the more frequent monogenic AID.

5-Therapeutic algorithm

General principle: In monogenic AID, treatment should be conducted using a "treat-to-target" approach.

-The clinical target is sustained remission with little to no flares for diseases with a remittent-recurrent course or significant improvement of symptoms for diseases with a chronic course, ultimately leading to restauration of quality of life.

-The biological target is the strict suppression of systemic inflammation between flares, assessed using biomarkers like CRP, to prevent the occurrence of inflammatory amyloidosis.

What to prescribe: Not all monogenic AIDs have a well-codified treatment (except for FMF and CAPS) and the purpose of this review is not to give an extensive list of what have been attempted in each one, therefore we will focus on those for which there is a relative consensus:

- FMF: Colchicine is the mainstay of treatment. IL-1β inhibitors are highly efficient but their use should be reserved for rare cases of colchicine resistance, accounting for 5 to 10% of FMF patients (35), intolerance or contra-indication, such as severe renal or hepatic failure (36,37).
- Cryopyrinopathies: Treatment is based on IL-1β inhibitors, which is very efficient to control symptoms except for central nervous system damage and deafness if previously existing.

- TRAPS: Mostly symptomatic treatment. However, the persistence of elevated serum markers of inflammation between attacks identifies patients at highest risk of developing AA amyloidosis and thus requiring potent IL-1β inhibitors.
- MKD: Common anti-inflammatory drugs such as corticosteroids, colchicine and non-steroidal anti-inflammatory drugs (NSAIDs) are generally not very effective in MKD. Recent studies have demonstrated the efficacy of IL-1β inhibitors, in particular canakinumab (37).
- DADA2: Only the management of vasculopathic presentations of DADA2 is currently well codified: it consists in the long-term administration of TNFα inhibitors, the only treatments that have proven effective for stroke prevention (38).

For VEXAS syndrome, the treatment is not yet codified, but it seems that JAK inhibitors, in particular ruxolitinib (39), seems to be more effective than anti-cytokine biotherapy; azacytidine (40) has also shown some effectiveness ; nevertheless, more data are required.

In cases of severe early-onset disease with cytopenia or macrophage activation syndrome, bone marrow allograft may be proposed

In case of associated hypogammaglobulinemia, polyvalent immunoglobulin may be proposed.

Monitoring & prognosis

The usual monitoring is clinical follow-up once or twice a year depending on the severity of the condition and the autonomy of the patient. Biologically, renal function should be measured at least once a year and proteinuria should be checked. Twice a year, blood inflammation should be checked by means of a hemogram and CRP at least. The liver balance must also be checked annually. In follow up, monitoring of Serum amyloid A (SAA) SAA can be discussed. Increased levels of SAA can be detected during inflammatory episodes as CRP does. Discordances between CRP and SAA have been described in FMF patients but SAA is usually not available in routine. A study in FMF patients proposed high sensitive CRP as a reliable substitute in countries without access to SAA dosage when an appropriated threshold is used. Medical teams who have SAA as a routine test can monitor SAA in addition to SAA if a discordance have been identified (41)Other examinations depend on the pathology and whether there are affected/destroyed joints, a weakened heart, some skin manifestations such as ulcers. A cardiological follow-up is proposed if there is pericarditis, tamponade. An ENT follow-up with audiogram is proposed in case of deafness. A follow-up

with the dentist is done annually. The prognosis is mainly related to kidney damage (+/- amyloidosis) and joint destruction.

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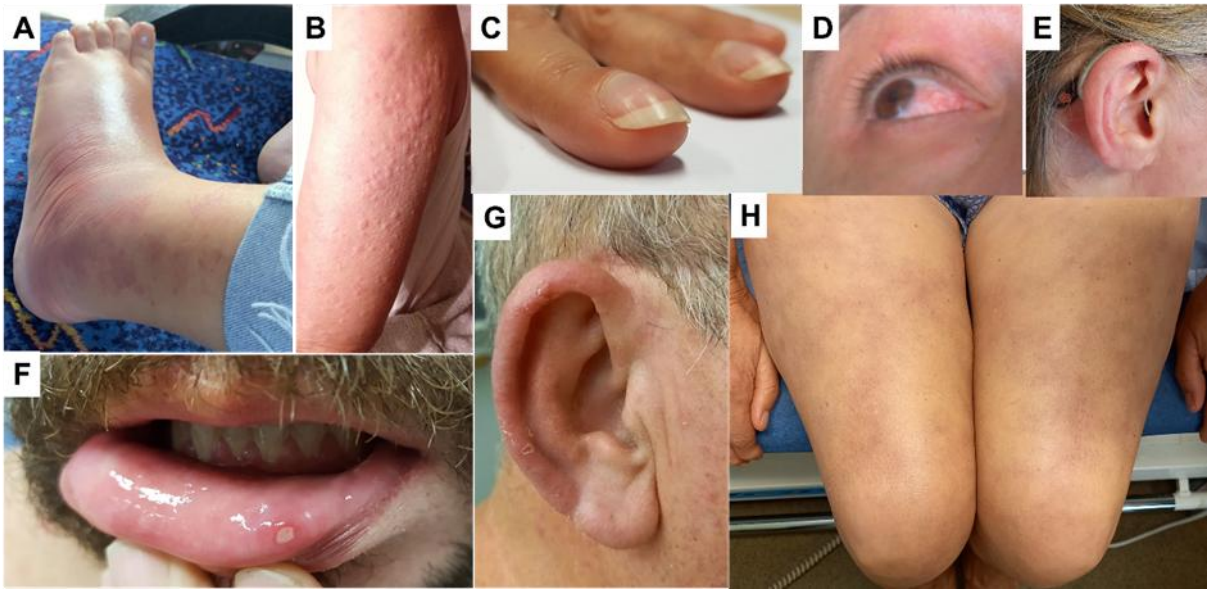
Figures and Table

Figure 1. Main clinical symptoms evocating AID.



A-Pseudoerysipela of one ankle in familial Mediterranean fever.

B-Cold induced urticaria eruption in cryopyrin-associated periodic syndrome.

C-Clubbing fingers in cryopyrin-associated periodic syndrome.

D-Conjonctivitis in cryopyrin-associated periodic syndrome.

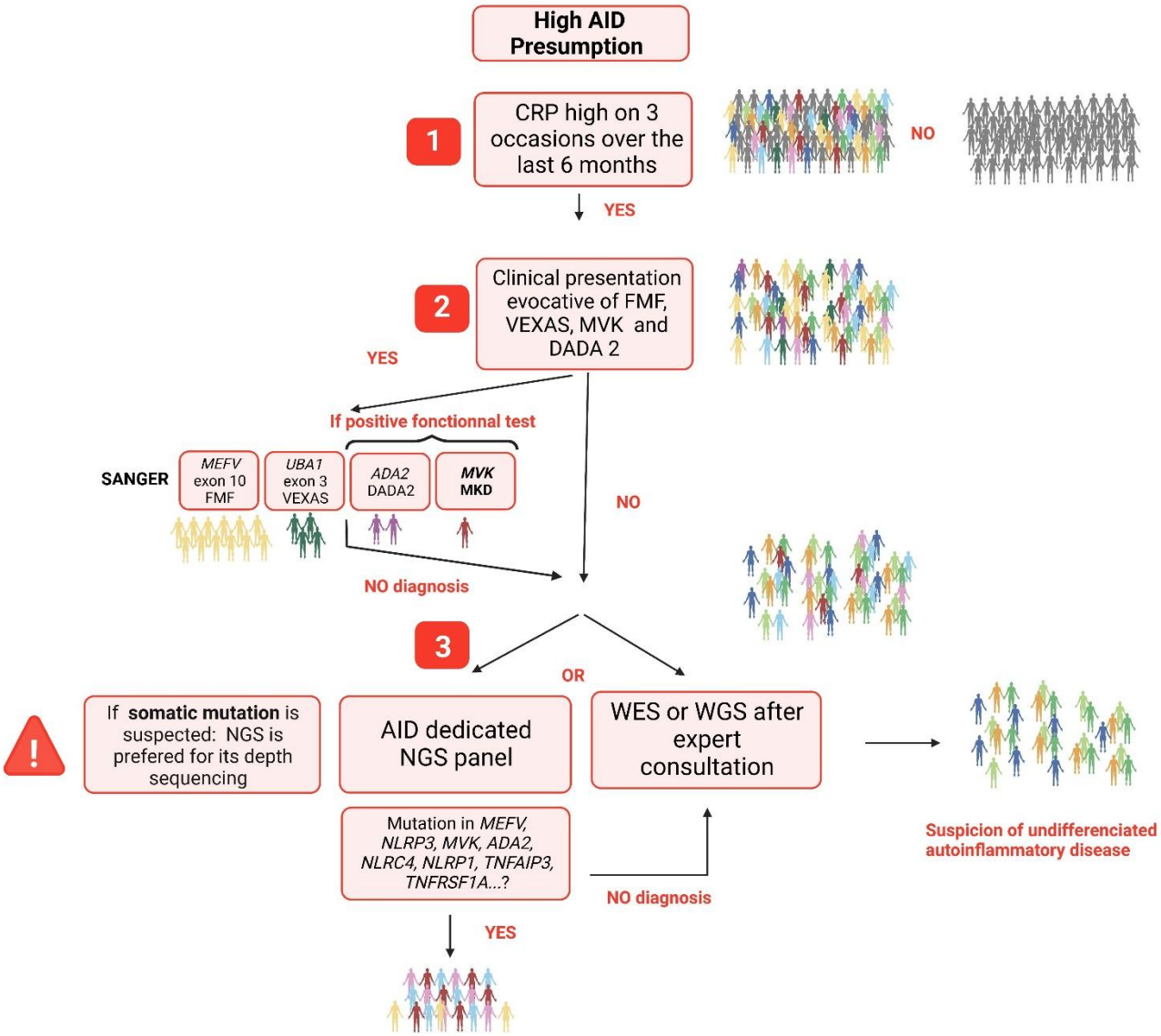
E-Hearing aid associated with sensorineural hearing loss

F-Buccal aphtous in case of mevalonate kinase deficiency or A20 haploinsufficiency

G-Ear chondritis in a patient with the VEXAS syndrome

H-Livedo associated with ADA2 deficiency.

Figure 2. Algorithm of Genetic exploration in case of a suspicion of AID



Tables

Table 1. Analytical grid when suspecting an 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 -Dominant transmission -Recessive transmission -Sporadic case -Consanguineous parents	-FMF -CAPS, TRAPS, HA20, PAID -MKD, DADA2 -VEXAS, or somatic AID -FMF, MKD, DADA2
2-Personal history	-Age at onset -early (before 2 years old) -during or after childhood -After 45 years old -Duration of crisis	 -CAPS, MKD, DADA2 -VEXAS; or somatic CAPS -FMF: 2 to 3 days -MKD: 5 to 8 days -TRAPS: 7 to 21 days -Chronic: VEXAS, CAPS
3-Clinical symptoms	-Digestive -Cutaneous (urticaria, erythema, aphtosis, livedo, acne, pyoderma gangrenosum (PD), neutrophilic dermatosis (ND)) -Rheumatic: arthritis/myalgia -Neurological (aseptic meningitis) -Ocular (conjunctivitis, uveitis) -ENT (hearing loss) -Recurrent infections -Chondritis	-FMF, TRAPS, MKD -urticaria: CAPS -livedo: DADA2 -bipolar aphtous: HA20 -acne, PG: PAID -ND: VEXAS, MKD - TRAPS -CAPS -CAPS -CAPS -DADA2 -VEXAS
4-Peripheral inflammation	CRP level and neutrophil cell count elevation during attacks Normal rate after attack resolution	All AID (except interferonopathies), especially inflammasomopathy
5-Diagnostic criteria	Only in some AID	-FMF -CAPS

FMF: Familial Mediterranean Fever; CAPS: Cryopyrin Associated Periodic Syndrome; TRAPS: Tumor necrosis factor-Receptor-Associated Periodic Syndrome; MKD: Mevalonate Kinase Deficiency; DADA2: Deficiency of Adenosine Deaminase 2; HA20:

Haploinsufficiency of A20; VEXAS: Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic; PAID: PTSPIP1 Associated Inflammatory Diseases;

Table 2. Main features of the more frequent monogenic AID

	Gene	Inheritance mode	Somatic mutation	Age at onset (years)	Main clinical features	Most con
FMF	*MEFV*	AR Rarely AD	Not yet published	Usually before 20	Febrile attacks of 2-3 days Abdominal (thoracic) pain Erysipelas like erythema Arthralgia (knees, ankles) Myalgia (lower limbs)	Colchicin IL-1β inh contra-in
CAPS	*NLRP3*	AD	Possible	Childhood	Cold induce urticaria Sensorineural deafness Ocular inflammation Headache Non erosive arthritis/ arthralgia Buccal (bipolar) apthous	IL-1β inh
TRAPS	*TNFRSF1A*	AD	Possible	Until early adulthood	Protracted febrile attacks of up to 3 weeks Abdominal pain Erythema, pseudocellulitis of limbs Arthro-myalgia Rare periorbital oedema	Symptom IL-1β inh attacks
MKD	*MVK*	AR	Not described	Early childhood	Febrile attacks of 7 days, sometimes triggered by vaccination Abdominal pain and diarrhea Cervical lymphadenopathies and hepatosplenomegaly Various cutaneous eruptions	IL-1β inh
DADA2	*DADA2*	AR	Not described	Childhood	Livedo racemosa Ischemic strokes Abdominal pain Arthromyalgia Mild to severe hypogammaglobulinemia Mild to severe cytopenia	TNFα inh IVIg for l Rarely H
HA20	*TNFAIP3*	AD	Not described	Childhood	Bipolar aphthosis Ocular inflammation Abdominal pain and diarrhea Arthromyalgia and folliculitis-like skin lesions Possible hepatic cytolysis Autoimmune thyroiditis	Not yet c Possible t
VEXAS	*UBA1*	X-linked	Constant	Adulthood, after 45 Mostly men	Fever Neutrophilic dermatosis Chondritis Thrombosis Lung infiltrates Macrocytic anemia	Not yet c Possible t
PAID	*PTSPIP1*	AD	Not yet described	Childhood	Severe acne Pyoderma gangrenosum Arthritis Pancytopenia and HSMG (in PAMI)	Not yet c Possible t

FMF: Familial Mediterranean Fever; CAPS: Cryopyrin Associated Periodic Syndrome; TRAPS: Tumor necrosis factor-Receptor-Associated Periodic Syndrome; MKD: Mevalonate Kinase Deficiency; DADA2: Deficiency of Adenosine Deaminase 2; HA20: Haploinsufficiency of A20; VEXAS: Vacuoles, Enzyme E1, X-linked, Autoinflammatory, Somatic; PAID: PTSPIP1 Associated Inflammatory Diseases; AD: autosomal dominant; AR: autosomal recessive; HSMG: hepatosplenomegaly; PAMI: PSTPIP1-Associated Myeloid-related proteinemia Inflammatory syndrome; IL-1β: Interleukin-1β; TNFα: Tumor Necrosis Factor α; IVIg: Intravenous Immunoglobulins

Abbreviations:

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

FCAS: Familial cold autoinflammatory syndrome

FMF: Familial Mediterranean fever

HA20: A20 haploinsufficiency

MKD: mevalonate kinase deficiency

MWS: Muckle Wells syndrome

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

WES: whole exome sequencing

WGS: whole genome sequencing

Conflict of interest:

None for the writing of this article

In the last 5 years, S G-L has received fees for expertise / advice and travel assistance during scientific congresses from SOBI and NOVARTIS laboratories;

L S have received travel assistance (s) to scientific congresses from SOBI.