Rheumatology 2005;44:1350–1353
Advance Access publication 14 June 2005
doi:10.1093/rheumatology/keh710

Review

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

A. V. Ramanan and A. A. Grom[1]

'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.

KEY WORDS: Systemic-onset JIA, Macrophage activation syndrome, Hemophagocytic lymphohistiocytosis.

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-articular 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 ankylosis 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

Department of Paediatric Rheumatology, North Bristol NHS Trust & Royal National Hospital for Rheumatic Diseases, Bath, UK and [1]William S. Rowe Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Submitted 11 May 2005; revised version accepted 13 May 2005.

Correspondence to: A. V. Ramanan, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK. E-mail: avramanan@hotmail.com

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 quotidian 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 well-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 (FHLH) 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 FHLH patients, has been impairment of cytotoxic functions. Thus, it has been demonstrated that most FHLH 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 FHLH 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 FHLH 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 aetiopathophysiological mechanisms. It is possible that SoJIA, given the similarities with secondary HLH, may even be a form of histiocytic disorder!

AAG is supported by NIH grants AR050828 and AR048928. The other author has declared no conflicts of interest.

References

1. Still GF. On a form of chronic joint disease in children. Med Chir Trans 1897;80:47–59.
2. Bywaters EG. George Frederic Still (1868–1941): his life and work. J Med Biogr 1994;2:125–31.
3. Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol 1998;12:245–71.
4. Wallace CA, Levinson JE. Juvenile rheumatoid arthritis: outcome and treatment for the 1990s. Rheum Dis Clin North Am 1991;17:891–905.
5. Schneider R, Laxer RM. Systemic-onset juvenile idiopathic arthritis. In: Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC, eds, Oxford Textbook of Rheumatology. Oxford: Oxford University Press, 2004:798–809.
6. Lindsley CB. Seasonal variation in systemic onset juvenile rheumatoid arthritis. Arthritis Rheum 1987;30:838–9.
7. Feldman BM, Birdi N, Boone JE *et al*. Seasonal onset of systemic-onset juvenile rheumatoid arthritis. J Pediatr 1996;129:513–18.
8. Oen K, Fast M, Postl B. Epidemiology of juvenile rheumatoid arthritis in Manitoba, Canada, 1975–92: cycles in incidence. J Rheumatol 1995;22:745–50.
9. Uziel Y, Pomeranz A, Brik R *et al*. Seasonal variation in systemic onset juvenile rheumatoid arthritis in Israel. J Rheumatol 1999;26:1187–9.
10. Lomater C, Gerloni V, Gattinara M, Mazzotti J, Cimaz R, Fantini F. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol 2000; 27:491–6.
11. Lang BA, Schneider R, Reilly BJ, Silverman ED, Laxer RM. Radiologic features of systemic onset juvenile rheumatoid arthritis. J Rheumatol 1995;22:168–73.
12. Nepom BG, Glass DN. Juvenile rheumatoid arthritis and HLA: report of the Park City III workshop. J Rheumatol 1992; 33(Suppl):70–4.
13. Thompson SD, Moroldo MB, Guyer L *et al*. A genome-wide scan for juvenile rheumatoid arthritis in affected sibpair families provides evidence of linkage. Arthritis Rheum 2004;50:2920–30.
14. Date Y, Seki N, Kamizono S *et al*. Identification of a genetic risk factor for systemic juvenile rheumatoid arthritis in the 5′-flanking region of the TNFalpha gene and HLA genes. Arthritis Rheum 1999; 42:2577–82.
15. Fishman D, Faulds G, Jeffery R *et al*. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369–76.
16. Ogilvie EM, Fife MS, Thompson SD *et al*. The –174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. Arthritis Rheum 2003;48:3202–6.
17. Donn RP, Shelley E, Ollier WE, Thomson W, British Paediatric Rheumatology Study Group. A novel 5′-flanking region polymorphism of macrophage migration inhibitory factor is associated with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2001; 44:1782–5.
18. De Benedetti F, Meazza C, Vivarelli M *et al*. Functional and prognostic relevance of the –173 polymorphism of the macrophage migration inhibitory factor gene in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2003;48:1398–407.
19. Keul R, Heinrich PC, Muller-Newen G, Muller K, Woo P. A possible role for soluble IL-6 receptor in the pathogenesis of systemic onset juvenile chronic arthritis. Cytokine 1998;10:729–34.
20. Rooney M, David J, Symons J, Di Giovine F, Varsani H, Woo P. Inflammatory cytokine responses in juvenile chronic arthritis. Br J Rheumatol 1995;34:454–60.
21. Pignatti P, Vivarelli M, Meazza C, Rizzolo MG, Martini A, De Benedetti F. Abnormal regulation of interleukin 6 in systemic juvenile idiopathic arthritis. J Rheumatol 2001;28:1670–6.
22. Muzaffer MA, Dayer JM, Feldman BM *et al*. Differences in the profiles of circulating levels of soluble tumor necrosis factor receptors and interleukin 1 receptor antagonist reflect the heterogeneity of the

subgroups of juvenile rheumatoid arthritis. J Rheumatol 2002; 29:1071–8.
23. Mangge H, Kenzian H, Gallistl S *et al*. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum 1995;38:211–20.
24. Quartier P, Taupin P, Bourdeaut F *et al*. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 2003;48:1093–101.
25. Kimura YP, Higgins G. Treatment of systemic JIA with etanercept: a follow-up study. Arthritis Rheum 2002;46:S481.
26. De Benedetti F, Martini A. Is systemic juvenile rheumatoid arthritis an interleukin 6 mediated disease? J Rheumatol 1998;25:203–7.
27. Prieur AM, Roux-Lombard P, Dayer JM. Dynamics of fever and the cytokine network in systemic juvenile arthritis. Rev Rhum Engl Ed 1996;63:163–70.
28. Yokota SM, Imagawa T. Phase II trial of anti-IL-6 receptor antibody (MRA) for children with systemic onset juvenile idiopathic arthritis. Arthritis Rheum 2003;48:S429.
29. Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31:2071–5.
30. Irigoyen PI, Olsen J, Hom C, Ilowite NT. Treatment of systemic onset juvenile rheumatoid arthritis with anakinra. Arthritis Rheum 2004;50:S437.
31. Henrickson M. Efficacy of anakinra in refractory systemic arthritis. Arthritis Rheum 2004;50:S438.
32. Prieur AM, Kaufmann MT, Griscelli C, Dayer JM. Specific interleukin-1 inhibitor in serum and urine of children with systemic juvenile chronic arthritis. Lancet 1987;2:1240–2.
33. Couzin J. Basic and clinical immunology meeting. And action! Dendritic cells go live. Science 2004;305:772–3.
34. Ramanan AV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. J Rheumatol 2003;30:401–3.
35. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421–6.
36. Stephan JL, Kone-Paut I, Galambrun C, Mouy R, Bader-Meunier B, Prieur AM. Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients. Rheumatology 2001;40:1285–92.
37. Davies SV, Dean JD, Wardrop CA *et al*. Epstein-Barr virus-associated haemophagocytic syndrome in a patient with juvenile chronic arthritis. Br J Rheumatol 1994;33:495–7.
38. Cuende E, Vesga JC, Perez LB, Ardanaz MT, Guinea J. Macrophage activation syndrome as the initial manifestation of systemic onset juvenile idiopathic arthritis. Clin Exp Rheumatol 2001;19:764–5.
39. Prahalad S, Bove KE, Dickens D, Lovell DJ, Grom AA. Etanercept in the treatment of macrophage activation syndrome. J Rheumatol 2001;28:2120–4.
40. Bloom BJ, Tucker LB, Miller LC, Schaller JG. Fibrin D-dimer as a marker of disease activity in systemic onset juvenile rheumatoid arthritis. J Rheumatol 1998;25:1620–5.
41. Athreya BH. Is macrophage activation syndrome a new entity? Clin Exp Rheumatol 2002;20:121–3.
42. Ramanan AV, Schneider R. Macrophage activation syndrome—what's in a name! J Rheumatol 2003;30:2513–16.
43. Emmenegger U, Reimers A, Frey U *et al*. Reactive macrophage activation syndrome: a simple screening strategy and its potential in early treatment initiation. Swiss Med Wkly 2002;132:230–6.
44. Favara BE, Feller AC, Pauli M *et al*. Contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 1997;29:157–66.
45. Goransdotter Ericson K, Fadeel B, Nilsson-Ardnor S *et al*. Spectrum of perforin gene mutations in familial hemophagocytic lymphohistiocytosis. Am J Hum Genet 2001;68:590–7.
46. Janka G, Imashuku S, Elinder G, Schneider M, Henter J-I. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:435–44.
47. Egeler RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol 1996;18:340–5.
48. Sullivan KE, Delaat CA, Douglas SD, Filipovich AH. Defective natural killer cell function in patients with hemophagocytic lymphohistiocytosis and in first degree relatives. Pediatr Res 1998;44:465–8.
49. Neeft M, Wieffer M, de Jong AS *et al*. Munc13-4 is an effector of rab27a and controls secretion of lysosomes in hematopoietic cells. Mol Biol Cell 2005;16:731–41.
50. Feldmann J, Callebaut I, Raposo G *et al*. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). Cell 2003;115:461–73.
51. Feldmann J, Le Deist F, Fischer A, de Saint Basile G. [Munc13-4 is essential for cytolytic granule fusion]. Med Sci (Paris) 2004;20:144–6.
52. Grom AA, Villanueva J, Lee S, Goldmuntz EA, Passo MH, Filipovich A. Natural killer cell dysfunction in patients with systemic-onset juvenile rheumatoid arthritis and macrophage activation syndrome. J Pediatr 2003;142:292–6.
53. Wulffraat NM, Rijkers GT, Elst E, Brooimans R, Kuis W. Reduced perforin expression in systemic juvenile idiopathic arthritis is restored by autologous stem-cell transplantation. Rheumatology 2003;42:375–9.
54. Villanueva J, Lee S, Giannini EH *et al*. Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. Arthritis Res Ther 2005;7:10.
55. Arnaout RA. Perforin deficiency: fighting unarmed? Immunol Today 2000;21:592 (author reply 593–4).
56. Arico M, Danesino C, Pende D, Moretta L. Pathogenesis of haemophagocytic lymphohistiocytosis. Br J Haematol 2001; 114:761–9.
57. Kagi D, Odermatt B, Mak TW. Homeostatic regulation of CD8+ T cells by perforin. Eur J Immunol 1999;9:3262–72.
58. Stepp SE, Mathew PA, Bennett M, de Saint Basile G, Kumar V. Perforin: more than just an effector molecule. Immunol Today 2000;21:254–6.
59. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood 2004;104:735–43.
60. Ramanan AV, Wynn RF, Kelsey A, Baildam EM. Systemic juvenile idiopathic arthritis, Kikuchi's disease and haemophagocytic lymphohistiocytosis—is there a link? Case report and literature review. Rheumatology 2003;42:596–8.
61. Ohta A, Matsumoto Y, Ohta T, Kaneoka H, Yamaguchi M. Still's disease associated with necrotizing lymphadenitis (Kikuchi's disease): report of 3 cases. J Rheumatol 1988;15:981–3.
62. Oliveira S, Destri UBW, Vasquez LCO, Ferman S, Romano S, Sztajnbok FR. Systemic juvenile idiopathic arthritis associated with Kikuchi's disease. Ann Rheum Dis 2000;59(Suppl):731.
63. Cousin F, Grezard P, Roth B, Balme B, Gregoire-Bardel M, Perrot H. Kikuchi disease associated with Still disease. Int J Dermatol 1999; 38:464–7.
64. Wong KF, Hui PK, Chan JK *et al*. The acute lupus hemophagocytic syndrome. Ann Intern Med 1991;114:387–90.
65. Breit W, Frosch M, Meyer U, Heinecke A, Ganser G. A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol 2000; 27:2696–702.
66. Halle F, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. Clin Exp Rheumatol 1991;9:297–302.
67. Speckmaier M, Findeisen J, Woo P *et al*. Low-dose methotrexate in systemic onset juvenile chronic arthritis. Clin Exp Rheumatol 1989; 7:647–50.
68. Woo P, Southwood TR, Prieur AM *et al*. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849–57.