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REVIEW ON ACUTE ONSET STILL DISEASE

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INTRODUCTION

Adult onset Still's disease (AOSD) is a rare inflammatory disorder that affects the entire body (systemic disease). The cause of the disorder is unknown (idiopathic). Still's disease was first described by an English physician, Sir George Frederic Still, who published in 1897 his monograph, On a Form of Chronic Joint Disease in Children, describing 22 children with signs and symptoms of the disease entity currently known as systemic onset juvenile idiopathic arthritis. In 1971, Eric Bywaters described 14 adults with similar presentation with systemic onset juvenile idiopathic arthritis.[1] Affected individuals may develop episodes of high, spiking fevers, a pink or salmon colored rash, joint pain, muscle pain, a sore throat and other symptoms associated with systemic inflammatory disease. The specific symptoms and frequency of episodes vary from one person to another and the progression of the disorder is difficult to predict. In some individuals, The disorder appears suddenly, disappears almost as quickly and may not return. In other people, adult onset Still's disease is a chronic, potentially disabling, condition. Various medications are used to treat individuals with adult onset Still's disease, affected individuals may respond to therapy differently. Adult onset Still's disease is the adult form of systemic juvenile rheumatoid arthritis (juvenile Still's disease). Most individuals with adult onset Still's disease develop some combination of the symptoms normally associated with systemic inflammatory disease.[2] Such symptoms include a spiking fever greater than 102.2 degrees Fahrenheit (39

degrees Celsius), joint pain (arthralgia) and inflammation (arthritis), muscle pain (myalgia), and a skin rash. The disorders are name after a British physician who first described systemic juvenile rheumatoid arthritis in the medical literature in 1896. The term "adult Still's disease" was first used in the medial literature in 1971, but cases that fit the description of the disorder appear in the medical literature as early as the late 1800s.[4] The goal of our paper is to summarize the current state of knowledge on the pathogenesis, diagnosis, classification, biomarkers and complications of AoSD, as well as the treatment strategy at each stage of the disease course.

1. Epidemiology

AOSD has a prevalence estimated at less than one case per 100,000 people.[5] By definition, AOSD affects patients older than 16 years old. Females appear to be more frequently affected than males.[1] Initially, the disease was characterized as affecting only young adults (that is, 16–35 years of age1); however, other series have identified cases in adults >35 years old and even in people >60 years old. The sex ratio is almost balanced, with only a slight female predominance.[5]

2. Pathophysiology

The etiology of AOSD is still unclear, while there is evidence that various mechanisms contribute to the pathogenesis of AOSD, mainly including genetic susceptibility, infectious triggers, activation of inflammation, and deficient resolution of inflammation. AOSD is categorized as a multigenic disorder. Familial trend has not been reported for AOSD yet, but some studies have found that genetic susceptibility and polymorphisms were associated with AOSD. Associations of AOSD patients and human leucocyte antigen (HLA) antigens, including HLA-Bw35 (first described), -B17, -B18, -B35, -DR2, -DR4, -DR5, -DQ1, -DRw6, -DRB1, and -DQB1 have been described in different ethnic groups.[6] Numerous infective agents have been postulated based on concurrent elevation of serology markers, for example Epstein-Barr virus, parvovirus B19, cytomegalovirus, human herpes virus, human immunodeficiency virus, coxsackie virus, mumps, rubella, echovirus, hepatitis A, B, and C viruses, campylobacter jejuni, chlamydia pneumoniae, echovirus, adenovirus, influenza virus, parainfluenza virus and Mycoplasma pneumonia.[6]

Neutrophil and macrophage activation remains a hallmark of AOSD, and is mediated by TNF-α, IL-1, interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-18 (IL-18). Over the past decade, the potential role of T-helper (Th) cells in the pathogenesis of AOSD has been

emerging. Chen et al found higher interferon-γ (IFNγ)-producing Th cells and higher Th1/Th2 ratios in the peripheral blood of AOSD patients compared with healthy controls, and these correlated with the clinical activity score and serum IL-18 levels in patients with AOSD10. Increased ratio of Th1/Th2 cytokine transcripts were also seen in the biopsy specimens of evanescent rash and synovitis from patients with AOSD. With treatment, clinical remission was associated with a marked decrease in the proportion of Th1 cells.

Th17 cells have also recently been implicated in the pathogenesis of AOSD. The frequencies of circulating Th17 cells positively correlated with the activity score, serum ferritin levels and serum levels of IL-1b, IL-6, IL-17, IL-18, IL-21 and IL-23 in AOSD patients.[6]

Many cytokines have been implicated in the pathogenesis of AOSD, including TNF-α14, IL1β15, soluble IL-2 receptor (sIL-2R)16, IL-616, IL816, IL-1717 and IL-1818. Of interest is that local expression of IL-18 by CD68+ liver macrophages is markedly increased in the liver parenchyma of AOSD patients with active hepatitis.[7] IL-18 levels were also significantly higher in those with active disease and correlated with serum ferritin levels and neutrophil counts. Interestingly, gene -607 (C/A) IL-18 promoter polymorphisms present in Chinese patients are associated with lower IL-18 levels.[8] This could possibly account for the much lower incidence of transaminitis observed in our patient cohort.

Potentially useful markers of disease activity and severity include CD6422, calprotectin23, macrophage inhibitory factor24, intercellular adhesion molecule-125 and macrophage-colony stimulating factor

3. Clinical Symptoms

Non specific 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. When all conservative treatments fail, practitioners realize they are facing a prolonged febrile illness without an obvious aetiology.[9] The diagnostic journey then begins.

Overall, rheumatic diseases comprise approximately 30% of cases with FUO, with AoSD being the most frequent group. 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. 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.[10]

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.

4. Diagnosis

In the early stages of the disease, diagnosis of AOSD is difficult. Before making a diagnosis of AOSD, other diagnoses including infections such as infectious mononucleosis, malignancies (especially lymphoma), and other rheumatic diseases such as systemic vasculitides should be ruled out. Numerous criteria have been proposed, but the Yamaguchi criteria30 remain the most sensitive. Major criteria include the presence of fever (temperature of greater than 390 C for longer than one week), leukocytosis of greater than 10x109 /L, typical rash and arthralgia of longer than two weeks. Minor criteria include the presence of sore throat, lymphadenopathy, splenomegaly, transaminitis and negative rheumatoid factor or ANA. The classification of AOSD requires the presence of five or more the criteria, of which two must be major criteria.

Table 1: Diagnostic criteria for AOSD (Yamaguchi).

Major criteria	Minor criteria
Fever > 39ºC, > 1 week	Sore throat
Arthralgia/ arthritis > 2 weeks or splenomegaly	Lymphadenopathy
Typical rash	Abnormal LFT
WBC > 10, 000 with > 80% PMNs and RF	Negative ANA

Exclusions: Infections, malignancy, rheumatological diseases. Five criteria with at least two major criteria. ASOD: Adult onset still's disease. WBC: White blood cell, ANA: Antinuclear antibody, RF: Rheumatoid factor, PMN: Polymorphonuclea.

The Yamaguchi criteria (1992), is the most widely used criteria to diagnose AOSD with a 93.5% sensitivity. In this criteria, there are 4 major and 4 minor criteria with 3 exclusion criteria. The 4 major criteria include: arthralgia more than two weeks, fever more than 39°C for more than 1 week, typical rash and leucocytosis for more than 10,000/mm^3 including more than 80% granulocytes. While the 4 minor criteria include: sore throat, lymphadenopathy or splenomegaly, liver dysfunction, negative RF and ANA. Five or more criteria must be met in order to make a diagnosis of AOSD, including 2 or more major criteria, after excluding infections, malignancies or rheumatic diseases.[11]

5. Complication

Important complications that can result from AOSD include liver failure secondary to fulminant hepatitis, DIC, and hemophagocytic syndrome. Fulminant hepatitis requiring molecular absorbent recirculating system (MARS) therapy and liver transplantation is rare and has been described in four patients to date.[12] The onset of fulminant hepatitis could occur either concomitantly at initial diagnosis or as late as three years after the initial diagnosis. All the cases were noted to have hepatic involvement at the time of AOSD diagnosis, and all had massive necrosis on liver histology. Hepatic encephalopathy complicating acute liver failure is secondary to accumulation of toxins such as bilirubin, bile acids, tryptophan, aromatic amino acids and ammonia in the blood. This is due to the inability of hepatocytes to clear these molecules from the circulation. MARS is an extracorporeal liver assistance device that utilises an albumin dialysate for the removal of albumin-bound toxins, and could benefit patients in the interim whilst waiting for an organ to be available for liver transplant.

Hemophagocytic syndrome is a rare but lifethreatening complication of AOSD. Prevalence of hemophagocytic syndrome in AOSD has been reported as 12%44. It is also known as "hemophagocytic lymphohistiocytosis" or "macrophage activation syndrome". Hemophagocytic syndrome is a clinicopathological syndrome characterised by hyperpyrexia, hepatosplenomegaly, transaminitis and elevated serum ferritin levels, all of which are also features of AOSD. Distinguishing features include that of decreased ESR and cytopenias, as compared to a raised ESR and leukocytosis which is usually present in AOSD flares.

Neuropsychiatric manifestations are also more common in hemophagocytic syndrome compared to AOSD, and include coma, seizures, meningism, mood disorders, delirium, psychosis and cognitive dysfunction. Histology is of utmost importance to look for the presence of hemophagocytes in the bone marrow trephine, as well as hemophagocytes in organs involved, such as the liver, spleen and lymph nodes. However, it is important to note that absence of hemophagocytes can occur in up to 20% of initial bone marrow specimens.[13]

6. Treatment

Treatment of AOSD is based largely on observational studies and retrospective analysis due to its rarity. To achieve satisfactory control of the disease, many physicians offer their patients disease modifying antirheumatic drugs (DMARDs) such as methotrexate, ciclosporin or azathioprine, although there is no robust evidence to support this practice.

6.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

The risk/benefit ratio being unfavorable, NSAIDs should no longer be considered as a first line treatment in AOSD but rather a supportive treatment during the diagnostic process and be reservedfor the early reminiscences of the disease whenever corticosteroids and disease-modifying antirheumatic drugs (DMARDs) prove insufficient.[17] Here, high-dose indomethacin (150–250 mg/day) should be used first.

6.2 Corticosteroids

Corticosteroids are effective in controlling the disease in about 65%of patients.[18,19] Their efficacy is greater in the systemic pattern of AOSD. Based on retrospective case series, the initial dosage ranged from 0.5 to 1 mg/kg/day. Patients with serious visceral involvementcould achieve a quick response with intravenous infusion of high-dose methylprednisolone. The response to corticosteroids is often quick: itoccurs within a couple of hours or a few days. The tapering begins usually after 4 to 6 weeks. Kong et al. have reportedthat patients treated with high prednisone dosage (≥40 mg, 0.8 mg/kg)achieved quicker remissions and had less relapses than those who re-ceived a lower dosage[88], which is consistent with the recent findings of Kim et al. Furthermore, incomplete-responder patients to a daily single dose of prednisone could achieve remission with multiple daily doses of prednisone or dexamethasone.[20]

6.3. Methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs)

While few data argue for a beneficial use of hydroxychloroquine in AOSD [19], methotrexate remains the most used DMARD in this disease, especially for its steroid-sparing effect. In 1999, Fautrel et al. reported on low-dose methotrexate (7.5–17.5 mg/week) in 26 steroid-dependent patients. Twenty-three (88%) patients achieved a partial remission and 18 (69%) a complete remission. Eleven patients (39%) stopped corticosteroids whereas the mean daily prednisone intake was decreased by 21.5 mg (i.e., 69%). he effect of methotrexate is the same in systemic and in chronic articular AOSD[18]; it allows controlling the disease in 40% to 70% of steroid-dependent AOSD patients. Thus, methotrexate should be added to prednisone when the latter fails to control the disease or in case of steroiddependence. The presence of liver enzyme abnormalities does not contraindicate methotrexate prescription, but a close biological monitoring is necessary.

6.4. Intravenous immunoglobulins (IVIG)

IVIG were significantly more prescribed in non-monocyclic, complicated and steroid-dependent AOSD although no data are available to support this choice. IVIG have no consequence on the course and prognosis of AOSD. Their corticosteroid-sparing ability remains to be determined. However, it may be worth to use IVIG in life-threatening manifestations as reported in RHL.[21]

6.5. Biologic agents

A growing body of evidence supports the efficacy of several biologic agents in the treatment of corticosteroid- and DMARD-refractory AOSD.

6.5.1. TNFα-blockers

The first open-label prospective trial of etanercept, a recombinant form of the human 75-kd TNF receptor fusion protein, in 12 refractory chronic polyarthritis was published in 2002.[22] AOSD reported impressive results with infliximab (3–5 mg/kg at weeks 0, 2, 6 and then once every 6– 8 weeks), a chimeric monoclonal antibody that binds to soluble TNFα and inhibits the interaction with its cellular receptors. Infliximab had a marked and rapid efficacy on both systemic and articular symptoms and also a steroid-sparing effect. In summary, TNFα-blockers may be interesting in chronic polyarticular refractory AOSD probably more than in the systemic patterns of the disease. Although a head-to-head comparison is not available, infliximab may be more effective than etanercept; it induced more remissions. Unfortunately,

the efficacy of TNFα-blockers seems to be limited in time and switching from one to another is useful in about 50% of cases.[23]

6.5.2. IL-1β antagonists

Anakinra is a recombinant receptor antagonist of IL-1 used in cryopyrin-associated periodic syndromes and other autoinflammatory diseases.[24,25] Its efficacy in AOSD (100 mg daily subcutaneous injection) supported the pivotal role of IL-1β in the pathogenesis of the disease.

6.5.3. IL-6 antagonists

IL-6 is markedly elevated in active AOSD and was considered as a suitable target in the treatment of refractory AOSD.[26] A few isolated reports have shown promising results with tocilizumab, a humanized anti-IL-6 receptor antibody that blocks membrane-bound and soluble IL-6 receptors in steroid-, DMARD-, TNFα blocker- and even cyclosporine-refractory AOSD.

7. CONCLUSION

A diagnosis of AOSD should be kept in mind in case of pyrexia of unknown origin particularly in a patient who presents with high-grade intermittent fever, polyarthritis and skin rash of more than two weeks duration. However, the patient should be extensively evaluated to rule out other differentials of AOSD like acute or chronic infections, autoimmune disorders, vasculitis and malignant disorders. Serum ferritin values can be powerful adjuncts in making the diagnosis of AOSD[12], where they are usually higher than other inflammatory diseases. We present this case of ASD to enlighten the difficulties concerning the diagnosis and the need of more accurate classification criteria. The lack of high sensibility methods to recognize ASD delays the diagnosis, therefore comprising the correct treatment to improve the outcome.

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