Rheumatology, 2022, **00**, 1–8
https://doi.org/10.1093/rheumatology/keac712
Advance access publication 28 December 2022
Review

British Society for Rheumatology RHEUMATOLOGY OXFORD

Review

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

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Abstract

Autoinflammatory diseases (AIDs) 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 four monogenic AIDs first described are called the 'historical' AIDs and include FMF (associated with *MEFV* mutations), cryopyrinopathies (associated with *NLRP3* mutations), TNF receptor–associated periodic syndrome (associated with *TNFRSF1A* mutations) and mevalonate kinase deficiency (MKD; associated with *MVK* mutations). In the last 10 years, >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 AID 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 for the diagnosis of the main monogenic AIDs among adult patients.

Keywords: 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]. 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. AIDs can be divided into two main categories: monogenic diseases and polygenic AIDs such as adult-onset Still's disease or Schnitzler syndrome. Polygenic AIDs are usually defined with diagnosis criteria and will not be discussed in this work. The most frequent monogenic AID is FMF [2]. The number of AIDs has been steadily increasing in recent years due to advances in genetics [3, 4]. However, although ≈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 AIDs 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 AIDs among adults in 2022.

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 fulfil a set of diagnosis criteria for a specific autoimmune or systemic disease or that does not respond to conventional immunosuppressants [5]. Fever is a main characteristic for most AIDs. The three main affected systems are the mucocutaneous system, with skin rash and/or mouth ulcers (Fig. 1); the musculoskeletal system, with arthromyalgia and/or arthritis; and the digestive system, with abdominal pain and diarrhoea. 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 [6–9].

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

Received: 9 June 2022. **Accepted:** 9 December 2022

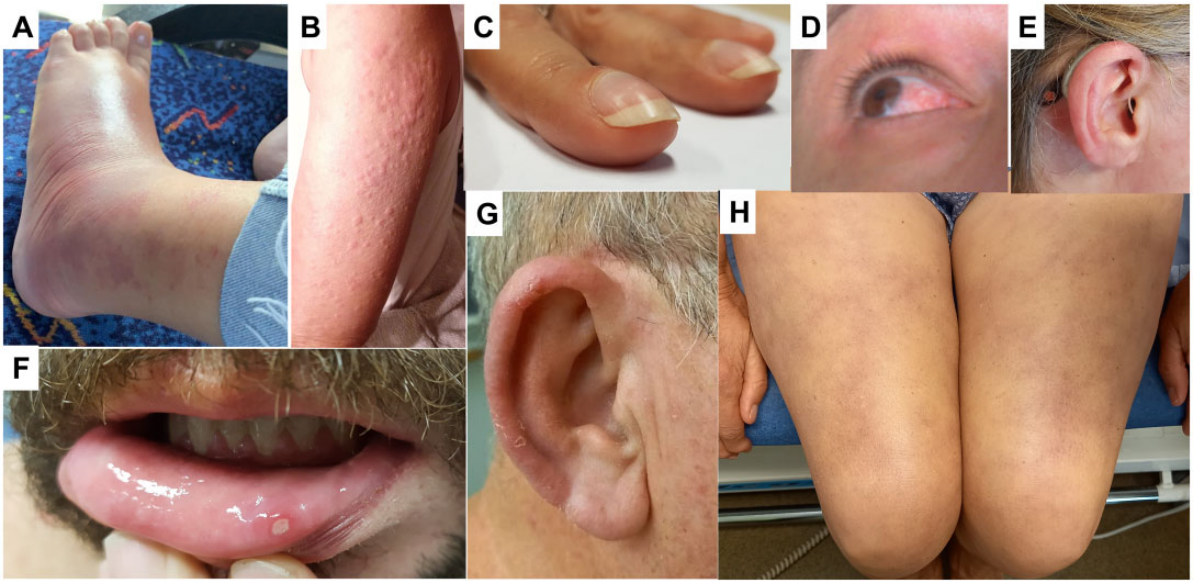

Figure 1. Main clinical symptoms of AIDs. (**A**) Pseudoerysipela of one ankle in FMF. (**B**) Cold-induced urticarial eruption in CAPS. (**C**) Clubbing fingers in CAPS. (**D**) Conjunctivitis in CAPS. (**E**) Hearing aid associated with sensorineural hearing loss. (**F**) Buccal aphthous in MKD or A20 haploinsufficiency. (**G**) Ear chondritis in a patient with VEXAS syndrome. (**H**) Livedo associated with ADA2 deficiency

markers such as elevated CRP and polynuclear neutrophil elevation. In practice, to suspect a monogenic AID in an adult, three results of elevated CRP on different occasions during attacks or attack-free periods (some patients can be chronically inflammatory between crisis) are required over a period of at least 6 months. Additionally, blood count is often helpful, typically showing neutrophilic leucocytosis, 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 (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome [10].

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 syndrome [10], cryopyrinopathies, Blau syndrome or NLRC4 inflammasomopathies [11], 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/her 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, Sephardic Jewish, Algerian, Tunisian, Moroccan, Egyptian, Lebanese or Syrian origins). The family tree also determines whether the patient is consanguineous 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. MKD or ADA2 deficiency). If there are several cases in the family with vertical transmission, a dominant disease should be considered [e.g. TNF receptor–associated periodic syndrome (TRAPS), familial cryopyrinopathies or A20 haploinsufficiency). In sporadic cases, the age of onset of symptoms may point to a neomutation that occurred in the foetal period [e.g. chronic infantile neurological cutaneous articular (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 AID after having carefully eliminated common pathologies responsible for chronic inflammation such as chronic inflammatory rheumatism and chronic infections [12]. 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.

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 variant hotspots, it should be considered only in situations when the clinical abnormalities are specific enough to make most other monogenic AIDs 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 also has poor performance in detecting somatic mosaicism and does 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) and *ADA2/CECR1*

Table 1. Analytical grid when suspecting an AID

Elements to investigate	Details to check	Most famous elements that usually point towards AIDs
Familial history	Mediterranean origin	FMF
	Dominant transmission	CAPS, TRAPS, HA20, PAID
	Recessive transmission	MKD, DADA2
	Sporadic case	VEXAS syndrome, somatic AID
	Consanguineous parents	FMF, MKD, DADA2
Personal history	Age at onset	CAPS, MKD, DADA2
	• early (<2 years old) or during or after childhood	VEXAS syndrome, somatic CAPS
	• >45 years old	FMF: 2–3 days
		MKD: 5–8 days
		TRAPS: 7–21 days
	Duration of crisis	Chronic: VEXAS syndrome, CAPS
Clinical symptoms	Digestive	FMF, TRAPS, MKD
	Cutaneous (urticaria, erythema, aphthosis, livedo, acne, PG, ND)	Urticaria: CAPS
		Livedo: DADA2
		Bipolar aphthous: HA20
		Acne, PG: PAID
		ND: VEXAS syndrome, MKD
	Rheumatic: arthritis/myalgia	TRAPS
	Neurological (aseptic meningitis)	CAPS
	Ocular (conjunctivitis, uveitis)	CAPS
	ENT (hearing loss)	CAPS
	Recurrent infections	DADA2
	Chondritis	VEXAS syndrome
Peripheral inflammation	CRP level and neutrophil cell count elevation during attacks	All AIDs (except interferonopathies), especially inflammasomopathy
	Normal rate after attack resolution	
Diagnostic criteria	Only in some AIDs	FMF
		CAPS

ND: neutrophilic dermatosis; PAID: PTSPIP1-associated inflammatory diseases; PG: pyoderma gangrenosum.

for deficiency of adenosine deaminase 2 (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 with gene panel sequencing, the main advantage of whole exome sequencing and whole genome sequencing is the possibility of reanalysing the data at a later stage, when new genes have been discovered. A diagnostic algorithm is proposed in Fig. 2.

Main monogenic AIDs

The most frequent monogenic recurrent fevers in 2022 worldwide are FMF, which is not a rare disease in Mediterranean countries, cryopyrinopathies, VEXAS syndrome, TRAPS, MKD, A20 haploinsufficiency, ADA2 deficiency and proline–serine–threonine phosphatase-interacting protein 1 (PSTPIP1)-associated AID. The other diseases are very rare (such as actinopathies and interferonopathies), with only a few patients in each country, especially among adults. We thus chose to provide a description of the most frequent AID and an introduction to the rarest below.

FMF

FMF mainly affects Sephardic Jews, Armenians, Turks 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 induces pro-inflammatory cytokine IL-1β and IL-18 release [13]. The symptoms usually begin in childhood and consist of recurrent febrile abdominal pain attacks lasting 48–72 h; thoracic pain (45%); inflammatory joint involvement affecting predominantly ankles, knees and hips (> 50%); erysipelas-like erythema, a specific skin involvement mostly on the ankles or feet (30%); and exertional myalgia (20%). Diagnosis relies on a 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 [3, 4]. Inflammatory (AA) amyloidosis is the main chronic complication and the leading cause of mortality in FMF [14].

Cryopyrinopathies

Cryopyrinopathies [cryopyrin-associated periodic syndrome (CAPS)] or *NLRP3* mutation-associated autoinflammatory diseases (*NRLP3*-AIDs) [1] include three dominant clinical entities: Muckle–Wells syndrome, familial cold autoinflammatory syndrome (FCAS) and CINCA syndrome, which are characterized by cold-induced urticaria [15]. Muckle–Wells syndrome patients display urticaria, chronic inflammation and even recurrent fever, sensorineural deafness, ocular

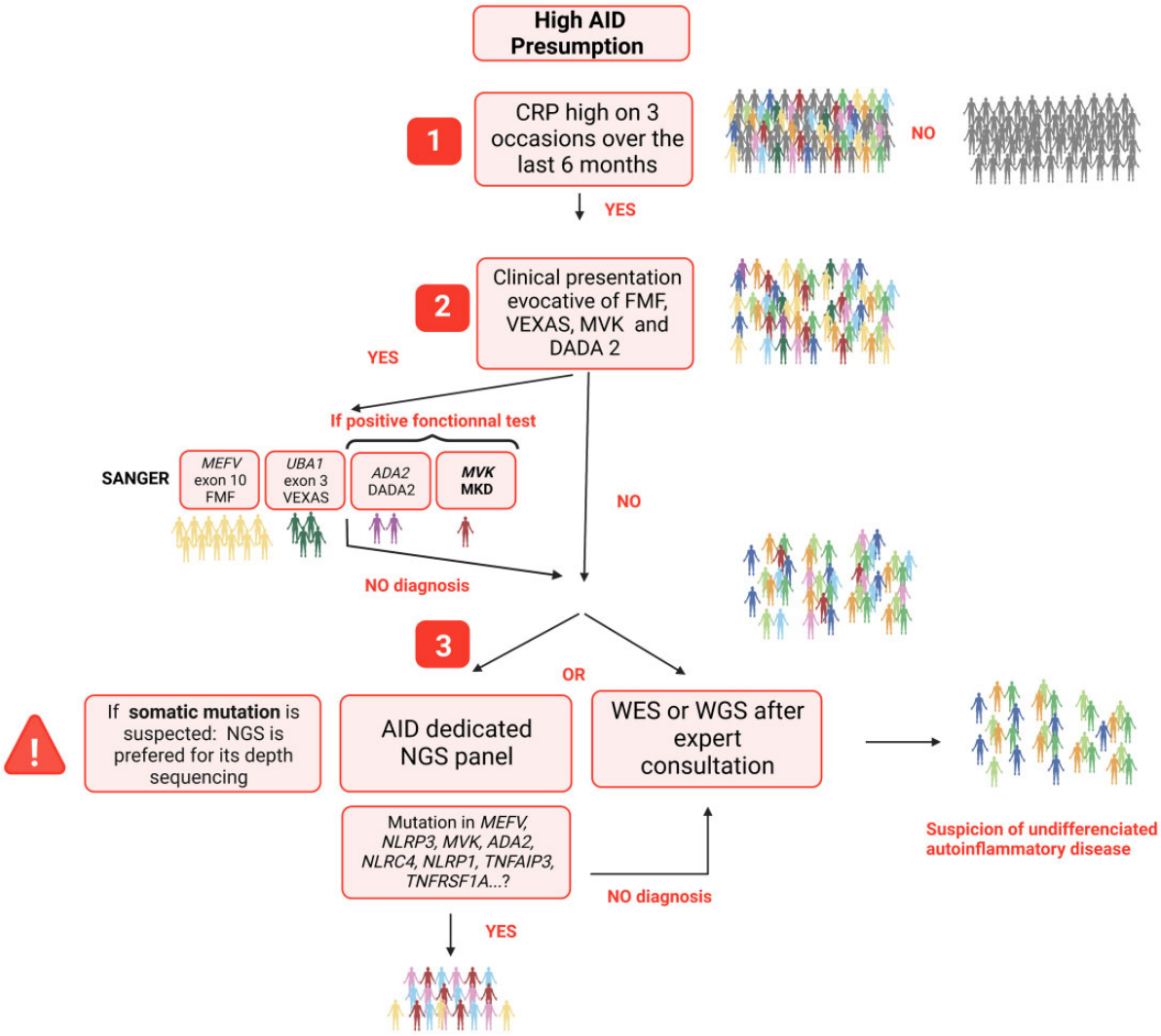

Figure 2. Algorithm of genetic exploration when suspecting an AID

inflammation, headache and 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 [11]. Thus, today, *NLRP3* mutations should be analysed preferentially by massive-parallel sequencing. AA amyloidosis can complicate all forms of CAPS and can lead to discovery of the disease.

TRAPS

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 [16]. 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, oedematous, warm placards of various sizes with blurred edges (pseudo cellulitis) on the upper and lower limbs, but they may also occur on the chest. Migratory myalgia is also specific, announcing the beginning of the crisis. Chest pain, scrotal pain, arthritis, orbital oedema and conjunctivitis are rarer. AA amyloidosis is the major and most feared complication of TRAPS.

MKD

MKD, formerly known as hyper-Ig D syndrome (HIDS), was first described in 1984 [17]. The disease begins in childhood with inflammatory attacks usually lasting 7 days and recurring every 4–8 weeks. The fever, which often exceeds 39°C, is often accompanied by abdominal pain, diarrhoea, 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 [18, 19]. MKD is very rarely complicated by AA amyloidosis. Whereas an elevated serum IgD level is not specific for MKD and is not seen in AIDs, 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.

DADA2

DADA2 is a complex autosomal recessive AID linked to loss-of-function variants of *ADA2*, which encodes adenosine deaminase 2 [20, 21]. Although symptoms usually appear before the age of 10, a significant number of patients are currently not diagnosed until adulthood [7]. 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 from an inflammatory vasculopathy mimicking polyarteritis nodosa, a hematologic phenotype mainly consisting of cytopenia of varying severity, or a humoral immunodeficiency ranging from isolated Ig class deficiency to symptomatic pan-hypogammaglobulinemia. Vasculopathic presentations account for nearly 80% of adult DADA2 cases, with livedo racemosa and ischaemic strokes being the main manifestations, as in children [7]. Strokes, however, appear less frequent than in cases diagnosed in childhood. In addition to livedo, adults may have more varied skin involvement than children, including chronic ulcers and nodules. DADA2 diagnoses rely on genetic testing, either targeted or not depending on the level of clinical suspicion, and assessment of the ADA2 activity level.

Haploinsufficiency A20

The A20 protein is a negative regulator of the nuclear factor κB pathway. Mutations in the *TNFAIP3* gene that encodes A20 lead to a dominant syndrome associating recurrent fever with bipolar aphthous, ocular inflammation, gastrointestinal symptoms, arthromyalgia and folliculitis-like skin lesions [4]. To date, >140 patients worldwide have been diagnosed, with a slight predominance of Asian origin, but overall it is cosmopolitan. Almost all of them developed symptoms in childhood.

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) [2]. The *UBA1* gene codes for the main E1 enzyme that initiates ubiquitination. The patients, all men >45 years of age, presented with often fatal inflammation with fevers and cytopenia (including macrocytic anaemia) 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.

PSTPIP1-associated AID

PSTPIP1 is a cytoskeletal adaptor protein, the mutation of which 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) [22] beginning in childhood, typically with sterile pauci-articular arthritis as the presenting sign of the disease [22, 23]. The joint symptoms tend to decrease around adulthood and cutaneous symptoms become more prominent [22].

PSTPIP1-associated myeloid-related proteinemia inflammatory syndrome (PAMI) [24–28] 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 [26]. A hallmark of the disease is the extreme concomitant increase in serum concentrations of calprotectin and zinc [26].

Type I interferonopathies

Type I interferonopathies refer to Mendelian autoinflammatory disorders characterized by a high genetic signature of the response in peripheral blood cells [29]. In this group of diseases, inflammation is minimal or absent and patients do not have a fever in the foreground. Excessive type 1 IFN (IFN-1) production may result from inappropriate stimulation of the IFN-1 response pathway or its defective down-regulation. To date, the most common IFN-1s are Aicardi–Goutières syndrome; stimulator of interferon genes (STING)-associated vasculopathy, infantile (SAVI); chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), now called proteasome-associated autoinflammatory syndrome (PRAAS); Singleton–Merten syndrome (SMS); spondyloenchondrodysplasia with immune dysregulation (SPENCD); X-linked reticular pigment disorder (XLRPD); ubiquitin-specific peptidase 18 (USP18) deficiency (also called pseudo-TORCH syndrome) and COPA syndrome [30, 31]. Symptoms usually develop in early childhood. Signs suggestive of IFN-1 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.

Actinopathies

Several mutations have been discovered in genes involved in the actin cytoskeleton, such as *CDC42* and *ARPC1B*; these diseases are currently called actinopathies [32]. Immune cell remodelling is involved in the pathogenesis of haematological/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 here.

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

Therapeutic algorithm

General principle

In monogenic AIDs, 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 restoration 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.

Table 2. Main features of the more frequent monogenic AIDs

AID	Gene	Inheritance mode	Somatic mutation	Age at onset (years)	Main clinical features	Most consensual treatment
FMF	*MEFV*	AR, rarely AD	Not yet published	Usually <20	Febrile attacks of 2–3 days Abdominal (thoracic) pain Erysipelas-like erythema Arthralgia (knees, ankles) Myalgia (lower limbs)	Colchicine in most cases, IL-1β inhibitors in case of colchicine resistance, intolerance, or contraindication
CAPS	*NLRP3*	AD	Possible	Childhood	Cold-induced urticaria Sensorineural deafness Ocular inflammation Headache Non-erosive arthritis/arthralgia Buccal (bipolar) aphthous	IL-1β inhibitors
TRAPS	*TNFRSF1A*	AD	Possible	Until early adulthood	Protracted febrile attacks of up to 3 weeks Abdominal pain Erythema, pseudocellulitis of the limbs Arthromyalgia Rare periorbital oedema	Symptomatic treatment of attacks, IL-1β inhibitors in case of persisting inflammation between attacks
MKD	*MVK*	AR	Not described	Early childhood	Febrile attacks of 7 days, sometimes triggered by vaccination Abdominal pain and diarrhoea Cervical lymphadenopathies and hepatosplenomegaly Various cutaneous eruptions	IL-1β inhibitors
DADA2	*DADA2*	AR	Not described	Childhood	Livedo racemosa Ischaemic strokes Abdominal pain Arthromyalgia Mild–severe hypogammaglobulinemia Mild–severe cytopenia	TNF-α inhibitors for vasculopathic phenotype, IVIG for humoral immune deficiency phenotype, rarely HSCT for severe haematological phenotypes
HA20	*TNFAIP3*	AD	Not described	Childhood	Bipolar aphthosis Ocular inflammation Abdominal pain and diarrhoea Arthromyalgia and folliculitis-like skin lesions Possible hepatic cytolysis Autoimmune thyroiditis	Not yet codified; possible to prescribe colchicine, TNF inhibitors, JAK inhibitors
VEXAS	*UBA1*	X-linked	Constant	Adulthood, >45 Mostly men	Fever Neutrophilic dermatosis Chondritis Thrombosis Lung infiltrates Macrocytic anaemia	Not yet codified; possible to prescribe steroids, ruxolitinib or azacytidine
PAID	*PTSPIP1*	AD	Not yet described	Childhood	Severe acne Pyoderma gangrenosum Arthritis Pancytopenia and HSMG (in PAMI)	Not yet codified; possible to prescribe IL-1β inhibitors if necessary

AD: autosomal dominant; AR: autosomal recessive; HSMG: hepatosplenomegaly; PAID: PTSPIP1-associated inflammatory diseases.

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 has 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 5–10% of FMF patients [33], intolerance or contraindication, such as severe renal or hepatic failure [34, 35].
- 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 NSAIDs are generally not very effective in MKD. Recent studies have demonstrated the

efficacy of IL-1β inhibitors, in particular canakinumab [35].
- DADA2: Only the management of vasculopathic presentations of DADA2 is currently well codified, consisting of long-term administration of TNF-α inhibitors, the only treatments that have proven effective for stroke prevention [36].

For VEXAS syndrome, the treatment is not yet codified, but it seems that Janus kinase (JAK) inhibitors, in particular ruxolitinib [37], seem to be more effective than anti-cytokine biotherapy. Azacytidine [38] 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 cases of associated hypogammaglobulinemia, polyvalent immunoglobulin may be proposed.

Monitoring and 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) should be discussed. Increased levels of SAA can be detected during inflammatory episodes. Discordances between CRP and SAA have been described in FMF patients, but SAA is usually not routinely available. A study in FMF patients proposed high-sensitivity CRP as a reliable substitute in countries without access to SAA dosage when an appropriate threshold is used. Medical teams who have SAA as a routine test can monitor SAA if a discordance has been identified [39]. Other examinations depend on the pathology and whether there are affected/destroyed joints, a weakened heart or skin manifestations such as ulcers. A cardiological follow-up is proposed if there is pericarditis or tamponade. An ENT follow-up with audiogram is proposed in case of deafness. A follow-up with the dentist should be done annually. The prognosis is mainly related to kidney damage (with or without amyloidosis) and joint destruction.

Authors' contributions

S.G.L. wrote the first draft. M.D., A.F. and G.B. edited and completed the draft. L.S. and G.G. edited the final version.

Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: In the last 5 years, S.G.-L. has received fees for expertise/advice and travel assistance during scientific congresses from Sobi and Novartis. L.S. has received travel assistance to scientific congresses from Sobi.

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