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Systemic juvenile idiopathic arthritis: New insights into pathogenesis and cytokine directed therapies

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A B S T R A C T

Systemic juvenile idiopathic arthritis (sJIA) is considered as a polygenic autoinflammatory disease. The prominent systemic clinical features, the marked elevation of inflammatory markers, and the absence of autoantibodies make this disease very different from the other juvenile idiopathic arthritis (JIA) forms. Innate immune mechanisms appear to play a central role: the over-production of inflammatory cytokines of innate immunity is a typical feature of sJIA. Increased understanding of the role of these cytokines has been translated into therapeutic approaches. Indeed, remarkable results have been observed with interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibitors both in clinical trials and in real life. Other inhibitors of these cytokines will be available in the near future, thereby increasing the therapeutic armamentarium. A better understanding of the pathophysiology of sJIA is still needed to identify IL-1 or IL-6 responders, define a potential window of opportunity for early cytokine blockade, and identify a targeted treatment for macrophage activation syndrome. Additional therapeutic targets are needed for a small proportion of patients who do not respond to either IL-1 or IL-6 inhibition.

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Introduction

Systemic juvenile idiopathic arthritis (sJIA) is classified among the juvenile idiopathic arthritis (JIA) forms, accounting for 10–20% of all JIA. The disease occurs in both genders in equal frequency and does not show preferential age at onset, with a broad peak between 1 and 5 years of age [1]. The prominent systemic clinical features, the pronounced acute phase response, the marked activation of the innate immune system, and the differential effects of anticytokine agents suggest that sJIA should be separated from other forms of JIA and should be considered as a polygenic autoinflammatory disease [2].

Clinical and laboratory features

The clinical features include fever, rash, arthralgia and arthritis, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, and serositis [3]. Arthritis may be absent at onset and appear during disease course and is more often symmetrical and poliarticular [4]. The most common laboratory findings in sJIA include marked elevation of erythrocyte sedimentation rate, C-reactive protein, and neutrophil and platelet counts. Anemia and elevated levels of ferritin and D-dimers are common. In contrast to other forms of JIA, patients with sJIA do not have autoreactive T cells and autoantibody production [5]. Macrophage activation syndrome (MAS) is the most severe potentially life-threatening complication of sJIA and is associated with high morbidity and mortality, with death rate ranging between 10% and 30%. Approximately, 10–15% of patients with sJIA develop overt MAS, while half of them present “subclinical” or “occult” MAS [6,7].

Classification and disease course

According to the presently used International League of Associations for Rheumatology (ILAR) classification criteria, sJIA is clinically defined by quotidian fever (for at least 3 consecutive days) over 2 weeks or more, arthritis, and at least one of the following symptoms: evanescent rash, generalized lymphadenopathy, hepatomegaly and/or splenomegaly, or sierositis [8]. The individual clinical course is variable. Between 40% and 50% of patients with sJIA present a monocyclic (a single phase lasting up to 24 months) or polycyclic (several disease flares separated by months or years of inactive disease) course with spontaneous remission. Approximately 50% of patients have an unremitting course with persistent prominent inflammation and progressive arthritis often involving an increasing number of joints [9]. Chronic arthritis is characterized by early destructive changes in the joints and ankyloses involving cervical spine, wrists, and midfoot [10]. Although arthritis is prominent in many of these patients, the peculiar clinical and laboratory features make this disease very different from the other forms of JIA. Indeed, it has been recently proposed to consider sJIA as an entity separated from JIA [11].

Pathophysiology

Although sJIA is an “old” disease, described by George F Still in 1897, the pathophysiology is still unclear. It is now well known that, similar to autoinflammatory diseases, innate immune mechanisms play a central role in sJIA. The role of the adaptive immune response appears to be limited compared with the other forms of JIA. Genetic studies have pointed to possible associations with polymorphisms in the regulatory sequences of proinflammatory cytokines [12–14]. These results were not confirmed in a very large sJIA population collected within the INCHARGE consortium. A detailed analysis of the HLA locus yielded an association with a class II locus [15]. Interestingly, the consortium also identified several sJIA susceptibility loci, with no intersection with those of other forms of JIA. They concluded that patients with sJIA had a unique genetic architecture, different from other forms of JIA [16]. Consistent with the difference with the other JIA subset, studies of gene expression profiles in blood cells of patients with sJIA reported a dysregulated innate immune response consistent with the overproduction of innate immune factors [17–19] that have been implicated in the pathogenesis of sJIA, such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), and phagocyte-specific S100 proteins [20]. In the past years, the

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