Adult-Onset Still’s Disease

Subjects: Rheumatology
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Adult-onset Still’s disease (AoSD) is a rare systemic autoinflammatory disease characterized by arthritis, spiking fever, skin rash and elevated ferritin levels.

Keywords: adult-onset Still’s disease ; autoinflammatory disorder ; systemic-onset juvenile idiopathic arthritis ; haemophagocytic lymphohistiocytosis ; macrophage activation syndrome

1. Introduction

Adult-onset Still’s disease (AoSD) is a rare systemic autoinflammatory disease characterized by arthritis, spiking fever, skin rash and elevated ferritin levels. The cause of this complex disorder, which usually affects young adults, remains unknown [1]. A London doctor named Bywaters first introduced the term AoSD in the medical literature in 1971 by describing this condition in a small group of 14 patients with an age range of 17 to 35 years [2]. The reason behind the nomenclature of this disease is that AoSD shares certain symptoms with Still’s disease in children, which is currently named systemic-onset juvenile idiopathic arthritis (SoJIA). Based on gene expression analysis, some regard SoJIA and AoSD as a single nosological entity [3]. Most recent estimates place AoSD incidence at 0.16 to 0.4 per 100,000 persons [4].

One of the most interesting current discussions in immunology is the newly introduced concept of a “crossroads between autoinflammation and autoimmunity due to the pathogenic involvement of both arms of the immune system” [5]. AoSD, like PFAPA (periodic fever with aphthous stomatitis, pharyngitis and adenitis) and Behçet’s disease, is a complex disorder with malfunctioning dysregulated immune system. On the one hand, it lacks the classical characteristics of autoimmune diseases, such as autoantibodies, but on the other hand, it has negative genetic testing in family histories, which is opposite to other autoinflammatory conditions [6].

The past two decades have seen a large body of immunological research on cytokines, which has attributed to both a better understanding of AoSD and significant advances in treatment. One major problem is that although biological drugs have made revolutionary changes in the management of a range of rheumatic conditions, many patients with AoSD are not benefiting from most of them [7]. In addition, every rheumatologist with a patient who had a life-threatening cytokine storm during macrophage activation syndrome (MAS) has deep respect for AoSD.

2. Autoinflammation and Autoimmunity

Autoimmunity was, historically, defined as a dysregulation of the adaptive immune system, exclusively involving B and T lymphocytes and leading to the production of autoantibodies directed against self. Autoinflammation, on the other hand, was strictly separated from autoimmunity and was previously considered to have a solely innate autoimmune aetiology. Recent studies on pattern recognition receptors (PRRs) were the breakthrough discovery that changed the way we approach these two phenomena and elucidated the pathology of a group of disorders where both arms interfere and contribute to the inflammatory response [8].

Autoinflammation in periodic fever syndromes is caused by an inborn error of the innate immune system that results in the perturbation of pattern recognition receptors (PRRs), such as the leucine-rich repeat containing family (NLR), leading to an inappropriate chain reaction towards both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns molecules released from injured tissues (DAMPs) [9].

In concert with this theory, genetic errors in the NLR pathway can trigger the onset of Crohn’s disease, a very well-known disorder that was classified as an autoimmune disease until recently. Currently, Crohn’s disease is considered an autoimmune disease with a prevalent autoinflammatory pathogenesis [10]. Moreover, a small subgroup of patients with rheumatoid arthritis show systemic inflammatory symptoms, such as fever and serositis, although this disease is not supposed to have a coexistent autoinflammatory background [11].

AoSD belongs to this group of disorders and is thought to be “the archetype of non-familial, or sporadic, systemic autoinflammatory disorders” [12].

2.1. Pathogenesis Part I: Who Started the Fire

The exact underlying cause of AoSD is not fully understood. We still do not know what exactly triggers DAMPs and PAMPs.

The causal inferences between genetics and AoSD are controversial. Human genetic factors apparently contribute to SoJIA in children, whereas the underlying genomic susceptibility in the adult form is unclear [13].

On the other hand, there is a high degree of similarity between infections and the onset of AoSD for fever, leucocytosis and elevated C-reactive protein (CRP). Logically, many investigators focused on identifying infectious triggers and described the occurrence of AoSD after infection with cytomegalovirus, Epstein-Barr, influenza, *Mycoplasma*, hepatitis, etc. [4]. We now know that cytomegalovirus may also trigger a relapse of AoSD [14]. Blood cultures and polymerase chain reaction (PCR) tests may, therefore, be useful for a differential diagnosis, although no specific diagnostic algorithms exist to date. It is currently still not clear which pathogenic viruses and bacteria should be included in the diagnostic workup. Remarkably, procalcitonin is not a reliable marker, since patients suffering from AoSD can show elevated procalcitonin levels without confirmed infection [15].

Other studies have examined the relationship between cancer and AoSD [16] and reported malignancy-mediated autoinflammation in breast cancer [17], thyroid cancer [18], melanoma, lung cancer and haematological malignancies, mostly lymphomas [19]. Despite increasing sophistication in the diagnostic workup for possible malignancies, there are no universally accepted guidelines for patients with AoSD, which makes daily clinical work more difficult. Positron emission tomography and computed tomography (PET/CT) scanning could be useful in difficult case scenarios to rule out solid tumours or large vessel vasculitis mimicking AoSD, but it is not routine practice because of the relatively high costs [20]. Bone marrow examination can rule out a haematologic malignancy or support the diagnosis of MAS.

In short, AoSD is a diagnosis of exclusion. The process of eliminating similar medical conditions is most likely to take a considerable amount of time. Table 1 summarizes the broad spectrum of differential diagnoses.

Table 1. Differential diagnosis of AoSD [12].

Infections	**Tuberculosis, toxoplasmosis, brucellosis, yersiniosis** **HIV, Epstein-Barr, cytomegalovirus, hepatitis, herpes, influenza, parvovirus B19, measles, rubella**
Malignancies	**Lymphoma, Castleman disease, myeloproliferative disorders, melanoma and colon, breast, lung, kidney and thyroid cancer** **In pediatrics also: leukemia**
Systemic diseases	**Systemic lupus erythematosus, idiopathic inflammatory myopathies, vasculitis, hereditary autoinflammatory syndromes, neutrophilic dermatosis, Sweet syndrome, reactive arthritis, sarcoidosis, Schnitzler syndrome, Kikuchi-Fujimoto disease** **In pediatrics also: other types of inflammatory arthritis**

2.2. Pathogenesis Part II: What Keeps the Fire Burning

PAMPs and DAMPs stimulate macrophages and neutrophils, leading to activation of specific inflammasomes via Toll-like receptors. Inflammasomes are multiprotein units that act as catalysts by activating the caspase pathway immediately after they come into contact with damage or illness. Caspase enzymes lead to overproduction of IL-1β, the hallmark of AoSD, and IL-18. IL-1β and IL-18 then promote further abnormal inflammation by several cytokine bursts, including IL-6, IL-8, IL-17, IL-18 and TNF-α. At this point, the patient is experiencing heavy systemic symptoms [21][22][23][24].

Furthermore, activated macrophages stimulate the release of excessive levels of ferritin. In addition to functioning as an iron storage molecule, ferritin also plays a central role in many conditions with an amplified inflammatory response, currently called “hyperferritinemic syndromes”, such as AoSD, MAS, catastrophic antiphospholipid syndrome and septic shock [25]. Ferritin has a key role in inflammation by promoting cytokine production, and at the same time, cytokines can regulate ferritin synthesis.

Moreover, analysis of accumulating data over the past years showed an enhancement of neutrophil extracellular traps (NET) in AoSD, which promotes the acute phase response by activating the NLRP3 inflammasome [26].

Additionally, dysfunctional natural killer (NK) cells, elevated T-helper Th1 and Th17 cells, enhanced IFN-γ and IL-17 levels, different alarmins, such as the S100 proteins, significantly higher IFN-γ-producing Th1 cells and Th1/Th2 cells ratios and advanced glycation end products complete the proinflammatory environment in many ways, which favours the abnormal response of the human immune system [27][28][29].

2.3. Pathogenesis Part III: Why Is Firefighting so Hard

The massive release of cytokines in patients with AoSD over a prolonged period of time can be fatal. Deficient resolution of inflammation may be mostly due to failures in immune system self-regulation. Deficient regulatory T cells, decreased or defective NK cells, insufficient production of anti-inflammatory cytokines or problematic circulation of advanced glycation end products (AGEs) have been hypothesized to cause these complex problems [30][31][32][33]. Surprisingly, the anti-inflammatory cytokine IL-10 levels are elevated during the higher state of inflammation and correlate with disease activity in AoSD [34].

3. Clinical Symptoms

Nonspecific symptoms such as fever, sore throat or arthralgia that usually bring patients with AoSD to medical attention are rather misleading. The similarities with an infection often obscure the diagnosis and lead to empirical antibiotic therapies. Italian and French studies have shown a diagnostic delay ranging from 1.5 to 4 years between the onset of symptoms and the final diagnosis of AoSD [4][35]. When all conservative treatments fail, practitioners realize they are facing a prolonged febrile illness without an obvious aetiology. The diagnostic journey then begins.

In a large retrospective study, which set out to analyse 1641 patients with fever of unknown origin (FUO), AoSD was responsible for 5.4% of cases [36]. Overall, rheumatic diseases comprise approximately 30% of cases with FUO, with AoSD being the most frequent group [37].

Fever is a cardinal symptom in AoSD and occurs in 60 to 100% of cases. Patients typically report two fever spikes daily, one in the morning and one in the evening, usually >39 °C. In 60 to 80% of patients, a macular or maculopapular evanescent salmon-pink skin rash on the proximal limbs and trunk accompanies high fever. Interestingly, this rash can disappear completely during afebrile intervals. Permanent skin rashes, on the other hand, presenting with urticaria, are warning signs for haematological complications. Both fever and skin rash are correlated with disease activity. Along with other nonspecific constitutional symptoms, such as weight loss and malaise, patients with active AoSD feel sick and miserable [1][4][38].

Arthralgia is also a cardinal symptom that is observed in 70 to 100% of patients, often accompanied by polyarthritis involving small joints, imitating rheumatoid arthritis. Some patients with chronic articular AoSD show severe osteodestructive features, which cause ankyloses and functional disability [39].

Other concomitant symptoms, such as pharyngitis, odynophagia, lymphadenopathy, splenomegaly, myalgia, pleuritis or abdominal pain vary from person to person. National registries and patient cohorts are a major determinant for successful characterization of clinical phenotypes in the field of rare diseases, such as AoSD. Table 2 shows the summary statistics of some observational studies and illustrates the heterogeneity of AoSD and SoJIA.

Table 2. Comparison of clinical features (%) of patients with AoSD and SoJIA.

Di Benedetto P, Cipriani P, Iacono D, et al. (2020) [40]	Hu QY, Zeng T, Sun CY et al. (2019) [41]	Sfriso P, Priori R, Valesini G, et al. (2016) [35]	Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. (2014) [42]	Fautrel B. et al. (2002) [43]	Tsai H. et al. (2012) [44]	Behrens E. D. et al. (2008) [45]	
Case number	**147**	**517**	**245**	**57**	**72**	**28**	**136**
Nationality	**Italy**	**China**	**Italy**	**France**	**France**	**Taiwan**	**United States**
Female	**39.5**	**72**	**47.3**	**53**	**nk**	**53.6**	**54**
Average age at onset	**45.2**	**37.7**	**38.8**	**36**	**35.2**	**8.7**	**5.7 Median 2**
Fever ≥ 39 °C	**100**	**91.3**	**92.6**	**95**	**84.7**	**100**	**98**
Rash	**74.8**	**79.9**	**67.7**	**77**	**70.8**	**67.9**	**81**

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Arthralgia/arthritis	**88.4**	**73.1**	**93**	**95**	**88.8**	**89.3**	**88**
Sore throat	**56.5**	**60.5**	**62**	**53**	**52.7**	**nk**	**nk**
Lymphadenopathy	**54.4**	**51.1**	**60.4 ***	**60**	**44.4 ***	**46.4**	**31**
Hepatomegaly	**nk**	**6.6**	**41.7**	**21**	**nk**	**nk**	**~7**
Splenomegaly	**66.7**	**34.4**	**60.4 ***	**30**	**44.4 ***	**21.4 ***	**~5**
Pericarditis	**21.1**	**14.1**	**17.3**	**19**	**20.8**	**nk**	**10**
Pleuritis	**19.7**	**nk**	**nk**	**18**	**nk**	**7.1 ***	**nk**
Myalgia	**64.6**	**32.5**	**nk**	**44**	**nk**	**nk**	**nk**
AoSD pneumonia	**12.2**	**nk**	**nk**	**nk**	**nk**	**nk**	**nk**
Abdominal pain	**13.6**	**nk**	**nk**	**18**	**nk**	**nk**	**nk**

nk = not known. * reported together as single variable.

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