Review Article

Juvenile chronic arthritis – clinical sub-groups with particular relationship to adult patterns of disease

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Introduction

Although the earliest recognition of chronic arthritis in childhood may possibly be attributable to the artist's canvas (Alarcon-Segovia *et al.*, 1983; Dequecker, 1984), it was George Frederic Still who initially described enough cases to make generalizations suggesting probable sub-groups amongst affected children (Still, 1897). Still also proposed that childhood arthritis formed a distinct disease entity from that affecting adults. There are no absolute diagnostic investigations but classification criteria have evolved (Brewer *et al.*, 1977; Wood, 1978), based variably on joint number, disease course, rheumatoid factor seropositivity and associated clinical features (e.g. rash, fever), into the major sub-groups of pauciarticular, polyarticular (IgM rheumatoid factor positive or negative) and systemic-onset juvenile chronic arthritis (JCA). With the advantage of long-term follow-up studies (Ansell & Wood, 1976; Calabro *et al.*, 1976; Dequecker & Mardjuardi, 1982) and the reappraisal of basic laboratory investigations, e.g. immunogenetic markers, anti-nuclear antibodies (ANA), and IgM rheumatoid factor (RF), it has become apparent that the dichotomy between the paediatric and adult age-groups, suggested by Still, may not be quite so clear-cut.

This review discusses progress in delineation of the sub-groups of JCA with particular emphasis on those conditions having clinical counterparts in the adult.

Systemic onset juvenile chronic arthritis

Systemic onset JCA is a multi-system disease in which patients, in addition to the classic triad of arthritis, fever and rash, frequently exhibit extensive lymphadenopathy and hepatosplenomegaly. Signs and/or

symptoms may indicate cardiac (Svantesson *et al.*, 1983), hepatic (Boone, 1977), cerebral (Jan *et al.*, 1972) and haematological involvement (Silverman *et al.*, 1983; Scott *et al.*, 1985); generalized growth retardation is common (Bernstein *et al.*, 1977). Hypergammaglobulinaemia frequently occurs but ANA and RF are absent.

It may develop at any age; however, the peak age of onset is less than 5 years, affecting either sex with equal frequency. The course of systemic JCA is unpredictable and the response to therapy frequently unsatisfactory. Of patients followed at Taplow the early indicators suggestive of a poorer prognosis have been persistent thrombocytosis and elevated IgA levels after 12 months of disease (Ansell, 1980a). Calabro *et al.* (1977) have suggested that two major sub-groups exist: one with a remitting, cyclic course without destructive synovitis and a second with progressive arthritis.

In our most recent follow-up of patients seen within three months of onset, 50% of those with systemic disease were in remission five years from onset, usually having had one major attack. The severity of residual in the joints varied from slight loss of extension of the wrists to widespread loss of movement at neck, tarsi, knees and elbows. The problem of persistent anteversion of the hips and poor development because of delayed walking due to systemic illness in young children, may cause problems in later life as these hips wear prematurely and cannot always be replaced by standard hip prostheses.

The remainder may have recurrent exacerbations, without ever settling, usually in association with intercurrent infections throughout childhood. It is such patients who show marked stunting of overall growth due to both chronic disease and the use of corticosteroids. These can also show widespread arthritis on poorly or abnormally developed joints. A few, some 5%, will have recurrent acute episodes, usually, but not necessarily, associated with intercurrent infec-

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tion, with months or years between attacks. One of our patients is still getting attacks 30 years from his first one. These last two groups are at particular risk for the late development of amyloidosis. This can lead to renal failure often in early adult life.

An apparently identical clinical disease may develop *de novo* in adult life – adult onset Still's disease (AOSD). Bywaters originally described AOSD in the 1966 Heberden Oration (Bywaters, 1967) since which time there has been an increasing literature on the subject. Medsger & Christy (1976) have proposed as diagnostic criteria: (a) fever greater than 39°C without other known cause; (b) arthritis; (c) negative ANA and RF, and (d) at least two of leukocytosis, rash, serositis, hepatomegaly, splenomegaly or lymphadenopathy.

Many extra-articular features described in systemic JCA have now been reported in AOSD including pericarditis/myocarditis (Bank *et al.*, 1985), hepatic dysfunction (Esdaile *et al.*, 1979), myositis (Schwarzberg *et al.*, 1982) and the development of amyloidosis (Harrington *et al.*, 1981). Although leukocytosis is typical in AOSD, leukopenia can occur (Scopelitis *et al.*, 1984). Of particular interest is the tendency to carpal and/or tarsal ankylosis which, although typical of JCA, is an unusual finding in other adult forms of inflammatory arthritis (Elkon *et al.*, 1982). Initially the prognosis was considered to be favourable in AOSD; however, patients may progress to a severe

destructive polyarthritis as demonstrated in Figure 1.

In contrast to some forms of JCA, a clear-cut immunogenetic (HLA) association has not been firmly established in systemic onset JCA. Increased frequencies of HLA-B8, Bw35, DR4, DR5 and Dw7 (Glass & Litvin, 1980; Miller *et al.*, 1985) have all been reported, the presence of Bw35 possibly relating to more limited joint involvement. Miller *et al.* (1985) demonstrated a significant increase in DR4 by comparing gene and haplotype frequencies of patients to their unaffected family members. We have also found an increase in DR4 (unpublished observation) and are presently examining immunogenetic markers to determine if particular haplotypes or associations will assist in the prediction of disease course; no association with the development of amyloidosis has been noted. Interestingly, despite the clinical similarities of AOSD to systemic onset JCA, different HLA associations have been reported in adult patients – B14, DR7 (Miller *et al.*, 1985) and Bw35, Cw4 (Terkeltaub *et al.*, 1981).

In systemic JCA clinical flares are frequently preceded by viral infections (DeVere-Tyndall *et al.*, 1984); however, the role of viruses in the initial pathogenesis of the disease remains unproven. In AOSD a variety of infectious agents have been implicated in the disease pathogenesis – e.g. mumps (Gordon & Lauter, 1982), rubella (Harth *et al.*, 1979) and yersinia enterocolitica (Colebunders *et al.*, 1984).

If specific aetiological agents can be shown to be associated with AOSD, the investigation of such cases may shed light on the pathogenesis of systemic JCA.

Pauciarticular-onset juvenile chronic arthritis

The association between pauciarticular-onset JCA, chronic iridocyclitis and ANA has been known for over 10 years (Schaller *et al.*, 1974; Petty *et al.*, 1973). Specific HLA associations have also been recognized within this subset of JCA patients. A recent international multi-centre study, reported at the IXth International Histocompatibility Workshop, confirmed that early onset pauciarticular JCA, particularly in children less than 6 years of age at onset, is associated with HLA-A2, DR5 and DRw8 (Ansell & Albert, 1985). No particular haplotypic combinations, including Bf or Gm allotypes, were apparent in connection with these antigens. On-going work in our laboratory has found a possible association with the complement genes for C4A4/C4B2 (Hall *et al.*, 1986), which are present in linkage disequilibrium with Bw39, DRw8. Despite a correlation between ANA positivity and DRw8 and the known association between chronic iridocyclitis and ANA, the multi-centre study failed to detect significant differences in the frequency of DR5 and/or DRw8 in those with iridocyclitis. This is in contrast to previous work demonstrating that not only is DR5 increased in those with eye disease but that specific DR5-bearing haplotypes (Bw44 or Bw35, Cw4) predispose to this complication (Miller *et al.*, 1984). It is anticipated that on-going international collaboration will enable further clarification of these associations.

Within the ANA positive, early onset pauciarticular JCA group, up to 40% of patients may progress to a polyarticular course ('extending pauciarticular') (Venning & Ansell, 1985). An increase in DRw8 is reported in those whose joint distribution remains pauciarticular (Balogh *et al.*, 1982); however, no investigations, including ANA fluorescence patterns or HLA haplotypes, have proved of definite prognostic use in predicting this group of patients. Some ANA-negative 'extending' pauciarticular patients ultimately develop skin manifestations of psoriasis, thus indicating a separate disease entity (Shore & Ansell, 1982), which probably bears its own specific HLA associations.

In adults a sero-negative pauciarticular pattern may occur; this is ANA-negative. There is no evidence, at this stage, that an increased frequency of A2, DR5 or DRw8 present in these patients. Chronic iridocyclitis does not appear to be a typical feature in adults with a pauciarticular joint distribution (Calin & Calin, 1982). It is possible that some of these patients will develop psoriasis later.

Juvenile spondyloarthropathies

The spondyloarthropathies, encompassing ankylosing spondylitis and the arthropathies associated with inflammatory bowel disease, psoriatic arthritis and Reiter's disease (complete or incomplete), may develop during childhood. As these rarely present with back pain in childhood but usually as an asymmetric arthritis and lack pathognomonic radiological abnormalities early in the disease course, the diagnosis of the spondyloarthropathies is difficult during childhood.

Of pauciarticular-onset male patients, particularly in those with an older age at onset (i.e. >9 years), many will subsequently develop ankylosing spondylitis. This clinical observation correlates with the demonstration of HLA-B27 in 90% of the patients and a family history of ankylosing spondylitis in 25% (Ansell, 1978). It is estimated that approximately 10–15% of adult patients with ankylosing spondylitis develop symptomatic disease during childhood (Schaller, 1979). Sacroiliitis, the hallmark of the spondyloarthropathies, is rare at presentation, both clinically and radiologically, in childhood. Peripheral arthritis, predominantly affecting the lower limbs, occurs more frequently in juvenile than adult ankylosing spondylitis. Although often pauciarticular at onset it may spread to six or seven joints often in an asymmetrical fashion. In a series by Marks *et al.* (1982) 77% of juvenile-onset versus 27% adult-onset ankylosing spondylitis patients presented with a peripheral arthropathy. Hip involvement, a relatively uncommon site of initial involvement in non-B27 related disease (Schaller, 1979) and enthesitis, particularly noticeable at the patellae and calcanei (Rosenberg & Petty, 1982), are useful clinical signs in differentiating those children who may ultimately develop into a spondyloarthropathy. Arnett *et al.* (1982) have described a B-27 related subgroup in teenage girls who have rheumatoid-like changes in the hands and neck limitation secondary to apophyseal joint fusion. Although acute iridocyclitis occurred during follow-up of one quarter of the patients in the Taplow series (Ansell, 1978), it is a rare presenting symptom (Calabro, 1983).

As previously stated, the diagnosis of ankylosing spondylitis ultimately requires radiological evidence of sacroiliitis +/- evidence of axial involvement (Bennett & Wood, 1968). In juvenile-onset ankylosing spondylitis, peripheral joint arthritis predates sacroiliitis involvement by an average of 5–6 years (Ansell, 1978; Garcia-Morteo *et al.*, 1983). While on average sacroiliitis was seen some 6 years from peripheral joint presentation, back limitation did not become obvious until 10 years or more and was not necessarily associated with pain. Both limitation of movement and radiological change can occur as late as

30 years from the peripheral arthropathy (Ansell, 1980b). The exact proportion who remain just with fused sacro-iliac joints is not known, nor are the factors which lead to late back problems. From a retrospective study of old patients, probably somewhat selected because of persistent disease, some 15% had active peripheral arthritis and progressive back problems over 25 years. Hip problems are particularly common in this group – while several have developed aortic incompetence. The late development of inflammatory bowel disease was almost 10% fifteen years from presentation of peripheral joints (Ansell, 1980b).

Radiological changes in the spine may not be apparent during the childhood years. The radiological changes that ultimately develop in the thoraco-lumbar spine do not differ, however, from those with adult-onset ankylosing spondylitis (Riley *et al.* 1971). Computed axial tomography appears to delineate early sacro-iliac changes better than standard radiography (Fam *et al.*, 1985); it is feasible, therefore, that advances in such investigational procedures may enable earlier diagnosis. As 8–10% of the 'normal' Caucasian population are HLA-B27 positive, the finding of this immunogenetic marker alone should not be used as a sole diagnostic indicator.

Psoriatic arthritis

Psoriatic arthritis also may not ultimately declare itself until adulthood as periods of up to 15 years may separate the skin and joint manifestations (Shore & Ansell, 1982). Asymmetric joint distribution, isolated dactylitis of fingers or toes, nail pitting and a family history of psoriasis, with or without arthritis, are important clues to diagnosis in children. In a series of 60 patients, 73% had a pauciarticular onset; however, 83% of these ultimately followed a polyarticular pattern of disease which was often particularly resistant to therapy (Shore & Ansell, 1982). In adults, psoriatic arthritis is reported to be associated with HLA-A26, B38, DR4, DRw7 (Murray *et al.*, 1980), B27, DR7 (Armstrong *et al.*, 1983) and Bw39 (McKendry *et al.*, 1984).

In a preliminary study the normal incidence of DR5 in those with pauciarticular onset contrasted with the high incidence in true JCA (Shore *et al.*, 1981). In a more recent series of 49 children with either definite or probable psoriatic arthritis, we have found B27 and DR1 are more prevalent (unpublished observation). The increase in DR1 may reflect linkage disequilibrium with B27; however it is of interest that B27 in juvenile ankylosing spondylitis does not show a similar association with DR1.

Polyarticular-onset juvenile chronic arthritis

Rheumatoid factor positive polyarticular JCA, although constituting the smallest sub-group of JCA patients, behaves similarly to, and is most likely to progress into, adult RA (Ansell, 1980). Subcutaneous nodules, osseous erosions and symmetrical involvement are common and, although rare, rheumatoid vasculitis (Ansell, 1978), Felty's syndrome (Rosenberg *et al.*, 1984) and lung involvement (Lovell *et al.*, 1984) are reported. An increased incidence of HLA-DR4 has been shown in these children, similar to adult series (Clemens *et al.*, 1983). It has been proposed that closely DR4-related D region antigens, LD '40' and Dw4, may be even more directly associated with disease susceptibility in affected children than the DR4 alone (Nepom *et al.*, 1984).

Seronegative polyarthritis may grumble on for many years tending to remit after 10 years or so, but sometimes relapsing in adult life – often after pregnancy. Radiological damage is late in those with a young age of onset, who do well in later life provided joint function has been well maintained. A particularly aggressive form of sero-negative arthritis which can be seen in teenagers and does not seem to relate to psoriasis or ankylosing spondylitis, is currently under study and may be associated with DR4. Overall, although seronegative polyarticular JCA is more common than RF-positive disease, it has not been as extensively investigated in relation to HLA associations. Bardin *et al.* (1985) report an increase in DR1 in seronegative adult RA, particularly in those of younger onset. An increase in DR1 has also been noted in seronegative polyarticular JCA (Arnaiz-Villena *et al.*, 1984). However, as the adult and juvenile forms do not necessarily share similar clinical pictures, this immunogenetic data is presently of uncertain significance in relating the two disease groups. Furthermore, a heterogeneity of clinical sub-groups is probably included within the seronegative polyarticular JCA patients, e.g. psoriatic arthritis and inflammatory bowel disease associated arthropathy without spondylitis.

Conclusion

Systemic-onset, seropositive polyarticular-onset and, to a lesser extent, the seronegative spondyloarthropathies share many clinical similarities between the adult and childhood forms of chronic arthritis. Apart from the seropositive polyarticular arthritis/DR4 and AS/B27 associations, immunogenetic markers differ between the two age-groups in their apparent disease associations. The pathogenetic significance of an individual's immunogenetic profile, as it may relate to disease susceptibility or clinical expression at vary-

ing ages, is unknown. By contrast, pauciarticular-onset JCA complicated by chronic iridocyclitis appears to be a specific paediatric disease without having an adult counterpart. The seronegative polyar-

ticular population may well include a variety of disease sub-groups, some of which possibly relate to the adult form of disease, but for which no serological marker is currently available.

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