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"Adult-onset Still's disease: a review"

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder characterised by high spiking fever, an evanescent salmon-pink rash and arthritis, frequently accompanied by sore throat, myalgias, lymphadenopathies, splenomegaly and neutrophilic leukocytosis. Aetiology is still unknown, however it seems that an important role is played by various infectious agents, which would act as triggers in genetically predisposed hosts. Diagnosis is a clinical one and may be lengthy because it requires exclusion of infectious neoplasms, including malignant lymphomas and leukaemias, and other autoimmune diseases. Different diagnostic or classification criteria have been proposed, but not definitely accepted. There are no specific laboratory tests for AOSD, but they reflect the systemic inflammation: the ESR is consistently high, while the rheumatoid factors and antinuclear antibodies are negative. High serum ferritin levels associated with a low fraction of its glycosylated component are assessed as useful diagnostic and disease activity markers. The clinical course can be divided into three main patterns with different prognoses: self-limited or monophasic, intermittent or polycyclic systemic and chronic articular pattern.

Therapy includes non-steroidal anti-inflammatory drugs, corticosteroids and disease modifying anti-rheumatic drugs: biological agents have recently been introduced and they seem to be very promising not only for the treatment but also for understanding the pathogenic mechanisms underlying the disease.

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown aetiology, characterised by spiking fever, usually exceeding 39° C, an evanescent salmon-pink rash, arthritis and multiorgan involvement [1,2]. The disorder owes its name to Sir George Frederick Still, who, in 1897, described twenty-two children with symptoms consistent with what is currently known as systemic onset juvenile idiopathic arthritis [3]. AOSD was established as an autonomous disease entity almost a century later, when Eric Bywaters described 14 adults patients presenting symptoms similar to those seen in paediatric Still's disease [4].

Epidemiology

Nowadays there is no agreement on the incidence and prevalence of the disease in different populations: AOSD occurs worldwide and women barely seem to be affected more often than men. AOSD usually affects young people, with 75% of the cases reporting disease onset between 16 and 35 years of age [5]. Nevertheless, onset of AOSD after the age of 60 has been described in some cases [6]. The incidence in the Brittany and Loire regions of France has been assessed at 0.16 per 100,000 persons. The mean age of the study population was 36 years, with two peaks of distribution respectively at 15-25 and 36-45 years [7]. In a Dutch study of 45 patients, women were 60% and the median age of presentation was 25 years (range 16 to 65 years), with 27% of the patients showing onset of symptoms after the age of 35 [8]. An epidemiologic analysis from Japan evaluated the incidence amongst men at 0.22 per 100,000 inhabitants and at 0.34 per 100,000 amongst women [9].

Etiopathogenesis

More than a century ago, Sir George Still reported that the aetiology of the disease he had described was "very uncertain" [3]. Uncertainty remains, but some progress has been made. Many studies evaluated a genetic predisposition, linking the disease with HLA antigens. In a retrospective survey of 62 patients from Canada, immunogenetic studies were executed on 55 of them, and HLA B17, B18, B35, and DR2 were significantly associated with AOSD [10]. However, other studies failed to

confirm these claims and reported other associations, including HLA-B14 and DR7, or Bw35 and Cw4, or DR4 and Dw6 [11]. In summary, no consistent results have been obtained from association studies between AOSD and HLA loci. This may result from a real absence of an association or from heterogeneity of the disease. Besides, a familial tendency has not been reported.

A Japanese study evaluated polymorphisms of the IL-18 gene and discovered that the frequency of the diplotype configuration of S01/S01 was significantly higher in AOSD patients than in healthy control subjects [12].

The constellation of abrupt onset, high fever, generalized adenopathy and leukocytosis suggest that AOSD may be a reactive syndrome, where a range of infectious agents trigger the disease in genetically predisposed hosts. These include viruses, such as rubella, CMV, EBV, human herpes virus 6, mumps, echovirus 7, parainfluenza, Coxsackievirus B4, adenovirus, influenza A, HBV, HCV and parvovirus B19, and others microbial agents like Mycoplasma pneumoniae, Chlamydia pneumoniae, Yersinia enterocolitica, Brucella abortus, and Borrelia burgdoferi [1,13].

Even abnormalities in cytokines production may play a pathophysiological role in AOSD. Patients with active, untreated AOSD seem to have a prevalence of Th1 cytokines in peripheral blood and tissues. The Th1 immune response increases production of interleukin (IL)-2, interferon (IFN) γ, and tumour necrosis factor (TNF) α, cytokines that concur in activating macrophages and natural killer (NK) cells, leading B lymphocyte to the production of IgG2a subtype and promoting cell mediated immunity [14].

Serum levels of IL-1, IL-6, IL-18, TNFα, and IFNγ are considerably higher if compared with controls [10,15,16]. High levels of IL-18 are observed in the acute phase of AOSD and this cytokine is considered to be the initiating factor for the inflammatory cascade that includes IFNγ, IL-6, and TNFα. Over production of IL-1, TNFα and IL-6 may account for symptoms observed in the disease and may provide possible therapeutic targets (Table 1).

Unlike rheumatoid arthritis and systemic lupus erythematosus, hormonal influences do not seem to be considered important in AOSD. Pregnancy does not appear to be a risk factor for the

development of the disease and does not increase the risk of relapses. Fetal outcomes are also normal in AOSD.

Clinical features

AOSD may affect several organs and it is worth recalling that the full constellation of symptoms may not be present at onset, and that the evolution to a "typical" case of AOSD may take several weeks or even months.

Fever, usually more than 39°C, is typically quotidian or double quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening, and it is transient [8]. In particular, incidence of fever was estimated at about 95.7% according to five of the largest retrospective studies [8,10,18,19,20]. Fever usually precedes the onset of other manifestations and, in the majority of the cases, it represents the reason for which the patient addresses the physician.

The classic rash is an evanescent, salmon-pink, macular or maculopapular eruption, which usually appears with the fever spike. The rash occurs in about 73% of patients, and it is predominantly found on the proximal limbs and trunk: it can be mildly pruritic (32% of the patients according to a Dutch study), and may be mistaken for a drug allergy. Histological findings show mild perivascular inflammation of the superficial dermis with infiltration of lymphocytes and histiocytes [10,19]. The typical Still's rash has only rarely been seen in other diseases, namely ulcerative colitis, vasculitis and leukemia. However, the presence of atypical cutaneous manifestations does not have to exclude the suspicion of AOSD because several cases with atypical cutaneous manifestations have been described as well (Table 2).

Arthralgia and arthritis occur in the majority of patients with AOSD, with incidences ranging from 64% to 100%. Arthritis may initially be mild, oligoarticular and transient, but it may evolve into a more severe, destructive, symmetrical and polyarticular form [19] over a period of several months., Joints usually involved are knees, wrists, and ankles, even though elbows, hips, shoulders,

metacarpo-phalangeal and metatarso-phalangeal joints, proximal and distal interphalangeal joints and temporo-mandibular joints may be involved too [10,19].

Useful signs for the differential diagnosis with rheumatoid arthritis, typically more frequent in cases of AOSD, are carpal and pericapitate abnormalities: changes in the wrist were described 6 months after disease onset with progressive joint space narrowing, especially in pericapitate or carpo-metacarpal regions: ankylosis may develop after 1.5–3 years [4]. During the initial acute phase of the disease, imaging is not helpful in establishing the diagnosis, but up to 41% of patients show a non erosive intercarpal and carpometacarpal joint space narrowing of the wrist. Joint fluid aspiration often reveals leucocytosis with a predominance of granulocyte polymorphonucleate [10,19].

Generalised myalgias, often rising with fever spikes, are usually found in the majority of patients with incidence ranging from 56% to 84% [8,10,18,19].

Liver abnormalities, such as hepatomegaly, and slight alterations in liver enzymes, are found in approximately 50–75% of patients: it is not possible to exclude that non-steroidal anti-inflammatory drugs (NSAIDs) may play a significant role in these variations [8,20,36].

Splenomegaly has been found in about 44% of patients [8,10,18,19,20]: lymphadenopathies also occur frequently, and lymph node biopsies demonstrate benign polyclonal B cells hyperplasia [37].

Sore throat is a typical sign that can precede fever and other symptoms: it seems to occur early in the disease course in 69% of the patients and it is particularly common in the first month of the disease. Its pathogenesis is still unclear, being attributed both to an inflammation of crico-aritenoid joints and an aseptic non-exudative pharyngitis [38].

Cardiopulmonary involvement like pleuritis (26.4%) or pericarditis (23.8%) have been observed [8,10,18,19,20]. Tamponade, myocarditis [39,40], pulmonary fibrosis, pleural effusions and adult respiratory distress syndrome have also been described [41].

Haematological complications, like pure red cell aplasia, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, have rarely been described: pancytopenia may be due to the haemophagocytic syndrome (HS). It is important to bear in mind that AOSD may begin with an HS

[42]. Furthermore, malignant lymphoma should not only be excluded for diagnosis, but they may be added to the large variety of complications associated with this disease [43]. Finally, cases of disseminated intravascular coagulation that have led to death have rarely been described [40].

The clinical course may be divided into three main patterns, with different prognostic implications:

1. Self limiting or monophasic pattern is characterised by a single disease episode with systemic symptoms like fever, rash, serositis, and organomegaly. Median time to remission is 9 months, and most patients get remission within 1 year [8]. This clinical pattern has a favourable prognosis and serious complications from disease or therapy are uncommon [8].
2. Intermittent or polycyclic systemic pattern is marked by recurrent disease flares, with or without articular symptomatology, interspersed by complete remissions. Subsequent flares become less severe and can occur many years after the first one [10].
3. Chronic articular pattern is characterised by a persistent active disease, dominated by the articular manifestations. Arthritis can be severe and lead to joint destruction [8].

Laboratory

Laboratory test results largely reflect the systemic inflammatory nature of the disease process and none of the findings is specific for AOSD [24]. An increased sedimentation rate is universal and there is no association with rheumatoid factor (RF) or antinuclear antibody (ANA) [1].

Serum ferritin and its glycosylated fraction are currently assessed as a useful diagnostic and disease activity markers. Ferritin is an acute phase protein closely associated with inflammatory processes, inclusive of the mechanisms underlying oxidative stress. Inflammation is linked with increased discharge of ferritin by the histiocyte-macrophage system and from damaged hepatocytes. IL-1β, IL-18, TNFα and IL-6 are cytokines that induce the greatest production of ferritin [44]. Serum ferritin levels in AOSD are usually higher than in other autoimmune or inflammatory diseases, and very high levels, between 3,000 ng/ml and 30,000 ng/ml, are not uncommon (normal range 40–200 ng/ml): even levels higher then 250,000 ng/ml have been reported. A cut off for ferritin levels of

1,000 ng/ml (fivefold the upper normal limit) has been used in many studies to be indicative of AOSD [44]. Besides, disease activity seems to be correlated with serum ferritin levels: these ones often normalise during remission, so that they may also be used as a tool to evaluate response to therapy. A retrospective French study with 49 patients employed a threshold of 1000 ng/ml in serum ferritin as diagnostic marker: a fivefold increase had 80% sensitivity and 41% specificity [45] while, in a Japanese study, sensitivity was 82% and specificity 46% [46].

However, elevated levels of serum ferritin can also be detected in other diseases, such as infections, malignancies, haemophagocytic syndrome and liver diseases like haemochromatosis or Gaucher's disease, so that the usefulness of this marker is limited in clinical practice [44].

A more specific diagnostic tool may be ferritin glycosylated fraction. Glycosylation is a process that protects serum ferritin from proteolytic enzymes. Healthy subjects have 50–80% of serum ferritin glycosylated, whereas this fraction falls to 20–50% in patients with inflammatory diseases. This can be explained both by saturation of glycosylation mechanisms that occurs in inflammatory diseases, and by lower clearance of non-glycosylated proteins by the histiocyte-macrophage system that occurs specifically in AOSD [44]. Glycosylated ferritin persists to low levels in both active phases of disease and in remission, so that it cannot be useful in monitoring the response to treatment.

Combining a fivefold elevation of the serum ferritin concentration with a glycosylate fraction ≤20%, diagnostic specificity enhances to 93%, while sensitivity drops to 43% [45].

Patients frequently have a marked leukocytosis, that is the result of a remarkable neutrophilia, probably secondary to bone marrow granulocyte hyperplasia [10,47]. Fewer than 2% of cases present a diminished white blood cell count, with obvious diagnostic difficulties.

Other haematological alterations include a normocytic normochromic anaemia, with Hb <10 mg/dl, which often associates with increased disease activity, and thrombocytosis [8,10,18].

Liver abnormalities are not uncommon: lactate dehydrogenase, γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, and bilirubin can increase in 75% of patients with AOSD and frequently rise concomitantly with fever and exacerbations of arthritis [5].

Diagnosis and classification criteria

Diagnosis is one of exclusion and the differential diagnosis may be lengthy (Table 3). Infectious, neoplastic and autoimmune diseases can mimic the clinical manifestation of AOSD. Cultures and serological tests can be helpful to exclude infections. Moreover, viral syndromes can be excluded if the symptoms remain over 3 months. The clinical and haematological profile are often sufficient in order to distinguish the disease from lymphomas and leukemias, but sometimes it may be necessary to resort to bone marrow or lymph node biopsy.

Other disorders frequently confused with the AOSD include reactive arthritis and the other spondyloarthropathies, vasculitides, dermatomyositis, haemophagocytic syndrome, Kikuchi's syndrome, Sweet's syndrome and granulomatous disorders [48].

There are several sets of classification criteria for AOSD, all developed from retrospective studies. Masson et al. in 1996 published a comparative study about criteria in AOSD: Yamaguchi's criteria [46] (Table 4) were shown to be by far the most sensitive (93.5%), followed by Cush's [49] (80.6%) and Calabro's [50] (80.6%). Specificity could not be evaluated due to lack of a control group [51]. In 2002, Fautrel et al. proposed a new set of classification criteria that took into consideration glycosylated fraction of serum ferritin and deleted exclusion criteria (Table 5). This set seems to be promising, because it provided a sensitivity of 80.6% and a specificity of 98.5%: however, it has to be validated in different populations before becoming broadly received [20].

Management

The management of AOSD is firstly directed at the acute systemic features of the disease.

Therapeutic strategies have been exclusively empirical, with data on treatment efficacy obtained from case reports, retrospective studies and small case series. The therapy of AOSD includes NSAIDs, glucocorticoids, and other disease modifying anti-rheumatic drugs (DMARDs) to control arthritis and systemic disease [1,4].

NSAIDs are traditionally considered first line therapy for musculoskeletal symptoms and fever, but NSAIDs monotherapy is effective in controlling disease in only 12% of patients [10,18]. Among NSAIDs, indometacin and naproxen seem to be more effective in controlling the disease compared with salicylates [8].

Most patients with AOSD are treated with steroids in the course of the disease, with responses ranging from 76% to 95% [1,6,49]. According to the clinical course of AOSD, patients may need increasing steroid treatment: prednisone is required for 57% of patients with the self limited pattern, for 67% with the intermittent and for 77% with the chronic articular one [10].

There are no prospective, clinically controlled trials about the use of DMARDs in AOSD. In clinical practice, their use should be proposed for cases in which the combination of NSAIDs and steroids fails or in which a tapering of steroid is necessary [1]. Many drugs have been tried in AOSD, including methotrexate (MTX), ciclosporin A, sulfasalazine, hydroxychloroquine, gold, penicillamine, azathioprine, cyclophosphamide, thalidomide, high-dose intravenous immunoglobulins (IVIg), anti TNFα agents, anakinra and rituximab with overall response across studies at approximately 40% [1].

Polyarthritis seems to be particularly susceptible to MTX treatment and it resolves completely in many patients, while the results of MTX on systemic manifestations have not yet been well delineated [1]. A small case series of six patients treated with ciclosporin A reported remission in 66% of cases, and improvement in the other 33% [52].

Treatment with sulfasalazine has been related with high drug toxicity (60% vs 15% of other drugs) [53], so this medication should be avoided in AOSD patients.

High dose intravenous immunoglobulin (IVIg) may be employed to achieve remission and control of early disease before the use of steroids [54].

A prolonged remission of refractory disease was also obtained using CD34-selected autologous peripheral blood stem cell transplantation [55].

Anti-TNFα agents have also been used in uncontrolled studies. In an observational series of 12 patients, addition of etanercept to the pre-study regimens of prednisone, MTX and NSAIDs, leads to an improvement in the number of tender and swollen joints count higher than 63% [56]. Even infliximab, a monoclonal chimeric anti-TNFα antibody, seems to be effective in AOSD: a European study of eight patients attempted to evaluate the long term outcome of patients treated with infliximab after the failure of treatments with corticosteroids and DMARDs: the clinical and serological responses improved rapidly in seven out of eight patients, and five of them went into long term remission even after discontinuation of therapy [1,57].

IL-1 receptor antagonist anakinra has recently emerged as a possible new therapeutic option [58].

As mentioned above, IL-6 represents an important inflammatory cytokine involved in the pathogenesis of AODS, and it may be a promising target, especially with the development of anti-human IL-6 monoclonal antibody tocilizumab [59]. A case of refractory AOSD successfully treated with rituximab has also been described [60].

Table 1 Cytokines involved in the pathophysiology of AOSD [from 17, modified]

Cytokine	***Source***	***Action***	***Effects in AOSD***
IL – 6	Monocyte- macrophages, T cells (Th2), fibroblasts, endothelial cells, keratinocytes	Increasing CRP levels Fever Hyperferritinaemia, hyposideremia Haemostasis abnormalities, Hepatosplenomegaly	High serum levels Often accompanies increased disease activity
IL – 8	Monocyte- macrophages, endothelial cells, fibroblasts	Chemotaxis Organomegaly (?)	High serum levels Not correlated with disease activity
IL – 18	Activated macrophages, Kupffer cells, dendritic cells, keratinocytes	Hepatic cytolysis Joint disease T cell CD 4 activation and IFNγ increasing Macrophagic activation Increasing IgE levels	Very high serum levels May be a diagnostic marker Often accompanies increased disease activity and severity Correlation with the serum ferritin during episodes
TNFα	Macrophages, T (Th1) and NK cells	Fever Cachexia Synovitis, joint destruction Haemostasis abnormalities	High serum levels Not correlated with disease activity
IFNγ	T (Th1) and NK cells	Activation and proliferation of macrophages Haemostasis abnormalities Hepatic cytolysis (IL 18)	High serum levels Not correlated with disease activity
sIL – 2R	Activated T cells	?	High serum levels during relapses Often accompanies increased disease activity
M - CSF	Macrophages, activated T cells, fibroblasts, endothelial cells	Proliferation and differentiation of macrophages Hemophagocytosis (?)	High serum levels during relapses

IL: interleukin; TNF: tumor necrosis factor; IFN: interferon; sIL-2R: soluble IL – 2 receptor ; M – CSF : macrophage – colony stimulating factor.

Table 2. Atypical cutaneous manifestations reported in association with AOSD [from 21, modified]	
Pruritus	Pouchot et al.[10]
Acne-like lesions	Ohta et al.[18]
Cutaneous pain	Ohta et al.[18]
Eczematous lesions	Ohta et al.[18]
Toxic eruptions	Ohta et al.[18]
Alopecia	Rowell et al.[22]
Angioedema	Soy[23]
Erythema chronicum migrans	Saito et al.[24]
Persistent plaques and linear pigmentation	Suzuki et al.[25]
Non-caseating dermal granulomas	Wissler et al.[26]
Fixed plaques	Lubbe et al.[27] - Thien Huong et al.[28] – Kaur et al.[29]
Urticaria	Setterfield et al.[30] - Salaffi et al.[31]
Vesiculopustules on the hands and feet	Lee et al.[32] - Bachmeyer et al.[33]
Generalized peau d'orange-like skin infiltration (diffuse cutaneous mucinosis)	Philips et al.[34]
Persistent generalized erythema	Fujii et al.[35]

Table 3. Differential diagnosis of AOSD [from 48, modified]	
Connective tissue diseases	SLE, mixed connettive tissue disease
Granulomatous disorders	Sarcoidosis, idiopathic granulomatous hepatitis, Crohn's disease
Vasculitis	Polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis
Infections	Viral infection (rubella, parvovirus B19, coxsackie, HBV, EBV, CMV, HIV), subacute bacterial endocarditis, chronic meningococcemia, tuberculosis, syphilis, Lyme disease
Malignancy	Leukemia, lymphoma, angioblastic lymphadenopathy
Other autoinflammatory syndromes	Familial mediterranean fever, criopirinopathies, familial cold autoinflammatory syndrome, hyper-IgD syndrome, PAPA syndrome, TRAPS, Schnitzler's syndrome, PFAPA syndrome, SAPHO syndrome

Table 4. Yamaguchi classification criteria [46]
Major criteria
Fever of at least 39°C, intermittent, lasting 1 week or longer Arthralgias of arthritis, lasting 2 weeks or longer Typical rash Leucocytosis (≥ 10 000/mm^3), with 80 % or more granulocytes
Minor criteria
Sore throat Recent development of significant lymphadenopathy Hepatomegaly or splenomegaly Abnormal liver function Negative tests for antinuclear antibody and rheumatoid factor
Exclusion criteria
Infections Malignancies Other rheumatic diseases
Diagnosis requires 5 or more criteria, 2 of which must be major

Table 5. Classification criteria proposed by Fautrel [20]
Major criteria
Spiking fever ≥ 39° C Arthralgias Transient erythematous rash Sore throat Polymorphonuclear cells ≥ 80% Glycosylated ferritin ≤ 20%
Minor criteria
Maculopapular rash Leucocytosis ≥ 10000/mm^3
Diagnosis requires at least 4 or more major criteria or 3 major + 2 minor criteria

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