Original Article

ADULT-ONSET STILL'S DISEASE : A DIAGNOSIS OF EXCLUSION

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ABSTRACT

Adult-onset Still's disease (AOSD), which was initially identified by Eric Bywaters in the 1970s , is an uncommon condition with an unidentified aetiology that affects a number of organs and systems. Spiking fever, arthritis, transient salmon-pink eruptions, lymphadenopathy, splenomegaly, and other signs are common clinical complaints. Neutrophilic leukocytosis, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), hyperferritinemia, and enhanced inflammatory factors are the frequent laboratory findings. Before making a diagnosis of AOSD, it is necessary to exclude other disorders because the pathogenic mechanism is still unknown. The two main types of treatment for AOSD are traditional treatment and biological treatment.

Introduction

Adult-onset Still's disease (AOSD), which was initially identified by Eric Bywaters in the 1970s (1), is an uncommon condition with an unidentified aetiology that affects a number of organs and systems. The illness resembled childhood-onset Still's disease, now known as systemic-onset juvenile idiopathic arthritis (SoJIA) and first reported by Sir John Still a century ago.

Despite the fact that the disease's precise pathogenic pathways are unknown, significant progress has been made to confirm the similarity between AoSD and SoJIA, and AoSD has evolved into the model for sporadic or non-familial systemic autoinflammatory disorders.(3-5)

Spiking fever, arthritis, transient salmon-pink eruptions, lymphadenopathy, splenomegaly, and other signs are common clinical complaints. Neutrophilic leukocytosis, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), hyperferritinemia, and enhanced inflammatory factors are the frequent laboratory findings.ANA, RF, and ENA panels are all negative.(6,7)

Epidemiology

Epidemiological research on AOSD is regionally focused and limited, and the study populations are typically quite small.

Studies done in France, Japan, and Turkey indicated that regardless of ethnicity, the incidence of AOSD was between 0.16 and 0.62/100,000 people (8-10). According to estimates, the prevalence rate is in the neighbourhood of 1-34 cases per million individuals, with two peaks in the age distribution at 15- to 25- and 36- to 46-years-old, and no overt gender bias (7). Recent investigations have shown that, independent of regional limits, the incidence and prevalence of AOSD have not altered appreciably.

However, these studies discovered that young adults aged 20–39 were the group most likely to have the condition, followed by women and those 50–59 years old . (10-14)

Clinical and Laboratory Manifestations:

The most frequent clinical symptom of AOSD patients is fever, which develops every day while they are in their active phase. Temperatures spike in the afternoon or early evening, frequently exceeding 39°Celsius, and the onset is sudden. Additionally, fever might occasionally resolve on its own. Fever is a crucial factor to take into account while evaluating a fever of unknown origin because it can occasionally be the only presenting sign of AOSD.(6,7)

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The second most frequent symptom of AOSD, whether or whether there is a fever, is arthralgia.(6) One or more joints may be affected. Arthralgia often begins as a mild, transient condition. Joint pain will then progress into chronic arthritis over time. (6)

Many cases of AOSD are characterised by fever and salmon-pink evanescent skin eruptions (ESEs). Previously, it was thought that the most distinct clinical indication of AOSD was these brief, itchy skin eruptions.(6,7) However, there is a growing consensus that atypical persistent skin eruptions (APSEs), which have distinct histological manifestations like focal parakeratosis and scattered necrotic keratinocytes in the stratum corneum and upper third of the epidermis, are specific to AOSD and that APSEs may represent the other end of a spectrum that also includes classical ESEs.Clinicians advise that APSEs may be a symptom of malignancy, necessitating careful follow-up, as certain case studies have demonstrated that hematologic or solid cancers can be secondary to AOSD with a 9-month median time of diagnosis after initial presentation.(15-17)

Pharyngitis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, pleurisy, and pericarditis are other symptoms that may accompany AOSD. (18)

AOSD is often categorised into three categories based on its clinical course: monocyclic, polycyclic, and chronic patterns. About 19–44% of people with AOSD exhibit the monocyclic pattern, which appears as systemic, self-limiting symptoms. These people only experience one flare, and after a few weeks or months, they reach full remission. Overall, 10-41% of patients show the polycyclic pattern, which is characterised by multiple, discrete recurrences in the body or in the joints with intervals of remission; 35-67% of patients show the chronic pattern, which is characterised by a high frequency of articular symptoms, typically affecting the wrists, knees, and ankles and which may develop into erosive arthritis. (6,7,19)

Aseptic meningitis, diffuse alveolar haemorrhage, thrombotic thrombocytopenic purpura, macrophage activation syndrome (MAS), and pulmonary arterial hypertension are a few uncommon but life-threatening complications of AOSD that should be identified early and treated promptly to reduce morbidity and mortality.(20)

In terms of laboratory results, leukocytosis with a high neutrophil percentage, hyperferritinemia, and raised ESR, CRP, procalcitonin (PCT), and lactate dehydrogenase (LDH) are frequently seen in AOSD. raised liver enzymes have also been documented.Glycosylated ferritin (GF), a newly discovered marker, typically drops to 20–50% in inflammatory circumstances. The level of GF is noticeably lowered in AOSD (20%) and should be taken into consideration for use in AOSD diagnosis (21). These criteria have the clear benefit that the diagnosis is not an exclusion (6); however, one drawback is that GF testing may not be routine in most facilities.

INNATE IMMUNITY

Toll like receptors(TLRs):

The innate immune system is triggered by infectious agents and environmental stimuli through TLRs.TLRs function is to sense and transfer signals, i.e DAMPs (damage-associated molecular patterns) and PAMPs(Pathogen associated molecular patters) to intracellular signalling pathways.(22).TLRS recruit neutrophils, causing inflammation to be activated and TH17-driven inflammatory responses to be amplified(23).Neutrophils have a greater capacity to form NETs,which in turn activates the pro inflammatory macrophages. S100 A8/A9 and A12 are components of NETs that serve as DAMPs.Theyactivate TLR4 and RAGES(receptor of advanced glycation end products)When compared to healthy controls, AOSD patients' dendritic cells had considerably higher TLR7 expression, which was also accompanied by raised transcript and protein levels of MyD88, IRAK4, and TRAF6, indicating activation of the TLR7-MyD88 pathway.(23,24,25)The soluble form of TREM-1 (sTREM-1) was discovered to be higher in the serum of AOSD patients, with a direct association to disease activity. TREM-1 is a key amplifier of inflammatory signalling.(26)

Macrophage activation

TLRs on macrophages recognise DAMPs and PAMPs and recruit adaptor molecules like MyD88 to activate the NF-B downstream cascade signalling pathway, which in turn triggers pro-inflammatory cytokine storms.(27,28,29).Macrophage migration inhibitory factor (MIF), a proinflammatory cytokine with the capacity to upregulate the expression of proinflammatory mediators, and macrophage

activation that have been reported to be elevated in the serum of AOSD patients and correlated with disease activity.

Hyperferritinemia:

Ferritin in the circulation and that absorbed into the skin are both connected with the severity of AOSD, and the release of ferritin is promoted by activated macrophages.(25)

NK Cell activity:

The number and cytotoxic function of NK cells were observed to be significantly reduced in AOSD compared to healthy controls, and this malfunction may cause macrophages and T cells to become too activated, favouring the development of AOSD. (31,32)

ADAPTIVE IMMUNITY:

In 2003, a serum cytokine investigation of AOSD discovered elevated levels of CD25, the IL2 receptor that is α-soluble.(87,88).Increased levels of IL-4,IL-3 reflects the Th2 cytokine profile.INF-γ , IL-12, and IL-2 are within normal levels in AOSD patients(89).Active AOSD has a TH-1 predominance (increase in IL-4, INF-γ)(90).Increase in TH-17 cells and TH-17 related cytokines are also associated with disease activity(91). CD4+ CD25 regulatory T cell,anti immune mechanism and TGF-β are reduced in AOSD, inversely correlating with disease activity.(92)

In conclusion, current research has established that AOSD is a condition that lies at the nexus of innate immunity and autoimmunity.

Genetics:

Current reports of AOSD, when combined with the epidemiological research stated previously, have not revealed any clear familial tendencies. Without substantial ethnic or geographic restrictions, AOSD can develop everywhere, but there is still a genetic component. Human leukocyte antigen class I and class II (HLA I, HLA II) genes, particularly HLA-B17, -B18, -B35, -DR2, -DR4, -DR7, and -Bw35, have been linked to AOSD, according to several research (33-35). While some research have identified a stronger correlation between AOSD incidence and HLA-DRB1*12and -DRB1*15, others have discovered a negative correlation between AOSD incidence and HLA-DR1 and -DRB1*04.(35,36) In Korea, Japan, Germany, and Turkey, changes in the MEFV gene have been linked to AOSD(37-40)The TNFRSF1A gene has also been linked to AOSD by Turkish researchers, but larger samples are still required for confirmation.(40)

One of the AOSD's top areas of research is gene polymorphism. Genetic variations in human IL-18 have been linked to AOSD susceptibility, according to research by N Kamatani et al. from 2002.(41) In Chinese patients with AOSD, Chen et al. discovered a functional relationship between the IL-18 gene-607 (C/A) promoter polymorphisms and the course of the disease. This genotype, with a low IL-18 level, may be a protective factor against the severity of AOSD and the development of chronic debilitating arthritis.(42) It has been revealed that functional promoter polymorphisms in the migration inhibitory factor (MIF) gene affect plasma MIF levels in AOSD and may be linked to disease susceptibility or clinical presentation(43).The gene encoding macrophage-CSF (M-CSF) and the rs11102024 T allele were related to higher M-CSF levels and a systemic rather than a chronic articular manifestation of AOSD, according to another study that found the SNP rs11102024, which is 5' upstream of colony-stimulating factor 1 (CSF1), was associated with AOSD (44). When Chen et al. investigated single-nucleotide polymorphisms (SNPs) involved in NLRP3-inflammasome signalling, they discovered that SNP rs11672725 of the CARD8 gene was significantly associated with AOSD susceptibility. They also discovered that NLRP3-inflammasome signalling was strongly associated with AOSD. Patients who had the rs11672725CC genotype were more likely to have systemic illness and low CARD8 levels.(45)

Last year, Hung, Chen, and Lan etal. published an update showing that SNPs of the gene for autophagy-related 16-like 1 (ATG16L1) have associations with the clinical phenotype of AOSD in particular. They also suggested that the AA/CC/TT haplotype of this gene may be connected to the systemic pattern of manifestation and specific clinical features of AOSD, such as skin rash(46).These results, however, need to be confirmed in a broader, more diversified group.

Infections:

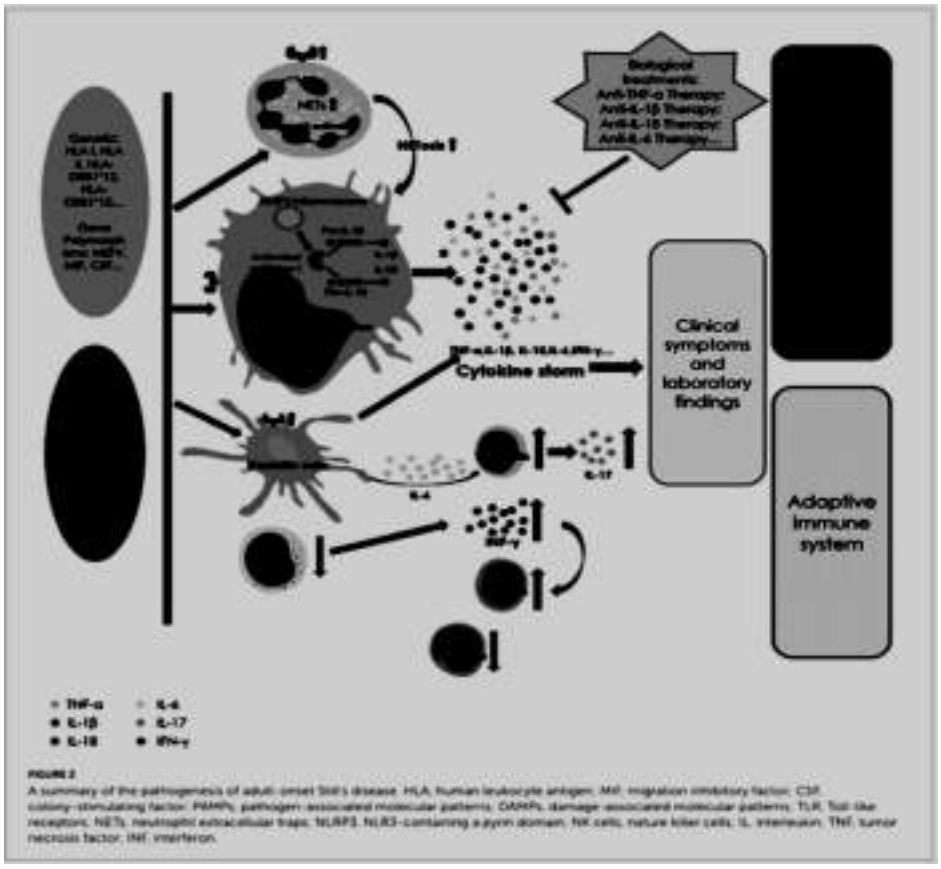
The usual suspects for the production of danger signals are bacteria or viruses. Numerous case reports discuss the development of AOSD

following viral or bacterial infections, such as those caused by the rubella virus, measles orbillivirus, mumps virus, Epstein-Barr virus, hepatitis A, hepatitis B, or hepatitis C viruses, HIV, cytomegalovirus, parvovirus B19, adenovirus, echovirus, human herpesvirus 6, influenza virus, parainfluenza viruses;Mycoplasma pneumoniae; Chlamydia pneumoniae; Streptococcus pneumoniae; Yersinia enterocolitica, Campylobacter jejuni, and Borrelia burgdorferi(6,7,47)

Additionally, before the onset of the illness or before a recurrence, patients frequently feel odynophagia (sore throat) or pharyngitis, which may be related to the infectious risk signal that activates TLRs and causes inflammation.

Cytokines:

There are specific danger signals, such as pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) which are likely the trigger for the pro-inflammatory cascade to begin. These danger signals are delivered to neutrophils and macrophages by particular Toll-like receptors (TLRs), which then trigger particular inflammasomes, most likely NACHT, LRR, and PYD domains-containing protein 3 (NLRP3), activating caspases and producing excessive amounts of active IL-1.(48-51). This process, which appears to be crucial to the pathogenesis of AOSD, causes a significant activation of innate immune cells and the overproduction of a number of pro-inflammatory cytokines, including as IL-6, IL-8, IL-17, IL-18, and TNF(48-51).An enhanced inflammatory response, often known as the cytokine "burst" or "storm," is caused by a number of active variables. Advanced glycation end products (AGEs) and several alarmins, such as the S100 proteins (with S100A12 appearing to be more specific to SOJIA), are implicated in these processes in addition to IL-1 itself, which confers retrograde activation of macrophages and neutrophils(49,51-55) In addition to amplification mechanisms, deficiencies or failures in regulatory or anti-inflammatory mechanisms, such as a lack of regulatory T cells or natural killer cells, a lack of IL-10 production, a lack of lipid mediator clearance, a lack of production of soluble receptors of AGEs (sRAGEs), or a lack of production of other resolution-associated molecular patterns (RAMPs), may contribute to the pathogenesis of autoinflammatory diseases.(56-59)



DIAGNOSIS:

The diagnosis of AOSD is still difficult for clinicians to make because there aren't any clear clinical symptoms or test indicators. Research and clinical studies have only confirmed two sets of diagnostic criteria. The criteria published in 1992 by Yamaguchi et al. (60), with a sensitivity of 96.3%, specificity of 98.2%, positive predictive value (PPV) of 94.6%, and negative predictive value (NPV) of 99.3%, is the one that is most frequently employed. The disadvantage of this approach is that it requires thorough exclusion of infections, cancerous tumours, and other connective tissue illnesses.The other is the Fautrel criteria, which has a sensitivity of 87.0%, specificity of 97.8%, PPV of 88.7%, and NPV of 97.5%.(6,61)

Yamaguchi criteria.	Fautrel criteria.
Major criteria	
Arthralgia lasting 2 weeks or more.	Arthralgia
Fever ≥ 39°C lasting 1 week or more	Spiking fever ≥39°C
Typical skin rash: maculopapular, non-pruritic, salmon-pink rash with concomitant fever spikes	Transient erythema
WBC ≥ 15 x 109 (N%>80%).	Pharyngitis, Neutrophil polymorphonuclear proportion (PMN) ≥ 80 % ; GF proportion ≤ 20%
Minor criteria	
Pharyngitis or sore throat	Typical Rash
Lymphadenopathy and/or. splenomegaly	WBC ≥ 10 x 109
Liver enzyme abnormalities (aminotransferases)	
ANA and RF:(-)	
Diagnosis	
At least five criteria, including two major criteria and no exclusion criteria (Absence of infection, malignant diseases, inflammatory disease)	Four major criteria or three major criteria and two minor criteria

TREATMENT

Before making a diagnosis of AOSD, it is necessary to exclude other disorders because the pathogenic mechanism is still unknown. Additionally, the majority of the treatment is empirical and is based on isolated cases, retrospective case studies, and tiny clinical trials. Addressing symptoms and reducing inflammation are the main goals of its treatment. Before choosing an effective therapy approach for a specific AOSD patient, some researchers stress the significance of taking into account the disease phase, primary clinical symptoms, and likely consequences(22,62) The two main types of treatment for AOSD are traditional treatment and biological treatment.

***Traditional therapies*:**

Nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, and disease-modifying antirheumatic medicines (DMARDs) are frequently used in classical traditional therapy. NSAIDs and corticosteroids are regarded as first-line treatments for AOSD.(7,18)

NSAIDs are typically prescribed to mild to moderately ill patients, and in less than 20% of such cases do fever and musculoskeletal symptoms go away.(18,22) Notably, reckless use of NSAIDS can result in serious side effects. For instance, excessive doses of indomethacin and aspirin can cause fulminant liver failure when the transaminase level is high(18).

About 60–70% of patients respond well to this treatment with corticosteroids, especially those with systemic symptoms, which are frequently utilised to decrease inflammatory reactions.

Clinically, corticosteroids are often started at a dosage of 0.5 mg to 1 mg/kg/day; however, starting prednisone at a dose of at least 0.8 mg/kg/day may lead to faster symptom relief and reduced relapse than starting at lower dosages. (63,64)

Intravenous high-dose corticosteroids might be considered if serious problems like macrophage activation syndrome (MAS) develop. The dosage of corticosteroids should be decreased gradually when clinical symptoms have subsided and test results have returned to normal. However, there are some negative side effects. Cushing syndrome, osteoporosis, and aseptic osteonecrosis have all been observed, in addition to 40–45% of individuals acquiring steroid dependency.(63,65)

For AOSD patients who do not respond to or are unable to tolerate first-line medication, DMARDs such methotrexate (MTX), cyclosporin A (CsA), and leflunomide are second-line therapies. The most popular DMARD used to treat this illness is MTX. According to a retrospective analysis of 26 AOSD patients, 23 patients responded to MTX at a dosage of 7.5–17.5 mg/week, with no difference between those who had extra-articular symptoms and those who did not, and 18 of them obtained complete remission(66). However, because MTX is hepatotoxic, it is important to monitor liver function while using it.

Colchicine:

Colchicine is a traditional, affordable, and easily accessible anti-inflammatory medication that is frequently used in autoinflammatory illnesses such familial Mediterranean fever (FMF) and gouty arthritis. It works by inhibiting the NLRP3 inflammasome, caspase-1 activation, and neutrophil recruitment(67,68,69). Colchicine, either alone or in combination, has recently been discovered by an increasing number of clinical specialists to be highly effective in the treatment of refractory AOSD. An AOSD case with pulmonary tuberculosis that Shi and Rao described was successfully treated with a 2-month regimen of 0.5 mg/bid per day of colchicine, leading to disease remission without recurrence(70).There have also been reports of AOSD patients who have MEFV gene mutations responding well to colchicine treatment(71). Colchicine has also demonstrated remarkable efficacy when used in conjunction with NSAIDs and immunosuppressive medications.(72,73)

TNF-α inhibitors:

The three most popular TNF-α inhibitorscurrently used in clinics are infliximab, etanercept, and adalimumab.They are more effective at treating the chronic articular pattern than IL-1 and IL-6 inhibitors, but less effective when it comes to suppressing systemic symptoms.The findings demonstrated that all patients' clinical symptoms, including fever, arthralgias, skin rashes, myalgias, and hepatosplenomegaly, resolved after receiving 3-5 mg/kg of infliximab on weeks 0, 2, and 6. All clinical manifestations and laboratory markers were discovered to be stable and normal after three cycles of infliximab treatment (74).

Etanercept in the treatment of AOSD was the subject of a paper released a year later. 12 AOSD patients with active arthritis who were resistant to DMARDs were treated with 25 mg of etanercept twice a week for six months, according to research. With the exception of two cases where patients withdrew due to a flare-up of their condition, all other patients experienced positive outcomes.(75)

IL-1β inhibitors

It is believed that focusing targeted therapy on the pro-inflammatory cytokine IL-1 has the most chance of having a therapeutic effect since it plays a significant role in the immunopathogenesis of AOSD**.**Rilonacept, canakinumab, and anakinra are now the most often utilised biologics in AOSD.

IL-18 inhibition

Tadekinig alfa (recombinant IL-18BP) has been the IL-18 inhibitor utilised in AOSD.Tadekinig alfa dosages of 80 mg or 160 mg were administered three times a week to patients, and after three weeks, over 50% of patients experienced fever remission and > 50% reductions in CRP readings from baseline after 3 weeks(76).IL-18 and IL-18BP are still effective biological treatment targets for

AOSD, despite the limited data. Going forward, additional nationwide multicenter clinical trials with bigger sample sizes are required.

IL-6 inhibitor

Tocilizumab can be given intravenously biweekly or monthly and has a rather lengthy half-life. Early case studies of the use of TCZ in AOSD indicated that inflammatory markers like CRP, SAA, and ESR quickly returned to normal and that both systemic and joint symptoms improved.(77-80)

Other treatments

Janus kinase (JAK) inhibitors baricitinib and tofacitinib have also been used to treat AOSD, although further research is needed to confirm their effectiveness and safety(81,82). Rituximab, a monoclonal anti-CD20 antibody that targets B cells, has been used successfully in refractory AOSD patients, according to reports (83,84,85).Additionally, it was observed that intravenous immunoglobulin (IvIg) was a successful and well-tolerated treatment for AOSD patients.(86)

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