Review

Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis?

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‘Science is the systematic classification of experience’
George Henry Lewes (1817–78), English philosopher, critic, dramatist, scientist.

Juvenile idiopathic arthritis (JIA) is prevalent in about 1 in 1000 children. The earliest formal description of this disease was by Sir George Frederick Still in 1897 [1]. This work was done when he was a registrar at the Hospital for Sick Children, Great Ormond Street, London [2]. In this initial description of 19 patients he identified three patterns of arthritis, one of which came to be known later as Still’s disease [now known as systemic-onset juvenile idiopathic arthritis (SoJIA)]. Over the next few decades it came to be appreciated that one form of arthritis in children is very different and dominated by the presence of systemic manifestations. Over the last two decades several paediatric rheumatologists have come together to classify juvenile arthritis for purposes of better disease identification and research. All along, the systemic form of juvenile arthritis was always recognized as belonging to a distinct group; in fact for several decades (and even now in some countries) the systemic form of juvenile arthritis was referred to as Still’s disease. In this article we will attempt to highlight the reasons why we feel that SoJIA is perhaps not best retained in the company of JIA.

**Epidemiology**

SoJIA constitutes 10–20% of all JIA [3]. However, two-thirds of the mortality seen with JIA is due to SoJIA [4, 5]. We believe that there are more differences between SoJIA and the other JIAs than there are similarities. The incidence of SoJIA is thought to be around 0.4–0.8 per 100 000. In contrast to the 2- to 3-fold female predominance for all juvenile chronic arthritis, there is an almost equal sex incidence in systemic-onset disease. SoJIA may occur at any age from the neonatal period to adolescence. The disease is also seen in adults and is known as adult-onset Still’s disease (AOSD). Although this diagnosis was popularized in 1971 by a report by Sir Eric Bywaters, similar cases had been sporadically reported throughout the last century. The non-arthritic systemic features of SoJIA make the possibility of a viral aetiology attractive, but there is no evidence to substantiate this hypothesis. Although there are some reports to suggest a seasonal distribution of SoJIA, this has not been corroborated by other reports [6–9].

**Clinical presentation**

In contrast to other JIA patients in whom the joint disease usually overshadows the more general symptomatology, in SoJIA extra-articular features such as spiking fevers, hepatosplenomegaly and vasculopathy are most prominent [1, 3, 10]. The typical fleeting pink macular rash, pleurisy, or pericarditis are common. Generalized enlargement of lymph nodes, especially in the axilla, is also typical. These patients often have marked polymorphonuclear leucocytosis and thrombocytosis. The joint involvement, like the rash, may be more marked at the time of the temperature elevation and sometimes may be entirely absent when fever is gone.

The clinical course at later stages of SoJIA is highly variable. Systemic features such as fever, rash and polyserositis tend to subside during the initial months to years of the disease. About half of the children with SoJIA recover almost completely, often after a pattern of oligoarticular disease. The other half continue to show progressive involvement of more and more joints. The joint disease seen in SoJIA is in some respects quite different from the other subtypes of JIA. Hip involvement occurs in almost 50% of the patients, is usually bilateral and is seen in patients with polyarthritis. Mid-foot disease with ankle involvement is seen more often in children with SoJIA than with other subtypes. Cervical spine ankylosis is also more commonly seen in SoJIA compared with the other subtypes of JIA. Early radiographic changes, including destructive changes, are quite characteristic of SoJIA, in one series one-third of patients had erosions and joint space narrowing, 8% had hip subluxation, and one patient developed ankylosis within 2 yr of disease onset [11].

**Pathogenesis**

Several lines of evidence suggest that the distinct clinical features of systemic JIA are associated with unique immunological abnormalities as well. For instance, on a genomic level one distinctive feature of the systemic form is the lack of strong major histocompatibility complex (MHC) Class II associations [12]. This is very different from other clinical forms of JIA in which the contribution of the MHC genes is quite significant. In fact, a recently completed genome-wide screen showed that most of the genetic predisposition to oligo-JIA is contributed by the MHC loci [13]. By contrast, in systemic JIA the most consistently reported genetic effects have been limited mainly to mild contributions from...
cytokine/chemokine gene polymorphisms. Particularly important are associations with polymorphisms involving the promoter elements and genes encoding tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) [14–16] and macrophage migration inhibitory factor (MIF) [17, 18]. The association with the single nucleotide polymorphism in the promoter region of the IL-6 gene is particularly intriguing. Two reported genotypes predispose to higher and lower IL-6 production, respectively. Studies in two different populations showed that the low-responder genotype was less common in systemic-onset juvenile chronic arthritis, especially in those children whose disease onset is under 6 yr of age [15].

The cytokines critical to the perpetuation of the inflammatory process in the systemic form of JIA also appear to be different from those in other JIA subtypes. Indeed, many clinical features of SoJIA including characteristic spiking fevers, skin rash, hypergammaglobulinaemia, hypoalbuminaemia, raised erythrocyte sedimentation rate, and fibrinogen may all be explained by an immune response involving the cytokines IL-1 and IL-6 and TNF-α [19–23]. However, treatment strategies aimed at the neutralization of TNF-α have had rather limited effectiveness in systemic JIA [24, 25]. This is in sharp contrast to an excellent response to this treatment in other clinical forms of the disease, suggesting that the role for TNF-α in the systemic JIA may be more limited. In contrast, the levels of IL-6 expression are much higher in systemic JIA and appear to correlate with the overall clinical activity of the disease and such distinctive clinical features as thrombocytosis, microcytic anaemia, growth retardation and osteopenia [21, 26]. Furthermore, studies of the unique quiescent fever pattern of systemic-onset juvenile chronic arthritis show that IL-6 concentrations rise and fall in concert with the temperature spikes and defervescences [20, 27]. Consistent with these observations, preliminary clinical experience with a biological agent neutralizing IL-6 activity is very promising [28]. Kineret, a biological agent that is aimed at the neutralization of the cytokine IL-1, also shows a great promise [29–31]. Kineret is a soluble IL-1 receptor antagonist similar to the naturally occurring IL1ra. Interestingly, in the first report describing the existence of naturally occurring IL-1 inhibitors (that eventually turned out to be IL1ra), these factors were detected in a urine sample from a febrile patient with systemic JIA [32]. More recently, Banchereau and colleagues presented new data implicating dendritic cells in the pathogenesis of SoJIA [33]. In this report, the expansion of dendritic cells was linked to increased IL-1 activity, thus providing another possible explanation for the high responsiveness to Kineret in this particular clinical group.

Strong association with so-called macrophage activation syndrome (MAS) may provide another clue to the understanding of the distinctive pathogenetic features of the systemic form of JIA. MAS is a severe, potentially life-threatening complication characterized by the excessive activation of differentiated macrophages, resulting in fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, serious liver disease, intravascular coagulation and neurological involvement. MAS is seen usually with SoJIA and very rarely with the other subtypes of JIA.

MAS accounts for the significant morbidity and mortality seen with SoJIA. A variety of triggers have been implicated in the pathogenesis of MAS associated with SoJIA, including viral infections, non-steroidal anti-inflammatory drug therapy, gold salts, sulphasalazine, methotrexate and etanercept [34–36]. MAS in SoJIA can be seen at the initial diagnosis, during a flare of the disease or even when the disease is in remission [37–39]. The exact incidence of this condition in children with SoJIA is not known. In one retrospective study from a tertiary institution, seven of the 103 children diagnosed with SoJIA over a 20-yr period developed MAS (6.7%) [35]. The authors, however, acknowledged that the true incidence of MAS might be much higher since mild cases of MAS are not always diagnosed. Indeed, the existence of mild MAS in patients with SoJIA, often not even requiring specific treatment, is increasingly recognized by many paediatric rheumatologists. Some even suggest that MAS and SoJIA are just ‘different ends of the same spectrum’. The presence of coagulation abnormalities [40] and greatly elevated serum ferritin levels, two distinguishing features of MAS, in the majority of patients with active SoJIA is certainly consistent with this notion. Not surprisingly, the poor definition of what constitutes true MAS has greatly complicated the development of the diagnostic criteria for MAS. It is now increasingly recognized, however, that MAS bears close resemblance to a histiocytic disorder, secondary haemophagocytic lymphohistiocytosis (HLH), a better-defined entity seen in a heterogeneous group of diseases including infections, neoplasms, haematological conditions and autoimmune disorders [41, 42]. In fact, it has been suggested that the term ‘MAS’ should be replaced with ‘autoimmune disease associated reactive HLH (ReHLH)’ [41, 42]. On the other hand, in a recent review of all instances of ReHLH in a setting of an adult hospital, about 40% of the reported patients met the criteria for adult-onset Still’s disease, prompting the authors to question the distinct nature of the two disorders [43]. To address this, studies utilizing new microarray technologies are currently in progress to determine the extent of similarities between SoJIA, MAS and ‘classic’ ReHLH.

The Histiocyte Society has classified histiocytic disorders into three major groups: (1) the dendritic cell-related disorders; (2) the macrophage-related disorders and (3) the malignant disorders [44]. HLH falls into the category of macrophage-related disorders and accounts for most of the patients in this category (Class II histiocytosis). There are two distinct types of HLH: (1) primary HLH, a familial and sporadic form commonly precipitated by viral infection; the familial form of primary HLH (FHHL) is an autosomal recessive disorder shown to be due to a number of different genetic mutations [45], and (2) secondary HLH; this has also been called virus-associated haemophagocytic syndrome (VAHS) and malignancy-associated haemophagocytic syndrome (MAHS) in the literature [46].

The most consistent immunological abnormality reported in FHHL patients, has been impairment of cytotoxic functions. Thus, it has been demonstrated that most FHHL patients have normal numbers of B lymphocytes and normal serum immunoglobulin levels [47]. The majority of these patients have surprisingly normal absolute lymphocyte counts and normal distribution of mature T-cell subsets. In contrast, the function of natural killer (NK) cells is markedly decreased or absent in virtually all patients [47, 48]. Cytotoxic activity of CD8+ cells is also defective. In about 40% of FHHL patients these immunological abnormalities have been linked to mutations in the gene encoding perforin, a protein that mediates the cytotoxic activity of NK and T cells. Other mutations recently implicated in FHHL appear to affect proteins that are involved in the delivery of perforin to the cell surface [49–51]. Because of this, despite normal amounts of perforin, cytotoxic cells fail to induce lysis of target cells. Remarkably, similar immunological abnormalities, i.e. poor NK cell cytolytic activity often associated with abnormal levels of perforin expression, have been reported to distinguish systemic JIA from other clinical forms of childhood arthritis as well [52–54].

The exact mechanisms that would link deficient NK cell and cytotoxic T-lymphocyte functions with expansion of activated macrophages are not clear. Two alternative explanations have been suggested in the literature. One is related to the fact that HLH/MAS patients appear to have diminished ability to control some infections [55, 56]. More specifically, NK cells and cytotoxic T lymphocytes fail to kill infected cells and, thus, to remove the source of antigenic stimulation. Such persistent antigen stimulation leads, in turn, to persistent antigen-driven activation and proliferation of T cells associated with escalating production of cytokines that stimulate macrophages. However, in many cases of MAS attempts to identify an infectious trigger have not been successful, and some episodes appear to be triggered by modifications in drug therapy rather than infection. Furthermore,
the importance of NK cells and perforin-based systems in the down-regulation of the cellular immune responses has been demonstrated in experimental animal systems where immune responses were elicited by anti-CD3 antibodies or staphylococcal toxins instead of viruses [57, 58]. It has been hypothesized by some authors that abnormal cytotoxic cells may fail to provide appropriate apoptotic signals for removal of the antigen-presenting cells and/or activated T cells after infection is cleared. Such T cells may continue to secrete cytokines including interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), two important macrophage activators. Subsequently, the sustained macrophage activation results in tissue infiltration and in the production of high levels of TNF-α, IL-1 and IL-6, which play a major role in the various clinical symptoms and tissue damage. Both hypotheses are consistent with the observations in the animal model of HLH in which neutralization of IFN-γ leads to almost complete abrogation of the syndrome, while neutralization of TNFα, IL-1 or IL-6 provides for only moderate alleviation of the symptoms [59].

A link with defective apoptosis may be further suggested by the association of MAS and Kikuchi’s disease, a necrotizing lymphadenitis, in patients with SoJIA. There are reports of at least nine patients in the literature with SoJIA, AOSD or systemic lupus erythematosus (SLE) with lymph node pathology suggesting Kikuchi’s disease who later went on to develop MAS, and it is possible that these two diseases represent underlying defects in apoptotic pathways and share common pathogenic mechanisms [52, 60–64]. The importance of identifying the underlying defects lies not only in potential early diagnosis of MAS but also in the ability to identify these children at the time of diagnosis of their rheumatic disease, when different management may potentially avert the development of MAS.

Taken together, these observations suggest that the role of the adaptive immune responses in systemic JIA may be rather limited compared with the other clinical forms of the disease. In contrast, the contribution of the innate component of the immune system including the monocyte/macrophage/histiocyte lineage and NK cells, may be much more prominent.

Response to other treatments

SoJIA does respond to steroids and possibly to no other therapeutic agent in the same fashion as patients with other clinical forms of JIA. Even in those children with SoJIA whose systemic disease has gone into remission and who are left with pure articular disease the arthritis is not responsive to the conventional disease-modifying anti-rheumatic drugs as are the other subtypes of JIA. Intra-articular steroids, which are used quite successfully in the management of other subtypes of JIA, appear not to be as effective in SoJIA [65]. Methotrexate, the second-line agent of first choice in JIA, is recognized to be less effective for both the systemic and articular manifestations of SoJIA [66–68]. In controlled studies of biological therapies (etanercept) the SoJIA subgroup of patients had a much poorer response than those with the other subtypes of JIA.

In summary, given the differences between SoJIA and the other types of JIA it is possible that SoJIA is a different disease, like SLE and juvenile dermatomyositis, which has arthritis as one of its clinical features. It is important to note this difference, as it should enable us to look further afield from the current therapeutic strategies and aetopathophysiological mechanisms. It is possible that SoJIA, given the similarities with secondary HLH, may even be a form of histiocytic disorder!

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