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Review

Cardinal signs of (auto)inflammation: from Celsus and Virchow to systemic autoinflammatory disorders and back to the basics

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ABSTRACT

About 2000 years ago, Celsus described four of the hallmarks of local inflammation: redness, swelling, heat and pain. In the 19th century, Virchow added loss of function to the list. However, it was only in 1999 after the description of the first periodic fever syndromes (PFS) that autoinflammatory disorders (AIDs) emerged as a distinct group and more than 40 syndromes have been included under the umbrella of autoinflammation so far. Nevertheless, advancements in the fields of human genetics and basic immunology are often insufficient to establish a definitive diagnosis in up to half of the patients with phenotypes typical of systemic AIDs, resulting in undifferentiated systemic AIDs. Moreover, PFS constitute only a small fraction of the whole universe of autoinflammation and fever is often absent in many systemic AIDs. Therefore, phenotype-guided treatment may be important in many cases of AIDs. In this review, we describe possible cardinal signs of systemic autoinflammation, correlating them with the five cardinal signs of local inflammation originally described by Celsus and Virchow. Five cardinal signs are proposed and specific systemic AIDs are described accordingly: fever, neutrophilic dermatosis, arthritis, panniculitis and sterile osteomyelitis.

KEYWORDS: autoinflammatory diseases, fever, neutrophilic dermatosis, arthritis, panniculitis, sterile osteomyelitis.

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1. Introduction

Cornelius Celsus was a Roman writer that described four of the hallmarks of local inflammation about 2000 years ago, pointing out redness, swelling, heat and pain as features of local inflammatory reactions: *"rubor et tumor cum calore et dolore"* (see Figure 1) [1]. Galen regarded inflammation as a local fever and heat was known to be the most significant among the four cardinal symptoms. [2]. Loss of function (*functio laesa*) was only added to the list by Rudolph Virchow in the 19th century [1, 3]. Virchow and Cohnheim correlated redness and heat with increased blood flow and swelling with exudation, while the role of phagocytic cells was highlighted by Élie Metchnikoff [1, 4]. He was awarded the Nobel Prize in Physiology and Medicine in 1908, sharing it with Paul Ehrlich, who proposed the concept of *horror autotoxicus* [5, 6]. Systemic inflammation appears to be more complex since the liver and neuroendocrine centers play a role in the synthesis of acute-phase reactants (APR), such as C-reactive protein (CRP) and serum amyloid A (SAA) [1]. After the description of the first periodic fever syndromes (PFS) including familial Mediterranean fever (FMF) and tumor necrosis factor-receptor associated periodic syndrome (TRAPS) and the proposal of the designation "autoinflammatory disease" by McDermott in 1999, the concept of autoinflammation

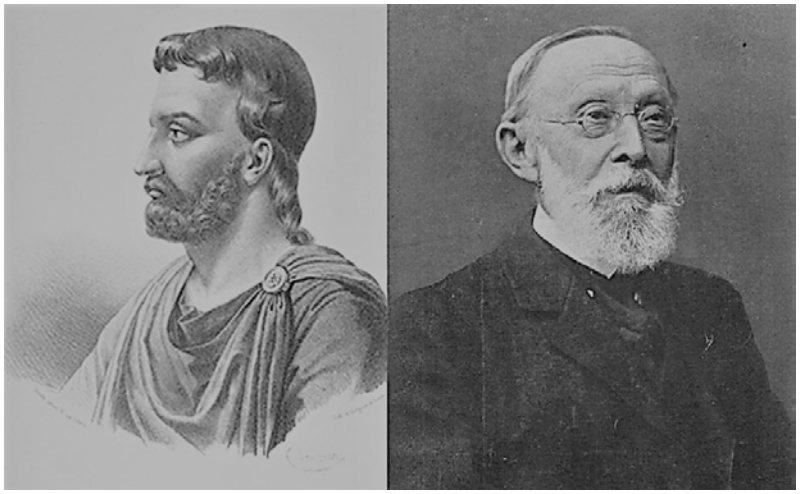

Figure 1. Original painting of Aulus Cornelius Celsus by Pierre-Roch Vigneron (left) and portrait of Rudolph Ludwig Karl Virchow by Carl Gunther (right). Adapted from Science Photo Library's website and Scientific Identity collection from Smithsonian Institution Libraries Digital Collection (free from copyright as stated in terms of use).

was corroborated in the fields of genetics and immunology [5]. Since then, more than 40 syndromes have been included under the umbrella of autoinflammation [7, 8].

A consensus group has recently defined autoinflammatory disorders (AIDs) as a group of clinical syndromes "caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated APR) and the lack of a primary pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)" [9-12]. This definition is less restrictive than original definitions and may result in classifying most of immune-mediated disorders as AIDs [13].

AIDs are usually monogenic disorders, but there are exceptions such as Schnitzler syndrome (SS) or periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome [10, 14, 15]. Inflammasomopathies (interleukin [IL]-1β-activation syndromes) are characterized by mutations in inflammasomes [16-18]. Type I interferonopathies are caused by activation of type I interferon (IFNαβ) signaling, while relopathies are a consequence of NF-κB pathway activation [19-21]. Many interferonopathies have autoimmune features and relopathies are often related to immunodeficiencies [22-24]. Although immunological and genetic data are very important, the concept of "undifferentiated" or "undefined" AIDs arises from the fact that in 40 to 60% of patients with phenotypes typical of systemic AIDs a diagnosis cannot be established [9]. In pathology, cardinal signs are defined as major clinical features by which diagnoses are established. In this review, we aim to describe the cardinal signs of systemic autoinflammation, putting them in parallel with the five cardinal signs of local inflammation.

For the purpose mentioned above, a semi-systematic review was carried out and the literature was searched by combinations of keywords such as "autoinflammatory disorders", "interleukin-1" and "classification" in Medline database. Articles focusing on organ-specific, complement-related, mixed-pattern and immunodeficiency-related AIDs were excluded. Clinical-based classification systems of AIDs were confronted with the original cardinal signs of inflammation described by Celsus and Virchow and five signs that occurred in a significant proportion of AIDs (e.g. fever, arthritis) or defined a specific clinical subset (e.g. panniculitis, sterile osteomyelitis) were selected. After careful reading of the included articles, five phenotypic groups were defined as shown in Figure 2 and Table 1.

2. Cardinal signs of autoinflammation

2.1. Fever

Fever constitutes the common cardinal sign of local inflammation, systemic inflammation and autoinflammation. It occurs early in life in almost 90% of patients with AIDs [25, 26]. Hereditary PFS correspond to the prototypic AID [27, 28]. Cohorts of patients with fever of unknown origin have shown that some AIDs are amongst the most common rheumatologic disorders [29, 30]. Overall, PFS have been grouped according to fever frequency: regular, variable and (nearly) continuous periodicity [31]. In this section, we have considered the "four" historical monogenic AIDs plus PFAPA syndrome [18, 32, 33].

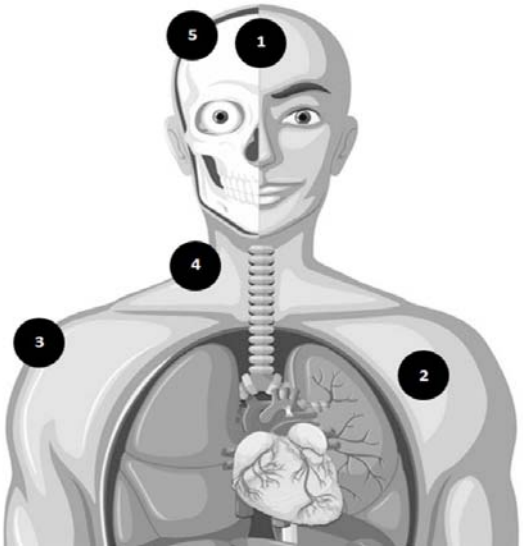

Figure 2. Cardinal signs of autoinflammation. 1 - Fever, 2 - Neutrophilic dermatoses, 3 - Arthritis, 4 - Panniculitis, 5 - Osteomyelitis.

FMF is the most common monogenic AID and occurs due to gain-of-function (GOF) mutations in MEFV gene [10, 34, 35]. Fever occurs in more than 90% of patients and may be the only manifestation; episodes are typically brief and last 12-36 hours [10, 36-39]. The age of onset is around 2.6-2.7 years [30, 40, 41]. Other symptoms include serositis, erysipeloid erythema, myalgia, large-joint monoarthritis, acute scrotum attacks and uveitis [36, 42, 43]. Besides Tel-Hashomer and Yalçinkaya criteria in FMF, Eurofever/PRINTO classification criteria for hereditary recurrent fevers have established two sets of criteria for the historical PFS mentioned in this section, one including genetic and clinical variables, and other with clinical variables only [44]. Colchicine should be started as soon as a clinical diagnosis is established [36, 45]. IL-1 antagonists are often very effective in refractory cases [45-48].

Cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies are intrinsic inflammasomopathies caused by autosomal dominant (AD) GOF mutations in NLRP3 and comprise three disorders within a spectrum of severity [33-36, 49-51]. Symptoms typically appear during the first months of age [17]. Familial cold-associated syndrome (FCAS) corresponds to the milder cryopyrinopathy, presenting with short episodes of cold-induced recurrent fever, conjunctivitis and urticarial nonpruritic neutrophilic rash [17,35]. Muckle-Wells syndrome (MWS) is often characterized by flares of cold-induced urticarial rash, fever, headaches, arthralgia and/or ocular inflammation lasting one to three days [31, 34, 52]. Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous articular syndrome (CINCA) is

Table 1. Cardinal signs of (local and systemic) inflammation and autoinflammation.

Inflammation		**Autoinflammation**
Local	**Systemic**	
Calor	Fever	Fever
Rubor	Peripheral vasodilation	Neutrophilic dermatosis
Dolor	Altered mental status	Arthritis
Tumor	Edema	Panniculitis
Functio laesa	Remote organ dysfunction	Sterile osteomyelitis

characterized by a continuous inflammatory state with arthropathy, chronic urticaria-like rash and central nervous system involvement [37, 52]. IL-1 inhibitors are the first-line treatment [36, 53, 54].

TRAPS, a protein-folding AID also known as familial Hibernian fever, results from autosomal dominant mutations in TNFRSF1A [17, 35]. The mean age of onset is around seven years [23, 34, 35]. Fever is present in more than 95% of patients and often lasts for more than 10 days, is unprovoked and near continuous in about 33%, while recurrence is less frequent than in other PFS [35, 36]. Other manifestations include arthralgia or myalgia, vomiting, abdominal pain, skin rashes, large-joint arthritis, serositis, lymphadenopathy and periorbital edema [34-36, 55]. Flares are treated with short courses of steroids [35, 36].

Mevalonate kinase deficiency (MKD) is an inflammasomopathy that includes hyperimmunoglobulin D and periodic fever syndrome (HIDS) and mevalonic aciduria (MEVA) [56, 57]. Both are caused by loss-of-function (LOF) mutations in MVK gene [17, 56]. HIDS or Dutch fever is characterized by a clinical triad of early-onset recurrent fever, cervical lymphadenopathy and abdominal pain [27, 47]. Fever usually lasts three to seven days and recur every four to six weeks; the first attack usually takes places around six months and up to ten years of age, persisting after 20 years of age in about 50% of patients [17, 37, 55, 58]. MEVA constitutes the severe form of MKD and typically manifests with recurrent fever, development delay, ataxia, myopathy, facial dysmorphia and cataracts [47, 55]. Mevalonaturia is often used for diagnostic purposes but MVK gene testing constitutes the gold standard [31, 58]. High-dose steroids are often very effective but IL-1 antagonists are used in refractory or steroid-dependent cases [10, 27, 58].

PFAPA syndrome is a polygenic AID that probably corresponds to the most common PFS in children [10, 11, 31]. Early-onset disease is typical with a median age at presentation of 2.5 years and a slight male preponderance [32, 35]. Febrile attacks are abrupt and typically last three to six days and recur every three to six weeks [17, 31]. These are often associated with pharyngitis, cervical adenitis and/or aphthous ulcers [10, 32]. Clinical criteria system scores have been proposed by Thomas, Cantarini and Eurofever/PRINTO [44]. Single-dose steroids and anakinra are often effective [17, 31, 32, 37].

2.2. Neutrophilic dermatosis

A rash is defined as a change in cutaneous appearance, with changes in color and/or texture. *Rubor* is a cardinal sign of local inflammation whose equivalent is peripheral vasodilation when regarding signs of systemic inflammation [4]. We have considered neutrophilic dermatosis as a cardinal sign of autoinflammation because urticarial rashes, generalized pustular psoriasis and pyoderma gangrenosum can take place in systemic AIDs even in the absence of fever. Neutrophilic dermatoses are characterized by epidermal, dermal and hypodermal infiltrates of neutrophils without infection or true vasculitis [59].

SS is an acquired AID resulting from mutations in NLRP3 whose pathogenesis is probably related to the presence of a monoclonal immunoglobulin M gammopathy [10, 35, 39]. It is also characterized by chronic urticaria-like rashes and systemic inflammation [17, 39, 52, 58, 60]. Exanthema constitutes the main criteria of SS and is often the first clinical sign, consisting of pink to red maculae, papules and/or plaques; angioedema and involvement of face and extremities are rare, and lesions usually last less than two days and are more pronounced during the evening [60]. SS commonly occurs in middle-aged patients [35, 52]. The Strasbourg criteria comprise two mandatory (chronic urticaria-like exanthema and IgM or IgG monoclonal gammopathy) and four secondary criteria [37, 60, 61]. IL-1 antagonists offer prompt symptomatic relief without paraprotein decrease [35, 60].

NRLP12-associated PFS is possibly caused by mutations in NLRP12, coursing with cold-induced episodes of fever, urticarial rash, arthralgia and myalgia that typically last two to ten days, but it is not certain that NRLP12 mutations can cause a distinct AID [10, 18, 36, 46].

Autoinflammation with infantile enterocolitis (AFEC) is a chronic inflammasomopathy [57, 62]. GOF mutations in NLRC4 can result in severe flares of autoinflammation that share both IL-1β and IFN-γ signatures with extreme elevations of IL-18 [18, 62, 63]. Two phenotypes were described: one courses with very early onset disease (mean

age 1.8 months), fever and macrophage activation syndrome (MAS), enterocolitis with secretory neonatal diarrhea, cutaneous rash and very high mortality; the milder phenotype has a later disease onset (mean age 39 months) with cold-induced urticaria, erythematous nodes, arthromyalgias, conjunctivitis and/or sicca syndrome [7, 18, 54, 57]. Diagnosis is confirmed by genetic testing [54]. Therapeutic options in the first phenotype include IL-1 and IL-18 antagonists; NSAIDs are often used in the second [18, 54].

PASH (pyoderma gangrenosum, acne, and suppurativa hidradenitis) syndrome results from increased CCTG repeats in PSTPIP1 that cause characteristic skin findings (pyoderma gangrenosum often appears later than hidradenitis suppurativa and acne), elevated APR during flares and, less often, fever [17, 43, 58, 64]. Biologics are not consistently effective and antibiotics might be reasonable [64]. Both PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne and suppurativa hidradenitis) syndrome and PAC (pyoderma gangrenosum, acne, and ulcerative colitis) syndrome may also be associated with PSTPIP1 mutations [34, 64, 65]. Instead, PASS (pyoderma gangrenosum, acne, and spondyloarthritis) syndrome courses with high fever and severe lower back pain during flares, and IL-1 antagonists appear effective for both skin and articular manifestations [64]. Like PASS syndrome, PsAPASH (psoriatic arthritis, pyoderma gangrenosum, acne and suppurativa hidradenitis) syndrome is a cutaneo-articular AID that lacks biological or genetic markers, whilst IL-1 and TNF antagonists represent the best solutions for prolonged remission [65, 66].

PAAND (pyrin-associated autoinflammation with neutrophilic dermatosis) syndrome results from p.S242R MEFV mutations [67]. It is characterized by recurrent fever, arthralgia, myositis, acne, sterile skin abscesses and pyoderma gangrenosum [57, 67]. Anakinra has been successful in most patients [43, 57].

DITRA is a recessive AID caused by mutations in IL-36 receptor antagonist (IL36-RA) [36]. It courses with generalized pustular psoriasis, but high-grade fever and absence of bone involvement differentiate it clinically from DIRA [10, 36]. Oral retinoids constitute the first-line therapy [36].

CARD14-associated psoriasis or CARD14-mediated psoriasis (CAMPS or PSORS2) is an inflammatory keratinization disorder that courses with fever and continuous inflammation, pustular and/or plaque psoriasis, nail pitting and psoriatic arthritis in 30% of patients [20, 34, 39, 49, 68-71]. Treatment options include retinoids, methotrexate, cyclosporine, TNF inhibitors and IL-17/23 inhibitors [20, 28, 43].

2.3. Arthritis

Arthritis corresponds to joint inflammation and is defined as tenderness and swelling of joints. As another cardinal sign of local inflammation, *dolor* or pain may be regarded in parallel with altered mental status (i.e., confusion, agitation) when considering cardinal manifestations of systemic inflammation [4]. Considering the common occurrence of arthritis in AIDs and that it is often associated with pain and malaise/ obtundation in children, we have regarded arthritis as another cardinal sign.

Blau syndrome (BS) arises from dominant GOF mutations in NOD2/CARD15 and typically manifests before five years of age [17, 34, 72]. Granulomatous inflammation of the joints, skin and uvea often gives rise to the clinical triad of symmetric polyarthritis, dermatitis and recurrent uveitis [17, 36, 72-74]. Arthritis corresponds to its first and most common manifestation, commonly oligo- or polyarticular arthritis and involves the wrists, metacarpophalangeal, first metatarsophalangeal and proximal interphalangeal joints, ankles and sometimes elbows; granulomatous infiltration can also involve periarticular structures and chronic arthritis can cause deformities [18, 72, 73]. Patients are often treated with steroids [46, 55, 73].

Yao syndrome or NOD2-associated autoinflammatory disease (NAID) has been reported in Caucasian adults with female preponderance and CARD15/NOD2 polymorphisms [72]. The clinical picture resembles BS with periodic fever (63%), articular symptoms, serositis, skin rashes, gastrointestinal complaints, aphthous ulcers and sicca-like syndrome [72, 75]. Joint involvement is periodic and takes place in 90% of patients, typically with non-erosive oligo- or polyarthritis of lower extremities [18, 75]. Therapeutic options include steroids, sulfasalazine, IL-1 and IL-6 inhibitors [72].

PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome is a rare autosomal dominant

extrinsic inflammasomopathy caused by GOF mutations in PSTPIP1 [16, 17, 47]. It commonly presents in early childhood with severe courses of recurrent sterile monoarticular erosive arthritis with massive polymorphonuclear infiltrates, but severe cystic acne, pathergy-like sterile skin abscesses and pyoderma gangrenosum commonly take place only during adolescence [16, 36, 76]. Diagnosis is based on clinical grounds [64]. Steroids are useful for arthritis, but TNF antagonists and anakinra have induced beneficial therapeutic effects in refractory cases [36, 43]. PAMI (PSTPIPI1-associated myeloid-related protein) syndrome is an early onset AID that courses with osteoarticular manifestations (80% of patients, including osteoarthritis and aseptic arthritis in more than 55%), skin lesions, hepatosplenomegaly, lymphadenopathy, nephropathy, growth and mental retardation [18, 77]. Anakinra is often effective [77].

Crystalline arthropathies, like acute gout and pseudogout, are caused by deposition of monosodium urate and calcium pyrophosphate crystals, respectively, in synovial fluid and periarticular tissues, which activate the NLRP3 inflammasome [52, 78]. In acute gout, arthritis typically affects the first metatarsophalangeal joint with severe pain, inflammatory signs and possibly fever [17, 79]. NSAIDs and colchicine are used as first-line treatment options [79].

2.4. Panniculitis

Panniculitis is defined as inflammation of the subcutaneous adipose tissue and typically manifests as tender skin nodules, often being associated with lipodystrophy. *Tumor* was originally described as a cardinal manifestation of local inflammation [4]. Edema (and increased capillary permeability) may be regarded as the corresponding sign of systemic inflammation. In this group, we have included AIDs that may cause swelling of subcutaneous tissue and can be clinically identified by visible or palpable tumefactions.

Proteasome-associated autoinflammatory syndromes (PRAAS) are type I interferonopathies usually caused by LOF mutations in proteasome components such as PSMB8 and include CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome, Nakajo-Nishimura syndrome (NNS) and JMP (joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy) syndrome [19, 20, 71].

CANDLE syndrome courses with high-spiking fevers during the first decade of life, along with fixed purpuric skin plaques with dermal neutrophilic infiltrates, lipodystrophy, periorbital edema, hepatomegaly, failure to thrive and chronic anemia [17, 36, 55]. Annular violaceous plaques are common in the trunk, may become purpuric and last for weeks, but panniculitis can also occur as erythema nodosum [53, 71]. Diagnosis is based on clinical grounds and confirmed by PSMB8 (or other proteasome subunits) gene mutation and/or biopsy [20, 55]. NNS is an autosomal recessive PRAAS [80]. It often starts with an early-onset pernio-like rash, but high periodic fevers, nodular erythematous rash, lipo-muscular atrophy, clubbed fingers with joint contractures and mental retardation can also take place [17, 80]. Diagnostic criteria have been proposed requiring at least five of eight clinical features [80]. JMP syndrome appears to be a more severe phenotype, manifesting with early-onset lipodystrophy, muscle atrophy, joint contractures, microcytic anemia and erythematous rash [17, 80]. In PRAAS, IL-6 inhibitors have been shown to normalize APR and anemia but not lipodystrophy, probably constituting the best therapeutic option along with JAK inhibitors [19, 36].

Otulipenia or OTULIN-related autoinflammatory syndrome (ORAS) is a relopathy caused by mutations in OTULIN [21, 39, 50]. Early-onset recurrent fever, neutrophilic dermatosis, panniculitis with painful nodular red rash, lipodystrophy, arthritis, diarrhea and failure to thrive have been described [39, 54, 67]. TNF blockade constitutes a very promising treatment option [18, 21].

2.5. Osteomyelitis

Functio laesa is the remaining cardinal sign of inflammation. Therefore, remote organ dysfunction can be regarded as the corresponding sign of systemic inflammation [4]. Therefore, we have considered sterile osteomyelitis (bone inflammation) as the last sign of autoinflammation. Chronic sterile osteomyelitis or chronic non-bacterial osteomyelitis (CNO) constitutes the common denominator among bone AIDs [16].

Chronic recurrent multifocal osteomyelitis (CRMO), or sterile osteitis, is a recessive AID

characterized by osteolytic painful lesions that usually start during childhood [17, 81]. NSAIDs are used as the first-line therapeutic option [16].

SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome has a female predominance and occurs mainly during the fourth and fifth decades of life, following a relapsing-remitting course [82]. Synovitis typically presents with erosive poly- or oligoarthritis and constitutes a probable extension of osteitis, which affects the anterior chest wall in up to 75% of patients; other manifestations include palmoplantar pustulosis and acne, hidradenitis suppurativa, sacroiliac sclerosis, enthesitis, seizures, venous thrombosis and ocular involvement [82]. Clinical criteria were proposed by Benhamou (1988) and Khan (2003) [82]. NSAIDs and analgesics are primarily used [43, 82].

Majeed syndrome (MS) is a NLRP3 inflammasomopathy caused by recessive LOF mutations in LPIN2 gene [17, 39]. It typically presents in the neonatal period with fever, sterile bone inflammation, lytic and/or sclerotic bone lesions, anemia and neutrophilic dermatosis [36, 81]. MS often resolves spontaneously; steroids are more effective than NSAIDs, whilst IL-1 antagonists have induced sustained clinical, radiographic and analytical improvements [16, 17, 20].

Deficiency of IL-1 receptor antagonist (DIRA) is a recessive AID caused by mutations in IL1RN gene [16, 36, 81]. It is characterized by early-onset multifocal osteomyelitis, lytic bone lesions, osteopenia, heterotopic calcifications, erythroderma, pustular dermatitis and systemic inflammation without prominent fever [16, 17, 36, 73, 81]. IL-1 inhibitors usually offer prompt and sustained remission [36, 43, 46, 54].

3. Conclusion

Along with laboratory evidence of systemic inflammation, the above-mentioned cardinal signs may virtually identify most cases of systemic autoinflammation. Except for fever, these signs represent organ-specific inflammation. Nevertheless, a major limitation is that many AIDs have overlapping cardinal signs. Uveitis, serositis, enterocolitis or aphthous ulcers could have been considered as cardinal signs of systemic AIDs, but they probably lack sensitivity and/or specificity. Previous diagnostic scores for molecular analysis of systemic AIDs have identified clinical variables to be associated with relevant mutations, but these tools have only focused on PFS. Regarding patients with undefined AIDs, different subsets have already been suggested (e.g., pericarditis, intellectual impairment). In order to diagnose AIDs in earlier stages, we have not considered late signs of inflammation or those related to hyperinflammation. Also, we have not considered vasculitis as a cardinal sign of autoinflammation, because classical vasculitis is uncommon in systemic AIDs [48].

Another limitation is that most AIDs that share autoimmune or immunodeficiency features escape from recognition, since only “pure” AIDs have been described. This overlap means that the separation between the innate and adaptive immune systems is not strict [7, 43]. We acknowledge that organ-specific (e.g. cherubism), complement-related (e.g., atypical hemolytic uremic syndrome), mixed-pattern (e.g. A20 and RELA haploinsufficiencies) and immunodeficiency-related AIDs (e.g. deficiency of adenosine deaminase-2) have been excluded from our analysis.

Earlier diagnosis on a clinical basis might have therapeutic implications, even though genetic testing is invariably necessary for definitive diagnosis. In about 40 to 60% of patients with phenotypes typical of systemic AIDs a distinct diagnosis cannot be established. Phenotype-guided treatment may be important in many patients and clinical-based classification systems have been proposed in the past [10, 34]. As long as genetic testing is not widely available, clinical-based classification systems and therapeutic trials will probably remain useful in clinical practice and may identify most pure systemic AIDs, as shown in Table 2.

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None.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

Table 2. Examples of diseases under each cardinal sign of autoinflammation.

Cardinal sign	Prototypic examples of AIDs	Others
Fever	FMF, CAPS, TRAPS, MKD, PFAPA	AFEC, CAMPS, CANDLE, CRMO, DADA2, DITRA, gout, MS, NAIAD, NAID, NNS, NRLP12, ORAS, PAAND, pseudogout, SS
Neutrophilic dermatosis	SS, NRLP12, AFEC, PASH, PAPASH, PAC, PASS, PsAPASH, PAAND, DITRA, CAMPS	APLAID, CANDLE, CAPS, DIRA, FMF, MS, ORAS, PAPA, PAMI, SAPHO
Arthritis	BS, NAID, PAPA, PAMI, gout, pseudogout	APLAID, CAMPS, CANDLE, CAPS, CRMO, DIRA, FMF, HIDS, NAIAD, NNS, ORAS, PAPASH, PASS, PsAPASH, SAPHO, SS, TRAPS
Panniculitis	CANDLE, NNS, JMP, ORAS	IBD, Sarcoidosis
Osteomyelitis	CRMO, SAPHO, MS, DIRA	Cherubism

AFEC – Autoinflammation with infantile enterocolitis; APLAID – autoinflammation, antibody deficiency, and immune dysregulation; BS – Blau syndrome; CAMPS – CARD14-mediated psoriasis; CANDLE – Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome; CAPS – Cryopyrin-associated periodic syndromes; CRMO – Chronic recurrent multifocal osteomyelitis; DADA2 – Deficiency of adenosine deaminase 2; DIRA – Deficiency of IL-1 receptor antagonist; DITRA – Deficiency of IL-36 receptor antagonist; FMF – Familial Mediterranean fever; IBD – inflammatory bowel disease; JMP – Joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy syndrome; MKD – Mevalonate kinase deficiency; MS – Majeed syndrome; NAIAD – NLRP1-associated autoinflammation with arthritis and dyskeratosis; NAID – NOD2-associated autoinflammatory disease; NNS – Nakajo-Nishimura syndrome; NRLP12 – NRLP12-associated periodic fever syndrome; ORAS – OTULIN-related autoinflammatory syndrome; PAAND – Pyrin-associated autoinflammation with neutrophilic dermatosis syndrome; PAC – Pyoderma gangrenosum, acne, and ulcerative colitis syndrome; PAMI – PSTPIPI1-associated myeloid-related protein syndrome; PAPA – Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PAPASH – Pyogenic arthritis, pyoderma gangrenosum, acne and suppurativa hidradenitis syndrome; PASH – Pyoderma gangrenosum, acne, and suppurativa hidradenitis syndrome; PASS – Pyoderma gangrenosum, acne, and spondyloarthritis syndrome; PFAPA – Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome; PsAPASH – Psoriatic arthritis, pyoderma gangrenosum, acne and suppurativa hidradenitis syndrome; SAPHO – Synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; SS – Schnitzler syndrome; TRAPS – Tumor necrosis factor-receptor associated periodic syndrome.

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