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A comprehensive review on adult onset Still's disease

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ABSTRACT

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology usually affecting young adults; spiking fever, arthritis and evanescent rash are commonly observed during the disease. Other frequently observed clinical features include sore throat, hepatomegaly, splenomegaly, lymphadenopathy and serositis. Furthermore, AOSD patients may experience different life-threating complications. Macrophage activation syndrome (MAS) has been reported up to 15% of AOSD patients and it is considered to be the most severe complication of the disease being characterised by high mortality rate. During AOSD, laboratory tests reflect the systemic inflammatory process showing high levels of erythrocyte sedimentation rate and C-reactive protein. In addition, the ferritin levels are typically higher than those observed in other autoimmune, inflammatory, infectious, or neoplastic diseases. Analysing AOSD disease course, 3 different clinical patterns of AOSD have been identified: i. monocyclic pattern, characterised by a systemic single episode; ii. polycyclic pattern, characterised by multiple, ≤ 1 year lasting, flares, alternating with remissions; iii. chronic pattern, related to a persistently active disease with associated polyarthritis. At present, AOSD therapeutic strategy is aimed at targeting pro-inflammatory signs and symptoms, preventing organ damage and life-threating complications and minimising adverse effects of treatment. However, the treatment of AOSD remains largely empirical, lacking controlled clinical trials. High dosages of corticosteroids are usually the first line therapy when the systemic symptoms predominate. Despite this treatment, a large percentage of patients experiences several flares with an evolution toward the chronic disease course and up to 16% of patients die during the follow up, due to AOSD-related complications. On these bases, in the last years, biological agents have been successfully used in refractory cases. Finally, multiple recent lines of evidence have suggested new insights in AOSD pathogenesis unmasking further therapeutic targets. In fact, small molecules, used in experimental MAS models, might represent new therapeutic options.

1. Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology usually affecting young adults. It is typically characterised by spiking fever, arthritis, evanescent rash and hyperferritinemia [1,2]. Still's disease was named after description, in 1897, of 22 children affected by systemic onset juvenile idiopathic arthritis (sIJA), by George Still [3]. Subsequently, in 1971, Eric Bywaters reported 14 adult patients, affected by skin rash, fever, polyarthritis, whose clinical picture strongly resembled the paediatric Still's disease, thus defining AOSD [4]. At present, despite the poor outcome in several patients, AOSD remains a multisystemic disorder of unknown etiology, difficult diagnosis, scarcely studied compared with other rheumatic diseases [1–5]. Due to the relatively low number of studies, the pathogenesis of the disease as well as the optimal management of patients are still not fully elucidated.

In this review, we focus on the pathophysiological steps leading to disease, clinical picture, diagnosis, possible therapeutic strategies of AOSD in the biologics era. We aim to provide useful information for physicians managing these patients.

2. Methods

We designed a comprehensive search of literature on AOSD, by a review of reports published in indexed international journals until up 31/12/2017. We followed proposed guidelines for preparing

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Table 1
Epidemiology of AOSD.

Epidemiology	
Incidence	0.16–0.4/100000 people
Prevalence	1-34 cases/1 million people
Gender distribution	equally distributed
Age of onset	bimodal peak at ages 15–25 and 36–46 years

AOSD, adult onset Still's disease.

biomedical narrative review [6]. MedLine (*via* PubMed) and Embase databases were searched. The bibliography of relevant articles was also hand-searched for identification of other potentially suitable studies.

3. Epidemiology

The available epidemiologic results report AOSD incidence in a range between 0.16 and 0.4/100000 people and estimated prevalence rate between 1 and 34 cases/1 million people (Table 1) [7,8]. Although in some series women seem to be more affected than men, AOSD is considered to be equally distributed between genders [9,10]. AOSD usually affects young people with a bimodal peak at ages 15–25 and 36–46 years [7–10]. However, an old age onset, after the age of 60 years, has been also reported [11–13].

4. Pathogenesis of AOSD

AOSD may be categorised as a multigenic autoinflammatory disorder at the crossroads of autoinflammatory and autoimmune diseases, due to its complex pathogenesis, involving both innate and adaptive immune system [2]. It is generally accepted that unknown factor(s), acting as second hit, may trigger a pathologic process in genetically susceptible patients finally leading to the activation of an aberrant inflammatory response, which is responsible of AOSD development, as summarised in Fig. 1 [1,2,5,11].

4.1. Genetic susceptibility

Although a familial trend has not been reported in AOSD, some genetic studies showed an association of the disease with different susceptibility genes [16–20]. Some associations between AOSD and HLA antigens have been reported, including HLA-B17, -B18, -B35, -DR2 and -DR4 [14]. In addition, AOSD patients show a more frequent association with both HLA-DRB1*12 and -DRB1*15 [15]. Recent papers suggested associations between HLA-Bw35 and HLA-DRB1*14 with a mild, self-limiting disease and association with HLA-DRw6 in patients experiencing joint involvement [16,17]. Furthermore, HLA-DRB1*1501 (DR2) and HLA-DRB1*1201 (DR5) were associated with chronic disease course of AOSD, whereas HLA-DQB1*0602 (DQ1) was more frequently expressed in patients with chronic and systemic AOSD [18]. More recently, polymorphisms in both interleukin (IL)-18 gene and in macrophage migration inhibitory factor (MIF) gene were proposed to contribute to the disease susceptibility [19,20]. Three haplotypes of IL-18, S01, S02 and S03, composed of 13 genetic polymorphisms covering 2 distinct promoter regions, were determined for 28 AOSD patients [19]. The Authors reported that the frequency of diplotype configuration of S01/S01 was significantly higher in AOSD patients and were associated with a higher IL-18 production compared with healthy controls [19]. Furthermore, both −173 G/C single nucleotide polymorphism (rs755622) and −794 $CATT_{5–8}$ repeat (rs5844572) polymorphism in the MIF functional promoter have been reported in AOSD [20]. The frequency of MIF -794 $CATT_5$ allele was increased in patients and was associated with a higher production of MIF compared with healthy controls. In AOSD patients, a high frequency of −794 $CATT_7$ containing MIF genotypes was observed in those with liver dysfunction. Haplotype analysis also revealed a high representation of the MIF haplotype defined by −173*C/-794 $CATT_5$ (C5) in AOSD patients, suggesting that functional promoter polymorphisms in the MIF gene may contribute to the disease susceptibility and/or in the clinical presentation [20]. Finally, the analysis of 4 hereditary periodic fever syndromes genes in AOSD has been recently performed [21]. Authors performed Sanger sequencing and quantitative analysis of all the coding regions of MEFV, TNFRSF1A, MVK and NLRP3 in 40 AOSD patients. Three rare variants in MEFV were identified and were associated with a severe disease

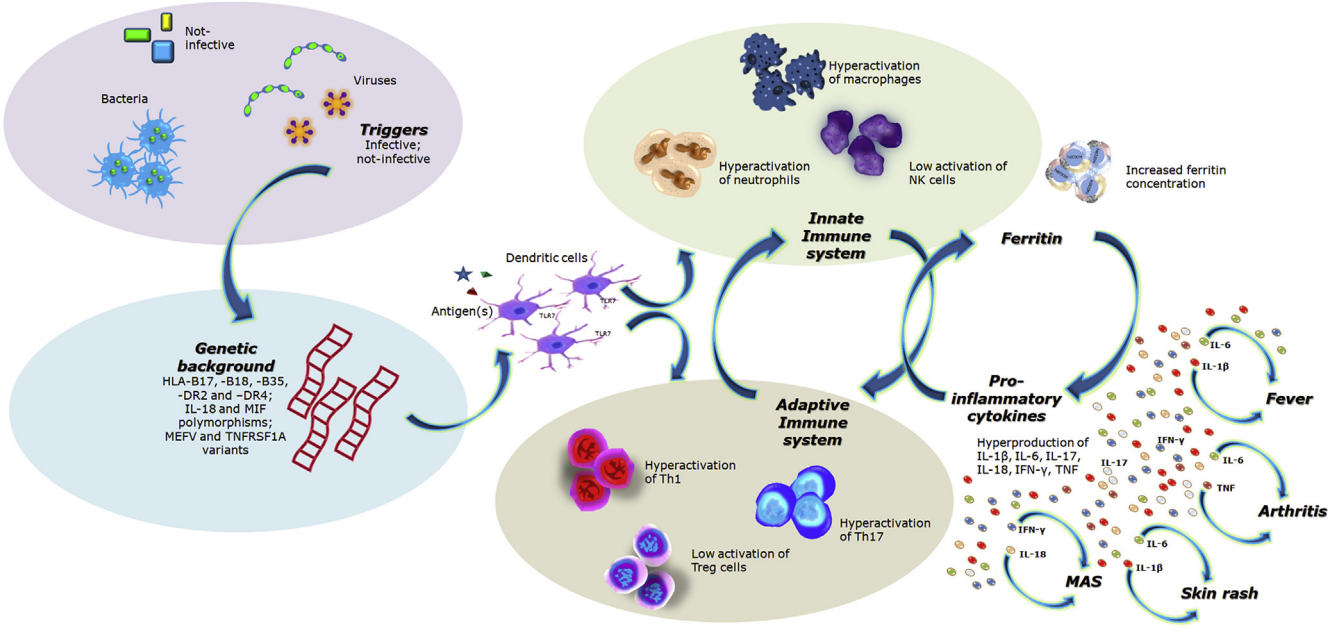

Fig. 1. AOSD may be categorised as a multigenic autoinflammatory disorder at the crossroads of autoinflammatory and autoimmune diseases, due to its complex pathogenesis, involving both innate and adaptive immune system. It is generally accepted that unknown factor(s), acting as second hit, may trigger a pathologic process in genetically susceptible patients finally leading to the activation of an aberrant inflammatory response, which is responsible of AOSD development.