

Supplement Review

Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis?

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Chapter summary

The chronic arthropathies of childhood share clinical and pathological features with rheumatoid arthritis (RA) in adults. Both are autoimmune diseases characterized by a destructive arthropathy. Both are likely to be complex genetic traits, with autoantibodies and with a type-1-T-helper-cell cytokine profile in disease tissues. In common with other autoimmune diseases, both have associations and linkage with human leukocyte antigen (HLA) genetic markers. However, there are also important points of distinction outlined in this chapter, which include substantial differences in clinical phenotype. Juvenile rheumatoid arthritis (JRA) is characterized by several subtypes, whereas RA is more homogeneous. There are differences in outcome: adults with RA tend to have a poorer outcome; in JRA, the outcome is more variable and can be predicted by phenotypes at presentation. In addition, patients with RA have a stronger family history of RA although both RA and JRA share an increased frequency of family history of other autoimmune diseases. The genetic markers present to variable degrees in the subtypes of JRA differ quite considerably from those of RA. This is particularly so with respect to HLA.

Keywords: arthritis, classification/diagnosis, juvenile rheumatoid arthritis, rheumatoid

Historical background

Rheumatologists have long known that the common chronic arthropathies of childhood have both similarities and differences from adult-onset rheumatoid arthritis (RA), although it is also recognized that a few patients with typical RA will present in childhood. Arthritis in children is more heterogeneous than RA, and just as in RA, the pathological basis for juvenile arthritis is being explored with molecular techniques. In his 1966 Heberden oration, Professor Eric Bywaters noted among his conclusions that every child has their own disease [1]. This truism is correct, but a great many similarities in pathophysiology between children with the same clinical

phenotypes are increasingly being defined. These features, including genetic markers, are different in many respects from the adult counterparts, although, overall, there are gross similarities (Table 1). This paper explores these similarities and differences in childhood arthritis compared with adult disease.

Classification of inflammatory arthritis in children and adults

The classification of inflammatory arthritis occurring in children and adults provide us some clues about the nature of these diseases. The American College of Rheumatology classification criteria uses the term 'juvenile rheumatoid

Table 1

Similarities and differences between RA and JRA/JIA

Feature	RA	JRA/JIA
Classification criteria	Single disease with different manifestations	Phenotypically and genetically distinct subtypes
Gender	Females > males	Females > males except in systemic arthritis
Age of onset	Puberty plus; peak 4th to 5th decade	Polyarticular: throughout childhood; peak 1–3 years of age Pauciarticular: early childhood; peak 1–2 years of age Systemic: throughout childhood; no peak
Extended multiplex families	Present	Very rare
Family history of other autoimmune disorders	Present	Present
Typical ocular involvement	Keratoconjunctivitis sicca	Chronic anterior uveitis
Prevalence	10/1000	0.86/1000
Ethnic distribution	Reported in all populations	EOPA is rare in non-Caucasians
HLA association	<i>HLA DRB1*0401, 0404, 0101</i> in Caucasians	EOPA: HLA-A2, -DR5, -DR8, - <i>DPB1*0201</i> . (HLA-DR4 is protective) Late pauciarticular: HLA-B27 Polyarticular: HLA-DR1, -DR4
Shared epitope	Defined; amino acid positions 67–74 of third hypervariable region	Not described
Growth/developmental issues	Rare	Common
Pathophysiology	Th1-mediated disease	Th1-mediated disease (Pauciarticular: Also Th2-mediated)
Autoantibodies	IgM RF common	IgM RF rare
Natural history	Majority have long-term disability	Fewer than half have long-term disability

EOPA, early-onset pauciarticular arthritis; HLA, human leukocyte antigen; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; Th, T helper.

arthritis' (JRA), which includes JRA of pauciarticular, polyarticular and systemic onset [2]. The European classification uses the term 'juvenile chronic arthritis' (JCA), which includes polyarticular arthritis, pauciarticular arthritis, systemic arthritis, juvenile ankylosing spondylitis, psoriatic arthritis and arthritis associated with inflammatory bowel disease. The more recent International League Against Rheumatism classification of 'juvenile idiopathic arthritis' (JIA) has seven subsets, including the spondyloarthropathies [3]. The very fact that there are different classification criteria, and each classification scheme has several subtypes, suggests that juvenile arthritis is not a single entity with uniform clinical, laboratory and immunogenetic features. (While we have used the term JRA, the text reflects the different terminology used by the authors cited.) The revised American Rheumatism Association criteria for RA, proposed in 1987, state that patients fulfilling any four of seven criteria fulfill the requirement for RA [4]. The terms 'classic' (or 'definite') RA and 'probable' RA were removed. Thus, RA in adults appears to be a single disease with different manifestations, while patients with one subtype of JRA clearly differ from patients with the other subtypes.

There are, however, similarities between some types of JRA/JIA and adult RA. Cassidy *et al.* studied children referred to the University of Cincinnati between 1958 and 1978 [2]. In all, 10% of all patients with JRA, and 20% of patients with polyarticular onset JRA were positive for rheumatoid factor (RF) by sheep cell agglutination titer. The authors found that those children that were initially RF-positive, or later became RF-positive, were likely to be older, female, more likely to be antinuclear-antibody-positive and have more small-joint involvement of the hands, whether their onset was polyarthritis or oligoarthritis. These children were more likely to have joint erosions and to experience a polyarthritic course. Thus, RF-positive polyarticular JRA is the subtype that most likely represents the occurrence of RA in a child and as such does not differ much from the adult form. This type probably accounts for about 5% of children with chronic arthritis. Systemic onset JRA, the subtype of JRA that resembles an infectious process, is characterized by fever and rash at onset and is accompanied or followed by arthritis. Adult-onset Still's disease is the adult counterpart of systemic onset JRA. The spondyloarthropathies occurring in children

resemble their adult counterparts as well. However, one of the distinct subtypes of inflammatory arthritis in children is pauciarticular JRA, especially those with early-onset pauciarticular arthritis (EOPA). EOPA is distinct not only from RA in adults, but also from the other subtypes of JRA in children. An adult counterpart of EOPA has not been described and this subtype of JRA is unique to childhood.

In addition to classifying of patients into various distinct phenotypic groups, the classification criteria also help to predict long-term outcome, on the basis of the phenotype at onset. A summary of published outcome studies found that over 30% of JRA patients had significant functional limitations after 10 or more years of follow-up [5]. Overall, patients with pauciarticular JRA had better articular outcomes, erosions being seen in 28% in a longitudinal study, versus 45% of patients with systemic JRA and 54% of the patients with polyarticular JRA [5].

However, a recent study by Guillaume *et al.* suggests that oligoarticular-onset JRA is a more severe disease than previously thought. After 6 years of follow-up of 207 patients with oligoarticular JIA, the probability of a polyarticular course was 50%, of joint erosion, 35%, of uveitis, 30% and of remission, 23% [6]. In this study, gender and age at onset were not identified as predictive of a poor articular outcome. A population-based outcome study of JCA from Sweden reported that at onset of the disease, gender is the greatest predictor of disability and that at follow-up, continued disease activity, followed by the presence of IgM-RF, are the greatest predictors of disability [7]. Interestingly, those whose monoarticular or pauciarticular disease extended later to polyarticular disease were as frequently classified into Steinbrocker functional classes II to IV as those who had polyarthritis at onset. In one study, patients with intermittent or persistent systemic JRA had poorer functional outcomes than those with a monocyclic course [8]. Another group reported that a polyarticular pattern and hip involvement at 6 months predicted a poor outcome in patients with systemic-onset JRA [9]. More recently, Zak and Pedersen reported that 37% of patients had active JCA 26 years after onset, 11% were in functional class III or IV and 22% had undergone surgery related to their JCA [10].

Although recent developments in medical and surgical treatments have improved the long-term outcome of patients with RA, an 8-year follow-up study of patients with seropositive RA showed that only 24% of patients had no progression in the radiological destruction of the joints of hands and feet [11]. Disease activity strongly influences functional capacity in RA, even in long-standing disease. After 12 years of follow-up in another study, disease activity was the main determinant of the functional status as measured by the Health Assessment Questionnaire score [12]. Several studies have reported increased

mortality rates in RA patients, with infections, pulmonary and renal disease and gastrointestinal bleeding being the major causes of death [13]. Patients with extra-articular RA had higher mortality rates than not only an age-matched general population, but also than the non-extra-articular RA group in another study [14]. Overall, JRA patients appear to have a better long-term outcome than do patients with RA.

Epidemiology of inflammatory arthritis in children and adults

The prevalence of definite RA among adults in the USA has been estimated to be approximately 10 per 1000, with an overall prevalence of 7 per 1000 for men and 16 per 1000 for women [15]. Thus, RA is a fairly common autoimmune disease occurring in approximately 1% of the adult population in the USA. The prevalence of JRA, however, is considerably lower, estimated to be between 57 to 113 per 100,000 children under the age of 16. The lifetime prevalence of JRA in a Mayo clinic (Rochester, MI, USA) population was 86.1 per 100,000 [16]. The incidence of JRA is estimated to be approximately 10 per 100,000 per year in children under 16 years of age. Thus JRA is a much less frequent autoimmune disease than its adult counterpart. Like RA, both pauciarticular and polyarticular JRA are characterized by a female-to-male ratio greater than 1. Systemic JRA, on the other hand, has no such female predilection. Both RA and JRA have been reported to occur in various populations of the world. While RA does occur in non-Caucasians, at least one type of JRA, EOPA, is relatively absent in non-Caucasians [17]. A meta-analysis of the epidemiology of JRA found that the predominant subtype is polyarticular JRA in Black, East Indian and Canadian aboriginal populations. In contrast, EOPA is the most frequent subtype in Caucasian populations both in Europe and North America [18].

Family history of autoimmune disorders

Patients with RA frequently have a positive family history of RA. In fact, several extended families with RA have been reported and there are many affected sibling pairs with RA. The availability of such affected sibling pairs has been conducive to the performance of at least three genome-wide scans of linkage in RA [19–21]. Although there are studies that report an increased prevalence of inflammatory arthritis among relatives of patients with JRA [22,23], a family history of inflammatory arthritis is less common in children, and extended multiplex pedigrees are extremely rare in JRA. Only about 300 affected sibling pairs with JRA are estimated to be in the USA [24], and about 180 of them have been entered into a Registry at Cincinnati Children's Hospital Medical Center (Cincinnati, OH).

Relatives of patients with RA have an increased prevalence of other autoimmune disorders besides inflammatory arthritis [25,26]. Thomas *et al.* described a significantly

higher prevalence of insulin-dependent diabetes mellitus (IDDM) and autoimmune thyroiditis among first- and second-degree relatives of patients with RA than in patients with degenerative arthritis [25]. Similarly, Lin *et al.* found that 7.8% and 2.8% of first-degree relatives of RA probands had autoimmune thyroid disease and IDDM, respectively, versus prevalences of 1% and 0.35% in the general population [26].

Case reports describe JRA patients with other autoimmune disorders such as type 1 diabetes mellitus, vitiligo, thyroiditis and autoimmune oophoritis. In an epidemiological study, we have shown that the relatives of patients with JRA have an increased prevalence of autoimmunity [27]. Information was collected from interviews of 110 patients with JRA, 23 families of affected sibling pairs and 45 healthy controls. Information was available on more than 1900 relatives. Overall, the relatives of JRA patients had a significantly increased prevalence of autoimmunity. The most frequent autoimmune disorder seen was Hashimoto's thyroiditis. The prevalences of RA among relatives of patients with simplex JRA and controls were not significantly different. Relatives of JRA-affected sibling pairs also had a higher prevalence of autoimmunity than controls. While there were no differences in the overall prevalences of autoimmunity among relatives of simplex and multiplex JRA families, the prevalence of inflammatory arthritis (JRA, ankylosing spondylitis and RA combined) was increased among the relatives of JRA-affected sibling pairs.

Genetic factors

The most extensively studied susceptibility locus for autoimmune disorders is the major histocompatibility complex (MHC) located on chromosome 6p. This region is densely packed with more than 200 genes [28] and several of these are essential to the immune system, including the human leukocyte antigen (HLA) genes. The genes of the MHC in general, and the HLA genes in particular, are highly polymorphic. Studies have consistently shown associations between HLA and several autoimmune diseases, including both RA and JRA. The HLA region is thought to account for half of familial cases of RA [29]. HLA associations are distinct for RA and JRA, demonstrating that the immunogenetic factors involved in susceptibility to these two diseases are indeed different. The class II HLA molecule HLA DR4 is associated with RA and is encoded by *HLA DRB1*0401* and *DRB1*0404* alleles. *HLA DRB1*0101*, which encodes HLA DR1, is also associated with susceptibility to RA in Caucasians. Other HLA DR alleles are associated with disease susceptibility in other ethnic groups.

However, the various HLA alleles that are associated with susceptibility to RA have a common determinant in the third hypervariable region of the DRB1 chain, encompass-

ing the amino acid positions 67–74 [30]. This common region, designated the shared epitope, is thought to play a crucial role in the interaction of the T cells with the peptide HLA complex. Those RF-positive RA patients with severe disease, with erosions and extra-articular features, are more likely to carry two DRB1 susceptibility loci alleles than are patients with milder forms of the disease [31]. Recently de Vries *et al.* studied 167 Caucasian RA patients and 166 controls [32]. They confirmed the association of susceptibility to RA with alleles encoding the susceptibility sequences of the shared epitope. They also showed that some alleles, including *DRB1*07*, **1201*, **1301* and **1501*, showed significant protective effects. Interestingly the protective alleles also shared a third motif in the hypervariable region. Independent homozygosity effects were observed both for susceptibility and for protective alleles. This suggests that amino acid substitutions at position 67–74 of the HLA-DRB1 molecule influences the HLA-associated risk (both susceptibility and protection) of RA.

JRA, like RA, also has associations with HLA. However the different clinical subtypes of JRA themselves differ in their HLA associations. For instance, the class I gene HLA-B27 has consistently been found to contribute risk for pauciarticular JRA, especially among older males. HLA-DR1 and -DR4, class II genes, have been reported to increase the risk for polyarticular JRA. Much as in adults with RA, HLA-DR4 is associated with RF-positive polyarticular disease in older children. Interestingly, this gene might be protective in patients with EOPA. In this subtype, combined class I and II MHC associations are seen. Other MHC-encoded genes such as LMP7 have also been shown to be associated with early-onset JRA [33]. HLA-A2, HLA-DR5, HLA-DR8 and *HLA-DPB1*0201* have all been shown to be associated with JRA by several investigators, and interactions between these alleles yield high odds ratios for EOPA [34–39]. It is possible that in this type of JRA, four individual genes (one HLA-A gene, two HLA-DR or DQ genes and an HLA-DP gene) may be involved [24]. Confirming the associations that have been reported, linkage between pauciarticular JRA and the HLA region has been shown both by using transmission disequilibrium testing in simplex families [40] and by allele sharing among affected sibling pairs [41]. Similarly, linkage between polyarticular JRA and the HLA region has also been shown by allele sharing among affected sibling pairs [41].

One of the unique features of JRA is that there appears to be a window of susceptibility, during which children with predisposing HLA alleles or combination of alleles are maximally susceptible to the development of JRA, suggesting gene–gene and gene–environment interactions [42]. In a study of 680 patients with JRA and 254 ethnically matched, unrelated controls, we used survival analysis to calculate the age by which 50% and 80% of

children with particular HLA alleles and combinations of alleles develop disease. Certain alleles were strongly associated with early susceptibility to pauciarticular JRA, including HLA-A2, -DR8, -DR5 and *-DPB1*0201*. Of the children carrying at least one of these alleles, 50% had disease onset before their third birthday. Among children who carry HLA-A2 and any two HLA-DR alleles (HLA-DR3, -DR5, -DR6, -DR8), the median age at onset of pauciarticular disease was only 2.7 years. Combinations of HLA-A2 and *-DPB1*0201* and one DR allele narrowed the window further to a median age at onset of 2.4 years. Gender strongly influenced the age at which many of the alleles have their effect. These results demonstrate the complex interactions between different HLA susceptibility alleles that influence the age of onset of JRA.

Several non-HLA susceptibility loci have been reported in connection with both RA and JRA. For instance, the macrophage-resistance gene *NRAMP1* regulates activation of macrophages for enhanced expression of tumor necrosis factor (TNF)- α , IL1- β and MHC class II. This gene has been implicated in susceptibility to RA [43]. Associations between *NRAMP1* and RA have been reported both in Caucasian [44] and in Korean populations [45]. Sanjeevi *et al.* showed that allele 3 of the *NRAMP1* gene increased the susceptibility of Latvian patients to JRA, whereas allele 2 conferred protection [46]. Polymorphisms of the genes related to the cytokine network have also been implicated in the pathogenesis of both JRA and RA and these findings have been supported by association studies.

The results of genome-wide scans from RA patients and families, in addition to confirming the linkage between RA and the HLA region, suggest the hypothesis that RA susceptibility loci overlap with loci implicated in other autoimmune disorders. Cornelis *et al.* reported the first genome scan in RA performed on 114 European RA sibling pairs [19]. Linkage was significant only for HLA and nominal for 19 markers in 14 other regions. Four of these regions overlapped loci implicated in IDDM. In a further study of a second set of families, linkage to one region (3q13) was extended significantly. This non-MHC locus could account for 16% of the genetic component of RA. In another genome-wide scan for allele sharing in 309 RA-affected sibling pairs collected in the USA, significant sharing was observed both within and outside the HLA region [20]. This study confirmed the linkage of the HLA locus to RA and revealed a number of non-HLA loci on chromosomes 1, 4, 12, 16 and 17, with the significance of evidence for linkage at $P < 0.005$. Not surprisingly, several of the regions positive for linkage were found to overlap with chromosomal locations implicated in other autoimmune disorders, including systemic lupus erythematosus, psoriasis and inflammatory bowel disease. Myerscough *et al.* tested for linkage and linkage disequilibrium between

IDDM susceptibility loci and RA [47]. Evidence for linkage disequilibrium was found for a microsatellite marker at IDDM8 and two markers at IDDM5. Another genome-wide scan performed on 252 affected sibling pairs with RA from the UK confirmed the significant linkage to the MHC region [21]. In addition, 11 non-HLA regions had suggestive or nominal linkage. Six of these regions had been previously identified in the other genome-wide scans [19,20]. Genome-wide scans are under way in JRA and have not yet been reported.

Clinical features

In general, the arthritis of RA is a symmetric polyarthritis. The metacarpophalangeal and proximal interphalangeal joints are typically involved in RA. Ulnar drift of the metacarpophalangeal joint with volar subluxation is characteristic of longstanding RA, which is accompanied by a radial deviation of the wrist [48]. In JRA, any joint can be affected, but large joints are most frequently involved. Smaller joints of the hands and feet are involved in polyarticular JRA. In longstanding arthritis of the wrist in JRA, there is shortening of the ulna, which results in bowing of the radius and in ulnar deviation of the wrist [49]. Characteristic deformities of fingers, such as swan-neck deformity and boutonnière deformity, can be seen in both RA and JRA. Localized growth disturbances seen with JRA, especially EOPA, most likely reflect the impact of arthritis on the growing skeleton rather than a genuine difference between juvenile and adult-onset arthritis. Involvement of the shoulder and hip are less frequent early on in the disease, both in RA and JRA.

Subcutaneous nodules occur in 20% of RA patients with positive blood tests for RF. Rheumatoid nodules are almost always confined to those children with polyarticular JRA. Rheumatoid vasculitis, which occurs in adults with RA, is rare in children and occurs most often in the older child with RF-positive polyarthritis. The overall prevalence of pericardial involvement in JRA is estimated to be around 3–9% [49] and such involvement is found only in children with systemic-onset disease. In adults with RA, pericardial involvement is more frequent, with echocardiographic evidence of pericardial effusion or other pericardial abnormality seen in almost 50% of patients with RA who have no clinical symptoms of cardiac involvement [50]. Felty's syndrome is defined as RA in combination with splenomegaly and leukopenia, characteristically occurring in patients with longstanding, seropositive, nodular RA. An increased risk for the development of lymphoproliferative malignancies in patients with Felty's syndrome has been reported [31]. While lymphadenopathy and splenomegaly are characteristic of systemic-onset JRA, Felty's syndrome is only uncommonly reported in JRA [51,52].

The common ocular manifestation of RA is keratoconjunctivitis sicca. Chronic uveitis is rare in adults with RA. In

children, however, keratoconjunctivitis sicca is rarely seen. In one series only 3 of 131 children with chronic uveitis developed keratoconjunctivitis [53]. Chronic nongranulomatous uveitis is one of the most devastating complications of JRA, responsible for visual loss in 11–30% of children with uveitis in recent series [54–56]. On average, uveitis has been described in 15–20% of patients with pauciarticular JRA and in about 5% of those with polyarticular JRA. Uveitis is rare in children with systemic onset JRA.

Pathological features

The articular pathology of JRA shares features in common with RA. Synovial biopsy specimens reveal villous hypertrophy and hyperplasia of the synovial lining. Cellular infiltration, predominantly with T lymphocytes, occurs early in the disease. The inflammatory process eventually results in progressive erosion and destruction of articular cartilage. Joint destruction is thought to occur later in the course of JRA than in adult disease [49]. The greater thickness of the juvenile articular cartilage could account for this difference. Both RA and JRA are believed to be mediated by the type 1 T helper (Th1) phenotype of lymphocytes [57–59]. Wedderburn and Woo have shown that the ratio of interferon (IFN)- γ :IL-4 production is much higher in synovial fluid T cells than in peripheral blood T cells in children with JIA. This was due to a very high number of IFN- γ -producing cells, both in the CD4 and CD8 populations. More recently, Scola *et al.* have demonstrated similar cytokine findings in the more-difficult-to-obtain JIA synovial tissues [60]. Similarly, Th1-related chemokine receptors CCR5 and CXCR3 have been found in synovial fluid [61] and also in synovial tissues (Scola *et al.*, unpublished). Cytokines that are involved in the inflammatory process are also similar, including TNF- α and IL1, enabling control of these responses by the use of appropriate, biologic disease-modifying agents. However, at least in the case of pauciarticular JRA, Th2-mediated inflammatory responses may have a role to play. Murray *et al.* showed that synovial fluid from patients with pauciarticular disease significantly overexpresses IL-4 messenger RNA relative to synovial fluid from patients with polyarticular JRA and RA [62]. Thompson *et al.* documented CCR4-bearing CD4 synovial fluid lymphocytes with a phenotype that was Th2-like in that they produced greater IL-4 than IFN- γ [63]. Raziuddin *et al.* found a distinctly enhanced mixed-Th1/Th2-cell-response cytokine pattern in patients with systemic JRA from Saudi Arabia [64].

Concluding remarks

Although there are similarities between the inflammatory arthritides occurring in adults and children, RA and JRA/JIA appear to be distinct phenotypically, except for the older child with RF-positive polyarticular arthritis. Furthermore, the various subtypes of JRA appear to be distinct entities and could represent different diseases with

distinct etiological and genetic factors. Paradoxically, clinically distinct autoimmune disorders do appear to share common genetic susceptibility factors, as has been shown by Becker *et al.* [65]. In this context, it is plausible that there are common genetic susceptibility factors that predispose an individual to an autoimmune disorder, with other genetic (especially HLA) and/or environmental factors that determine the type of specific disorder and its manifestations.

Glossary of terms

EOPA = early-onset pauciarticular arthritis; HLA = human leukocyte antigen; IFN = interferon; IL = interleukin; IDDM = insulin-dependent diabetes mellitus; JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; MHC = major histocompatibility complex; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumor necrosis factor; Th1 (Th2) = type 1 (type 2) T helper.

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