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Oligoarticular and polarticular JIA: epidemiology and pathogenesis

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Summary

Juvenile idiopathic arthritis (JIA) refers to a group of chronic childhood arthropathies, currently classified into subtypes primarily on the basis of clinical features. Research has focused on the hypothesis that these subtypes arise through distinct etiologic pathways. In this Review, we discuss four subtypes of JIA: persistent oligoarticular, extended oligoarticular, rheumatoid-factor positive polyarticular and rheumatoid-factor-negative polyarticular. These subtypes differ in prevalence between ethnic groups and are associated with different HLA alleles. Non-HLA genetic risk factors have also been identified, some of which reveal further molecular differences between these subtypes, while others suggest mechanistic overlap. Investigations of immunophenotypes also provide insights into subtype differences: adaptive immunity appears to have a prominent role in both polyarticular and oligoarticular JIA, and the more-limited arthritis observed in persistent oligoarticular JIA as compared with extended oligoarticular JIA may reflect more-potent immunoregulatory T-cell activity in the former. Tumor necrosis factor seems to be a key mediator of both polyarticular and oligoarticular JIA, especially in the extended oligoarticular subtype, although elevated levels of other cytokines also are observed. Limited data on monocytes, dendritic cells, B cells, natural killer T cells, and neutrophils suggest that the contributions of these cells differ across subtypes of JIA. Within each subtype, however, common pathways appear to drive joint damage.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a term that collectively refers to a group of chronic childhood arthropathies, which together constitute the most common rheumatic condition in children. The latest (2001) International League of Associations for Rheumatology (ILAR) criteria define seven subtypes of JIA: systemic JIA (sJIA), oligoarticular JIA, rheumatoid factor (RF)-negative (RF^-) polyarticular JIA, RF-positive (RF^+) polyarticular JIA, enthesitis-related arthritis (ERA), psoriatic arthritis and undifferentiated JIA.(1) The ILAR classification includes persistent and extended oligoarthritis as subcategories of oligoarticular JIA, but not as distinct subytpes. Discussion regarding the robustness of this classification scheme continues, however,.(2–5) This Review focuses on developments regarding the epidemiology, genetics and immunopathogenesis of the oligoarticular and polyarticular subtypes. Progress in the understanding of sJIA, which appears to be an autoinflammatory rather than an autoimmune disease,(6) and of ERA, which is a clinically well-defined subtype typically associated with HLA-B27,(7) while of interest, are beyond the scope of this discussion.

Oligoarthritis is defined as arthritis affecting 4 or fewer joints during the first 6 months after disease onset, excluding children with enthesitis and boys after age 6 with HLA-B27*. Oligoarthritis is subdivided into persistent and extended forms, based on the number of joints affected after the first 6 months; that is, 1–4 and more than 4 joints, respectively. RF^+ and RF^- polyarthritis both affect 5 or more joints during the first 6 months of the disease; RF^+ disease is defined by two or more positive RF tests.(1) Table 1 summarizes the main clinical features associated with these four subtypes. Clinical differences imply distinct pathogenetic pathways for these subtypes, although current treatment approaches do not distinguish extended-oligoarticular, RF^+ polyarticular and RF^- polyarticular disease. Our understanding of the molecular basis of JIA subtypes is still unfolding, as discussed in this Review. Of note, the interpretation of some studies is confounded by changing schemes for JIA classification (Box 1) and by analyses that combine subtypes to increase patient numbers.

EPIDEMIOLOGY

The reported incidence and prevalence of JIA vary widely, in part because JIA is a heterogeneous condition that is identified clinically without specific diagnostic tests. Available numbers are likely to underestimate the true incidence and prevalence of JIA, because of under-diagnosis and because most studies are clinic- rather than community-based.(8–10) In a comprehensive survey of data published as of 2002, Manners and Bower(11)concluded that the incidence of chronic arthritis of childhood ranges from 0.008 to 0.226 per 1000 children, and that the prevalence ranges from 0.07 to 4.01 per 1000 children worldwide. Recent US and Canadian studies report the incidence of JIA to be 0.041 to 0.061 per 1000 children.(12–14). The best estimate of JIA prevalence in the US uses data recorded in the 2001–2004 National Ambulatory and National Hospital Ambulatory Medical

*In older classification schemes (see text box), the term pauciarticular disease was used, and this subtype included subjects with ERA or extended oligoarticular disease.

Care Survey. Based on ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes, approximately 294,000 US children aged 0–17 years (95% CI' 188,000–400,000) are affected by the broadly defined "arthritis or other (similar) rheumatic conditions".(15)

The major JIA subtypes vary by sex ratio and age at onset.(7) Girls are overrepresented in groups of patients with oligoarticular JIA and polyarticular JIA. Age at onset for oligoarticular JIA peaks at 2–4 years; by contrast, age at onset of polyarticular JIA has a biphasic pattern, with peaks at 1–4 years and 6–12 years of age, with RF^+ disease contributing disproportionately to the second peak.

In North America and Europe, the relative frequencies of JIA subtypes are 10–30% RF^- polyarticular, 5–10% RF^+ polyarticular, and 30–60% oligoarticular.(7) Studies of multi-ethnic communities from North America and from Europe suggest that, with the exception of RF^+ polyarticular JIA, European ancestry is an important predisposing factor for JIA, especially for extended oligoarticular JIA and antinuclear-antibody (ANA)-associated JIA with uveitis.(16, 17) Conversely, patients of African American or Native American descent are more likely to have RF^+ polyarticular JIA than children of European descent (16, 18, 19). Studies from different geographic areas are difficult to compare, but it seems that in Asia the overall prevalence of JIA is lower than in Europe and North America (20–22) and that ERA is particularly common.(20–23) The prevalence of uveitis in oligoarticular and polyarticular JIA subtypes is seemingly highest in Scandinavia and lowest in East Asia and India.(24) Black South African patients, like African Americans, have a higher rate of RF^+ polyarticular JIA and lower rate of arthritis with uveitis compared to children of European descent.(25)

Environmental influences are hypothesized to contribute to JIA pathogenesis, but specific agents have not been identified. In some reports, JIA is more prevalent in rural than urban settings.(26, 27) A single study conducted in Manitoba, Canada in 1975–1992 correlated cyclic increases in JIA incidence with the prevalence of mycoplasma infection.(14) Introduction of measles–mumps–rubella vaccination in Finland did not change the annual incidence of JIA, which argues against these infections as triggers of JIA.(28) An increasing incidence of JIA seems to be a worldwide trend, although the incidence of chronic pediatric arthritis in Rochester, Minnesota reportedly decreased from 0.150 cases per 1000 children (1960–1969) to 0.078 per 1000 children (1980–1993).(29, 30) Further work is needed to confirm incidence trends and to identify factors that contribute to these patterns.

Overall, epidemiological data corroborate clinical evidence that JIA subtypes represent discrete conditions. Data showing the influence of ethnicity on subtype susceptibility imply a role for genetics in JIA risk. To reveal more-detailed hypotheses on the pathogenesis of these subtypes, however, we must turn to studies of immunogenetics and immunophenotyping.

PATHOGENESIS

The presence of associations between HLA class II alleles and susceptibility to both oligoarticular and polyarticular JIA implicates $CD4^+$ T cells in these subtypes. The specific

class II alleles associated, however, differ between the subtypes, which strongly suggests differences in molecular mechanisms. Indeed, as knowledge of $CD4^+$ T cell subsets has grown, models of their involvement in oligoarticular and polyarticular JIA have been refined and support the idea that mechanistic differences exist. Available evidence also argues that antigen-driven autoimmunity is insufficient to explain all the features of oligoarticular and polyarticular JIA,(31) and implicate the involvement of both innate and adaptive immune responses. These issues are the focus of the rest of this Review.

Genetic factors

Data from family and twin studies were among the first to imply that susceptibility to JIA is inherited (reviewed elsewhere(32)). For example, siblings of probands are 15-fold to 30-fold more likely than the general population to develop JIA.(33)

All JIA subtypes are probably complex genetic traits, as they lack single-gene, Mendelian patterns of inheritance. Inherited risk factors for both disease susceptibility and disease severity have been reported (Tables 2–4). The highly polymorphic HLA genes confer the strongest genetic effects in JIA, and, to a large extent, HLA allelic associations confirm clinically defined subtypes, including differences between persistent and extended oligoarthritis (Table 2). Initial findings on HLA genetic risk from association and linkage studies have been confirmed by genome wide association studies (GWASs) (34, 35). HLA effects are observed within an age-window-of-effect, and gender also influences the age at which some of the associated alleles have their effect (36). Associations of HLA-A, HLA-B and HLA-DR with oligoarthritis are observed in girls but not boys, which raises the possibility of further heterogeneity in disease pathogenesis.(37) Shared HLA allelic associations imply a mechanistic relationship between extended oligoarticular JIA and RF^- polyarticular JIA; however, this relationship might be modified by the effects of differences in the associated HLA-DP alleles for these subtypes. Evidence suggests that different alleles confer susceptibility in different ethnic groups, as is the case for other MHC-associated diseases.(38–40) A caveat of interpreting genetic studies that use pre-ILAR classification criteria is that the patient groups are possibly heterogeneous; for example, the pauciarticular subtype could include $HLA\text{-}B27^+$ cases.(4)

HLA class II has been estimated to account for ~20% of the sibling recurrence risk in oligoarticular and polyarticular JIA, which implies a role for non-HLA genes.(41) Approximately 100 non-HLA genes have been investigated for an association with JIA; however, many studies do not have the statistical power to detect moderate or mild gene effects, particularly after stratification for JIA subtype. Nevertheless, associations with some non-HLA genes have been confirmed (Table 3). Some of these genes, such as *PTPN22* and *IL2RA* (also known as *CD25*), are associated with multiple autoimmune diseases, (42) an observation that is consistent with the occurence of various autoimmune disorders in families of JIA probands.(43) A 2009 GWAS found evidence of an association between *VTCN1*, a gene that encodes a negative regulator of T-cell-mediated responses, and JIA susceptibility.(35) Other candidate non-HLA genes are reportedly associated with risk of both oligoarticular and polyarticular JIA subtypes, including genes that encode regulators of innate immunity such as the proinflammatory cytokine macrophage migration inhibitory

factor (MIF). By contrast, some studies reveal subtype-specific genetic effects. A GWAS found linkage of different chromosomal regions to oligoarticular and polyarticular JIA subtypes, and distinction between early-onset and late-onset disease.(34) Another study found *TNFAIP3* and *C12orf30* variants associated with oligoarticular JIA, and a *STAT4* variant associated with polyarticular JIA.(44) The unique association between oligoarticular JIA and *IL-2RA/CD25* (42) which is highly expressed on regulatory T cells, suggests the possibility that these cells have a particular role in this subtype. Some, but not all, cytokine gene associations distinguish the subtypes (Table 4). The association of a low-expression-level allele of osteopontin with persistent oligoarticular JIA is consistent with the more-limited disease observed in this subtype as compared with extended oligoarticular JIA, and further argues for a pathogenic distinction between the two forms of oligoarticular JIA (45). Overall, observed genetic associations lend further support to the idea that the oligoartcular and polyarticular subtypes have different etiologies, but also argue that certain immunological pathways, such as MIF-driven inflammation, could contribute to pathology across subtypes.

Immune-related factors

T cells and autoantigens—Associations of HLA alleles with polyarticular and oligoarticular JIA imply a role for adaptive immunity, and especially T cells, in the pathogenesis of these subtypes. A number of lines of cellular evidence support this possibility, the oldest being the presence of T-cell and plasma-cell infiltrates in affected joints. However, there are some differences in T-cell phenotype in oligoarticular compared to polyarticular JIA, providing clues to subtype-specific mechanisms.

One aspect of T-cell biology that might have a role in JIA is impaired thymic function. Accelerated loss and premature aging of naïve $CD4^+$ T cells, the latter detected as telomeric erosion, have been reported in oligoarticular and polyarticular JIA, independent of treatment.(46) A study of all JIA subtypes, however, found no difference in thymic function between patients with JIA and controls.(47) Difficulty discriminating between recent thymic emigrants and long-lived peripheral naïve T cells could be one of the reasons for these discordant results; markers that better distinguish these two T-cell populations may clarify the role of thymic function in JIA.(48)

Evidence of T cell activation is a feature of patients with oligoarticular and polyarticular JIA, although critical or initiating antigens have not been determined. Activated $CD4^+$ T cells are found at increased levels in circulation(49) in comparison to healthy, age-matched children and in the synovium, with the CD4:CD8 ratio being higher in polyarticular JIA joint tissue compared to oligoarticular JIA.(50) Selected $CD4^+$ clones not abundant in circulation are expanded within the joints in oligoarticular patients, (51) but precipitating antigens for these expansions have not been identified. Evidence for auto-reactivity of circulating T cells includes responses to the joint-related proteins aggrecan and fibrillin, the latter primarily in patients with polyarticular JIA.(52) Several heat shock proteins (HSPs) are also potential autoantigens in JIA. Highly conserved across species, HSPs are produced in response to cell stress. Circulating T cells from oligoarticular and polyarticular JIA patients, but not controls, react to human HSP60.(53, 54) Human HSP70 is expressed on

synovial cell membranes in all JIA subtypes and might act as an autoantigen. Alternatively, ligation of HSP70 and autoantigens may promote autoantigen processing and presentation.(55)

Autoreactive $CD8^+$ T cells have also been implicated in the pathogenesis of polyarticular and oligoarticular JIA. Activated $CD8^+$ T cells are found in circulation(49) and in the synovium,(50) with a suggestion of higher levels of activation in the oligoarticular JIA compared to the polyarticular subtype. Consistent with re-distribution of these cells to the joints, absolute numbers of circulating $CD8^+CD45RA^+$ (naïve) T cells are decreased in oligoarticular JIA in comparison to healthy, age-matched controls, even after clinical remission.(56) Several studies have addressed potential autoantigenic specificities of $CD8^+$ T cells. Peptides from self-HLA proteins (HLA DRB1*1101, DRB1*0801 and DRP1*0201) with homology to Epstein–Barr-virus-derived peptides trigger cytotoxicity and proinflammatory cytokine production from peripheral blood $CD8^+$ T cells of patients with oligoarticular JIA.(57) In a study of patients primarily with polyarticular JIA, peripheral blood cytotoxic T cells lysed autologous synovial cells and keratinocytes *in vitro*.(58) Mechanisms of loss of $CD4^+$ and $CD8^+$ T-cell tolerance to autoantigens could include molecular mimicry (that is, cross-reactive responses to self-peptides that resemble pathogen-derived peptides) and inflammation-induced epitope spreading.

T cells in inflamed synovia of patients with polyarticular and oligoarticular JIA are predominantly activated memory type 1 T helper (Th1) cells, which are $IFN\gamma^+$ and $CD45RO^+$.(59) Evidence suggests that these cells home to the joint where they receive further activation by Th1- polarizing stimuli. Synovial fluid from patients with polyarticular JIA has been found to contain interleukin (IL)-12, a key inducer of Th1 cells. (60) The CC-chemokine receptor (CCR) 7, which controls the migration of memory T cells to inflamed tissues, is expressed on a subset of synovial fluid $CD4^+$ T cells in patients with oligoarticular and polyarticular JIA.(61) Levels of CC-chemokine ligand (CCL) 21, the ligand of CCR7, are elevated in synovial fluid of polyarticular and oligoarticular JIA patients in comparison with blood levels. $CCR7^+$ synovial $CD4^+$ T cells have higher expression levels of the Th1-biased CXC-chemokine receptor (CXCR) 3 than do $CCR7^-$ cells, and the $CCR7^-$ population is more enriched with the Th-1-biased chemokine receptor $CCR5^+$ as compared to $CCR7^+$ cells.(59) Synovial cells express transcripts encoding the ligand for CXCR3, CXC-chemokine ligand (CXCL) 10 (also known as IP-10), and the ligands for CCR5, CCL3 (also known as MIP-1α) and CCL5 (also known as RANTES).(61–63) One model that accounts for these observations is that $CCR7^+CXCR3^+$ cells might be recruited directly to the synovium, where they may become effector cells that downregulate CCR7 and upregulate CCR5; CCR5, in turn, may be the main receptor used for migration within the synovial tissue.(61) Furthermore, CCL5 may enhance T-cell production of IFNγ.(64) While effector T cells in the synovial fluid of both polyarticular and oligoarticular JIA patients express higher IFNγ:IL-4 ratios than their peripheral blood counterparts,(65) IL-4 is more prominent in the synovial compartments of patients with oligoarticular JIA compared with polyarticular JIA. This pattern is consistent with the more-limited arthritis associated with this subtype, and suggests a deviation from Th1 towards Th2-biased phenotypes.(66) In polyarticular JIA, even peripheral blood mononuclear cells have elevated levels of genes induced by IFNγ.(67)

A new paradigm suggests that a key inflammatory $CD4^+$ T-cell subset produces IL-17, and that the development of this subset is negatively regulated by Th1 cells.(68) The inflamed joints of all JIA subtypes are enriched in IL-17-producing T cells, and high levels of IL-17, in excess of serum levels, are detected in synovial fluid in polyarticular JIA.(69, 70) IL-17 potently induces synoviocyte production of IL-6, matrix metalloproteinases (MMPs) 1 and 3, and IL-8 (which is chemotactic for neutrophils), all of which have been implicated in joint damage.(70)

The extent of synovial inflammation is probably influenced by the balance between inflammatory cells and regulatory $CD4^+$ T cells (Treg cells), which are detected as $CD25^{hi}CD127^{lo}FOXP3^+$ cells.(71) In active synovitis, Treg cell function is apparently insufficient. One reason may be high synovial levels of IL-7 and IL-15, which are found in polyarticular and oligoarticular JIA and are associated with the induction of T-cell proliferation and abrogation of Treg-cell-mediated suppression of immune activation.(72, 73) In addition, the frequency of Th17 cells is inversely related to the frequency of $FOXP3^+$ Treg cells in the synovium.(69)

Evidence particularly implicates the activity of these anti-inflammatory T cells as a disease-limiting mechanism in oligoarticular JIA. Compared with the circulation, there are more $CD4^+CD25^+$ Treg cells in oligoarticular JIA synovial fluid, and these have higher suppressive capacity than peripheral cells.(74) Higher numbers of circulating $CD4^+CD25^{hi}$ Tregs are observed in persistent compared to extended oligoarticular JIA,(74) polyarticular JIA or sJIA.(75) A regulatory mechanism may involve reactivity to HSP: in individuals with persistent oligoarticular JIA, an HSP dnaJ epitope stimulates synovial mononuclear cells to expand T cells with suppressive activity ($CD4^+CD25^+CTLA4^+$ T cells).(76) T-cell reactivity to human HSP60 is associated with remission in oligoarticular JIA; the protective mechanism seems to involve induction of IL-10 production by $CD30^+$ T cells.(77, 78) In summary, it seems that proinflammatory T cells are recruited to the joint in both oligoarticular and polyarticular JIA, where they drive inflammation, but this activity is perhaps better controlled by regulatory mechanisms in persistent oligoarticular disease than in extended oligoarticular disease.

Antigen-presenting cells: dendritic cells and B cells—T-cell activation is dependent on antigen-presenting cells, the most potent of which are dendritic cells (DCs). DCs are thought to participate in the initiation, maintenance and/or regulation of inflammation in JIA, although few studies provide direct evidence for this. In oligoarticular and polyarticular JIA patients, conventional DCs (cDCs) and IFNα-producing DCs (plasmacytoid dendritic cells [pDCs]) are enriched in synovial fluid compared with the circulation.(79) One study found synovial fluid DCs to be more numerous in polyarticular JIA than in oligoarticular JIA and found lower numbers of circulating DCs to be associated with a reduced response to treatment. (80) Within synovial tissue, pDCs are found at lymphoid follicle-like structures, while cDCs are mostly found at the lining and sublining layers, which suggests that DC subtypes mediate distinct processes in the joint.(79) cDCs expressing RANK (receptor activator for nuclear factor κ B) are found in the joints of patients with oligoarticular and polyarticular JIA.(81) RANK-mediated activation of DCs leads to increased survival of these cells and production of inflammatory cytokines.(82)

Further investigation of DC migration to and function in the joint microenvironment is warranted.

The major autoantibody specificities found in JIA (ANA, RF, and anti-cyclic citrullinated peptide [CCP] antibody) have not been directly implicated in disease development, although they serve as biomarkers of clinical subsets. ANA is associated with uveitis in oligoarticular JIA, and IgM RF and/or anti-CCP antibodies are associated with erosive disease in polyarticular JIA.(83) Ravelli *et al*. have proposed that ANA^+ patients form an homogenous group, regardless of the course of arthritis; that is, ANA^+ oligoarticular JIA patients share clinical features with ANA^+ polyarticular JIA patients but not ANA^- polyJIA patients.(17) Microarray data from Griffin *et al*. also indicate that ANA^+ polyarticular JIA patients with early-onset disease might represent a subgroup separate from other patients with RF^- and RF^+ polyarticular JIA.(84)

Analyses of B-cell populations in JIA are few. Expansions of $CD5^+$ B cells, a minor B-cell subset, are observed in oligoarticular and polyarticular JIA (as well as Rheumatoid Arthritis).(49, 85) $CD5^+$ B cells typically produce antibodies against bacterial wall components, but are also a source of low-affinity multispecific antibodies. Whether $CD5^+$ B cells produce disease-related autoantibodies in JIA is not known. Given the efficacy of rituximab for RA, and the renewed interest in B cells as pathogenic effectors,(86) more studies of B cells in JIA are likely to be forthcoming.

Monocyte/macrophages and proinflammatory cytokines—Elevated levels of proinflammatory cytokines are found in the circulation and synovial compartments in patients with JIA. Serum levels of tumor necrosis factor (TNF) are elevated in oligoarticular and polyarticular JIA,(87) as are serum levels of IL-6, but the highest IL-6 levels are found in sJIA.(87–90) Circulating IL-1β can be elevated in oligoarticular and polyarticular JIA, (89) although this finding is not consistent.(87) In active arthritis, levels of proinflammatory cytokines are generally higher in synovial fluid than in circulation, mostly likely due to local production. For example, complexes of IL-6 and a soluble form of the IL-6 receptor, which bind to surface gp130 on chondrocytes and fibroblats, are thought to trigger further IL-6 production by these cells.(91)

On the basis of subtype-specific responses to anti-cytokine therapies, particular cytokines seem to be primary effectors in JIA subtypes. For polyarticular JIA and extended oligoarticular JIA, blockade of TNF has been efficacious, arguing for a crucial role for TNF in these subsets.(92) TNF is inhibited endogenously by its soluble receptors, and its damaging effects in polyarticular JIA might be attributable to a reduced ratio of soluble TNF receptor to TNF. (93) A recent study of transcriptional profiles of peripheral blood mononuclear cells from patients with newly diagnosed polyarticular JIA identified a subgroup with elevated expression of monocyte-associated genes, including genes that encode the monocyte markers CD64 and CD14. This subgroup included primarily RF^+ individuals, which raises the possibility that monocyte-driven inflammation is of particular importance in these patients.(84)

A key observation in all JIA subtypes is that, while levels of inflammatory cytokines are higher during active disease, levels are abnormal during clinical remission,(90) which suggests that remission represents a state of compensated inflammation that is overwhelmed during disease flare.

Innate immune dysfunction in JIA subtypes—Although HLA associations and other immunophenotypic data argue strongly for dysregulated adaptive immune responses in oligoarticular and polyarticular JIA, recent evidence also suggests an important role for innate immune activation in these subtypes. Levels of protein S100A8 and S100A9 (or their heterodimeric form S100A8/S100A9) and S100A12, which are secreted products of activated neutrophils and monocytes, are increased in the serum in oligoarticular and polyarticular JIA, and their concentration correlates positively with degree of inflammation.(94) These molecules belong to the damage-associated molecular pattern proteins (DAMPs), which act as endogenous danger signals and activate immune cells and vascular endothelium.(95) Direct cytotoxic effects of the S100 proteins may also contribute to tissue damage.(95) In patients with polyarticular and oligoarticular JIA, protein S100A8/S100A9 levels correlate positively with disease activity and increase before onset of clinical flare, which suggests they act early in the inflammatory cascade associated with periods of disease activity.(96) Levels of protein S100A12 also correlate positively with, and may be early mediators of, disease activity for oligoarticular JIA and polyarticular JIA.(97)

Although neutrophils are the most abundant cell population in JIA synovial fluid, few studies have concentrated on this cell type. Gene expression analysis suggests neutrophil abnormalities exist in polyarticular JIA patients. Expression of more than 700 genes, including IFNγ-related and IL-8-related genes, differs in patients with polyarticular JIA compared with healthy controls and some differences persist after response to therapy(98) or even during drug-free clinical remission.(99) The the NADPH cycle is dysregulated in neutrophils from patients with active and inactive RF- polyarticular JIA, which suggests an intrinsic neutrophil defect in these patients.(31)

Synovial inflammation and tissue damage—Within each of the oligoarticular and polyarticular JIA subtypes, a subset of patients suffers significant joint damage: the RF^+/anti-CCP^+ group in polyarticular JIA, and patients with the extended oligoarticular phenotype of oligoarticular JIA.(100, 101) The processes mediating joint damage appear to be shared across JIA subtypes. The hallmarks of inflamed synovium are increased vascularization and endothelial activation. Factors such as vascular endothelial growth factor, osteopontin, and reactive oxygen species induce the formation of new vasculature, thereby facilitating an influx of inflammatory cells. Inflammatory cells subsequently drive the activation of RANK-expressing osteoclasts and proteases, especially MMPs, which increases the ratio of MMPs to their inhibitors, tissue inhibitor of metalloproteinases (TIMPs). Cartilage and bone destruction ensues, enhanced by a reduced capacity for tissue repair (for example, due to increased osteoblast apoptosis) in the setting of inflammation.(102–108), (109)

CONCLUSIONS

Using clinical phenotypes, epidemiological data and HLA immunogenetics as a foundation, the ILAR criteria for JIA subtypes were defined by consensus conference and have been used globally for clinical and translational research and for the development of practice patterns and treatment algorithms. Implied in this subtyping is the hypothesis that different forms of chronic arthritis in childhood arise through distinct etiopathological pathways. Evidence reviewed here lends support to the general idea of differences in pathogenesis between subtypes. However, some results suggest areas of mechanistic overlap, even between oligoarticular and polyarticular JIA, for example, contributions of Th1 cells, MIF-driven innate immune activation and S100 proteins to joint inflammation. Other results imply further heterogeneity than is captured in the current classification scheme. Based on epidemiological and new molecular data, the ANA+ arthritis subgroup may prove to be mechanistically distinct. The subcategories of persistent and extended oligoarticular JIA may eventually be recognized as independent subtypes, with a defining role for CD4+ CD25+ T reg cells in controlling inflammation in the persistent form. However, much remains to be done to generate full molecular pictures of these conditions. Fortunately, the collaborative research effort that is probably necessary to achieve this goal is starting: an international team of investigators will soon begin working towards developing a biological classification system for JIA (ILAR II, personal communication, R. Yeung).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- Epidemiologic, genetic and immunophenotypic evidence suggests that oligoarticular (persistent and extended) and polyarticular (RF+ and RF−) JIA subtypes are distinct etiopathological conditions.
- Reported incidence and prevalence of JIA vary widely, due partly to lack of specific diagnostic tests and to rarity of community-based studies.
- Inherited susceptibility factors (both HLA and non-HLA) generally differ among JIA subtypes, although some overlap in the latter suggests shared immunological pathways.
- Evidence supports a key role for T-cell-driven inflammation in oligoarticular and polyarticular JIA and suggests a contribution of regulatory T cells to limiting disease in persistent oligoarticular JIA.
- Dysregulation of cytokines, especially tumor necrosis factor, contribute to oligoarticular and polyarticular JIA pathogenesis, and persistent cytokine abnormalities argue that clinical remission is a state of compensated inflammation.

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Table 1

Clinical features of JIA subtypes in white patients from the USA and Europe

Feature	Oligoarticular JIA			Polyarticular JIA	
	Overall	Persistent	Extended	RF$^-$	RF$^+$
Age at onset	Peak at age 2–4 years	—	—	Biphasic pattern: early peak at age 1–4 years, later peak at age 6–12 years	Late childhood or adolescence
Female:male ratio	3:1	—	—	3.2:1	5.7:1
Number of joints affected	1–4 joints in the first 6 months	1–4 joints throughout the disease course	5 or more joints after first 6 months	5 or more joints	5 or more joints
Pattern of arthritis	Affects large joints asymmetrically in the first 6 months (commonly knees and ankles)	Pattern maintained throughout the disease	After 6 months small joints also affected. Presence of ankle and/or wrist involvement within the first 6 months is more common in this subcategory. Erosive disease.	Polyarthritis in large and small joints Tends to be symmetric, and to affect fewer joints than polyarticular RF$^+$ JIA	Symmetric polyarthritis in large and small joints, similar to adult rheumatoid arthritis
Frequency	30–60% of all JIA	50% of all oligoarticular JIA*	50% of all oligoarticular JIA*	10–30% of all JIA	5–10% of all JIA
Uveitis‡	17–26%§	14–26%§	17–36%§,//	4–25%§	0–2%
Systemic symptoms (e.g. fever, weight loss, anemia)	Absent	—	—	Rare	Present
Anti-nuclear antibody	75–85%	70–80%	80–95%	50–80%	~ 55%
Rheumatoid factor	Absent	—	—	Absent	Present¶
Anti-CCP antibody#	0–6%	0–9%	0–6%	50–80%	~ 55%
Treatment[109]	—	NSAIDs, intra-articular corticosteroids	NSAIDs, methotrexate, TNF inhibitors**,‡‡	NSAIDs, methotrexate, TNF inhibitors**	NSAIDs, methotrexate, TNF inhibitors**

*4–6 years after disease onset.

‡Risk factors for uveitis include ANA$^+$, young age at diagnosis, female sex and oligoarticular JIA subtype.

§Higher percentage reported in Finland.[24]

//Uveitis generally develops before extension of arthritis.[110,111]

¶RF detected in two or more tests at least 3 months apart during the first 6 months of the disease

#Using a synthetic CCP variant, Low *et al*. found CCP$^+$ for in 60% of patients with oligoarticular JIA and 93% of those with polyarticular RF$^-$ JIA[112]

** Patients refractory to this treatment can be administered other medications including a second anti-TNF agent, sulfasalazine, CTLA4–Ig, rituximab, and leflunomide; no consensus exists on the order of introduction of these medications.

Evidence suggests that extended oligoarticular JIA responds to a similar or perhaps greater extent than polyarticular JIA to methotrexate and anti-TNF agents, and comparably to CTLA4-Ig (D. Lovell, personal communication,[113–116])

Abbreviations: +, positive; −, negative; CCP, cyclic citrullinated peptide; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor; NSAIDs, Non-steroidal anti-inflammatory drugs.

Table 2

HLA alleles associated with oligoarticular and polyarticular JIA in white populations

Clinical subtype of JIA	Susceptibility alleles	Protective alleles
Oligoarticular (both persistent and extended) **[AU: OK?OK]**[32,117,118]	A2, DRB1*08, DRB1*11, DPB1*0201, DQA1*04, DQB1*04	DRB1*04, DRB1*07
Persistent oligoarticular[117,118]	DRB1*13	DRB1*04
Extended oligoarticular[117]	DRB1*01	DRB1*04
RF^- polyarticular[32,117,118]	DRB1*08, DQA1*04, DPB1*03	DRB1*04, DRB1*07
RF^+ polyarticular[32,117,118]	DRB1*04, DQA1*03	DQA1*02
Uveitis[117,119,120]	DRB1*11, DRB1*13	DRB1*01 (Zulian et al, 2002)

Abbreviations: JIA, juvenile idiopathic arthritis; RF, rheumatoid factor

Table 3

Associations of non-HLA genes with JIA susceptibility independently replicated in white populations

Gene	Subtypes of JIA tested	Subtypes with significant findings	Function of gene product
IL2RA/CD25[42]	All ILAR subtypes	persistent oligoarticular JIA	α chain of the high-affinity IL-2 receptor
MIF[*121–123]	All ILAR subtypes	All ILAR subtypes[§]	Pro-inflammatory cytokine; inhibits macrophage migration
PTPN22[124–126]	All ILAR subtypes except 'other arthritis'	Oligoarticular, polyarticular	Protein tyrosine phosphatase May inhibit the T-cell receptor signaling pathway Predisposing allele is a gain-of-function mutant
SLC11A1 (also known as *NRAMP1*)[127,128]	OligoarticularJIA, polyarticular JIA	Oligoarticular, polyarticular	Transport of divalent cations in endosomes of macrophages, neutrophils and dendritic cells
TNF[‡129–131]	All ILAR subtypes	Oligoarticular, polyarticular	Pro-inflammatory cytokine
VTCN1 (also known as *B7H4*)[//35]	Persistent and extended oligoarticular JIA, RF^- and RF^+ polyarticular-JIA	Oligoarticular (persistent and extended), Polyarticular (RF^- and RF^+)	Negatively regulates T-cell-mediated immune response
WISP3[132]	All ILAR subtypes except other arthritis	Polyarticular-course JIA (including extended oligoarticularJIA, RF^- and RF^+ polyarticular JIA)	Involved in postnatal skeletal growth and cartilage homeostasis

Abbreviations: IL, interleukin; ILAR, International League Against Rheumatism; JIA, juvenile idiopathic arthritis; MIF, macrophage migration inhibitory factor; RF, rheumatoid factor; PTPN22, protein tyrosine phosphatase, non-receptor type 22 (lymphoid); SLC11A1, solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1; NRAMP1, Natural resistance-associated macrophage protein 1; TNF, tumor necrosis factor; VTCN1, V-set domain containing T cell activation inhibitor 1; WISP3, WNT1 inducible signaling pathway protein 3.

*Also associated with poor outcome in oligoarticular JIA, polyarticular JIA and systemic JIA[133,134].

‡Also associated with poor outcome and poor response to treatment.[135–137]

§Other arthritis included in one study only

//Results of genome-wide association study

Table 4

Other non-HLA genes associated with JIA - single reports*

Gene	Subtypes of JIA tested	Significant associations	Function of gene product
IL-1 family of genes[138–141]	All ILAR subtypes	Susceptibility for oligoarticular JIA (*IL1A*, *IL1RN*), JIA (*IL1B*)‡ sJIA (*IL1A*, *ILF10*, *IL1RN*, *IL1R2*)	*IL1A*, *IL1B* pro-inflammatory cytokines *IL1RN* IL-1 receptor antagonist *IL1R2* receptor for IL-1α, IL-1β and IL-1RN
IL6§[142,143]	Oligoarticular JIA, polyarticular JIA, sJIA	Susceptibility for sJIA	Immunoregulatory cytokine
IL10[144,145]	All ILAR subtypes except other arthritis	Disease course of extended (as opposed to persistent) oligoarticular JIA// Susceptibility for sJIA	Immunoregulator cytokine Inhibits the synthesis of a number of cytokines
IL15[146]	ANA$^+$ JIA	Susceptibility for ANA$^+$ JIA	Structurally similar to IL-2 Involved in T and NKcell homeostasis and controls CD8 T cell memory expansion together with IL-2
IL18¶[147]	Oligoarticular JIA, polyarticular JIA, sJIA	Susceptibility for oligoarticular JIA	Belongs to the IL-1 family Pro-inflammatory cytokine
SPP1[148]	Oligoarticular JIA	Disease course of persistent oligoarticular#	Osteopontin Immunomodulator Involved in bone remodeling
STAT4[44]	All ILAR subtypes	Susceptibility for RF− and RF$^+$ polyarticular JIA	Essential mediator of signals from IL-12 receptor
TNFAIP3[44]	All ILAR subtypes	Susceptibility for and protective effects in oligoarticular JIA	Modulates inflammatory response by regulating NF-kB signaling

*All studies, except as noted, conducted in white populations.

‡Association with JIA as a whole, without specificity to particular subtypes

§Two studies showed an association between *IL6* and systemic JIA but with different ages of disease onset (< and > 5 years of age).

//Genotype associated with lower IL-10 production.[144,149]

¶Association found in Japanese population; polymorphism association with higher IL-18 production in sJIA.

#Polymorphism associated with low expression of osteopontin

Abbreviations: +, positive; −, negative; ANA, anti-nuclear antibody; IL, interleukin, ILAR, International League Against Rheumatism; JIA, juvenile idiopathic arthritis; NF-κB, nuclear factor NF; sJIA, systemic JIA; IL2RA: interleukin 2 receptor, alpha; ANA, anti-nuclear antibody; SPP1, secreted phosphoprotein 1; Stat4, signal transducer and activator of transcription 4; TNFAIP3, tumor necrosis factor, alpha-induced protein 3