Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis

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Introduction

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic childhood disease; its onset is before 16 years of age and it persists for at least 6 weeks. JRA encompasses a heterogeneous group of diseases that is classified according to 3 major presentations: oligoarthritis, polyarthritis, and systemic onset diseases. These presentations may originate from the same or different causes that involve interaction with specific immunogenetic predispositions, and result in heterogeneous clinical manifestations. An arthritic joint exhibits cardinal signs of joint inflammation, such as swelling, pain, heat, and loss of function; any joint can be arthritic, but large joints are more frequently affected. Extra-articular manifestations include high fever, skin rash, serositis, and uveitis. The first 2 types of JRA are regarded as T helper 1 (Th1) cell-mediated inflammatory disorders, mainly based on the abundance of activated Th1 cells in the inflamed synovium and the pathogenetic role of proinflammatory cytokines that are mainly produced by Th1 cell-stimulated monocytes. In contrast, the pathogenesis of systemic onset disease differs from that of other types of JRA in several respects, including the lack of association with human leukocyte antigen type and the absence of autoantibodies or autoreactive T cells. Although the precise mechanism that leads to JRA remains unclear, proinflammatory cytokines are thought to be responsible for at least part of the clinical symptoms in all JRA types. The effectiveness of biologic therapy in blocking the action of these cytokines in JRA patients provides strong evidence that they play a fundamental role in JRA inflammation.

Key words: Juvenile arthritis, Child, Cytokines, Inflammation

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic childhood disease; its onset is before 16 years of age and it persists for more than 6 weeks. The JRA nomenclature represents an exclusion diagnosis that includes all forms of chronic childhood arthritis of unknown origin. JRA is the most common chronic rheumatic illness in children and is a significant cause of both short- and long-term disabilities. The heterogeneity of this disease suggests that different factors likely contribute to its pathogenesis. The current
understanding of JRA indicates that it arises in a genetically susceptible individual due to environmental factors. Moreover, it has been proposed that an antigen-driven autoimmune process mediates the inflammatory pathology of some cases of arthritis (e.g., oligoarthritis, polyarthritis). In contrast, there are no signs of lymphocyte-mediated, antigen-specific immune responses in individuals with systemic onset disease. Recent investigations in the pathophysiology of systemic onset disease have indicated that this disorder is due to an uncontrolled activation of the innate immune system. Regardless of the differences in the underlying pathogenesis of the various types of JRA, proinflammatory cytokines are consistently overproduced and are related to the clinical manifestations in all types of JRA. Modulation of these cytokines results in improvement of clinical outcome, which strongly suggests that these cytokines play important roles in JRA.

Currently, 3 separate classification systems are used to categorize individuals under 16 years of age with chronic arthritis. These include the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the International League of Associations for Rheumatology (ILAR). Because none of these systems are perfect models, some JRA patients fulfill criteria for more than one subtype, whereas others are difficult to classify into any of the specific subgroups. Both the ACR and EULAR criteria are based solely on the onset type as it is manifested during the first 6 months of disease, whereas the ILAR criteria also include the course type over an unknown period of time thereafter, in order to further distinguish the group of patients with oligoarticular disease.

Epidemiological studies of JRA have been hampered by a lack of standardized criteria and case ascertainment, which has resulted in wide-ranging results. For instance, the reported prevalence of JRA ranges from 0.007 to 4.01 per 1,000 children, and the annual worldwide incidence varies from 0.008 to 0.226 per 1,000 children. However, the actual incidence and prevalence of JRA in the Asian population, including Korean children, have not been well quantified because most large epidemiologic studies performed to date have been based on populations of patients who were mainly of European ancestry. Of note, one previous study from Japan showed that JRA had a relatively low overall prevalence among the population, suggesting lower incidence and prevalence in children of Asian origin than those of European origin. Furthermore, there are significant differences in JRA subtype distribution among the different ethnic groups as well.

### Pathogenesis

#### 1. Associations of human leukocyte antigen (HLA) and non-HLA molecules in JRA

The genetic basis of JRA is complex, but it has been estimated that the sibling recurrence risk of developing the disease is around 15%. To date, only 2 genetic risk factors, HLA and protein tyrosine phosphatase non-receptor 22 (PTPN22) genes, have been unequivocally confirmed as JRA susceptibility genes in multiple populations. The most well-established genetic factors for JRA are the HLA genes. Because the main function of HLA molecules is presenting antigenic peptides to T cells, HLA associations with JRA imply that this disease may be caused by an unidentified arthropigenic antigen. Many associations between subsets of JRA and the various HLA molecules have been described previously in the literature. However, both the strength of these associations and the associated alleles vary between the JRA subtypes. Specifically, oligoarthritis has been consistently associated with HLA-A2, HLA-DRB1*11, and HLA-DRB1*08. Rheumatoid factor (RF)-positive polyarthritis is reportedly associated with HLA-DR4 in children, similarly to in adults. Moreover, the presence of HLA-B27 confers an increased risk of enthesitis-related arthritis. PTPN22 encodes a lymphoid-specific phosphatase (Lyp). A variant in the coding region of this gene, which is reportedly associated with a number of autoimmune diseases, has also been identified as a susceptibility locus for JRA. The effect size of PTPN22 varies somewhat between JRA subtypes but, in general, is more consistent than that of HLA genes. A few other genes, including macrophage inhibitory factor, interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α, have also been associated with JRA in different populations and subtypes. However, these discussed genes may collectively account for only a small proportion of the total genetic contribution to disease.

#### 2. Inflammatory mediators of joint damage

Synovial membranes of JRA patients contain activated T and B cells, plasma cells, and activated macrophages that are recruited via an intense neovascularization process. Host tissue cells, including activated synovial fibroblasts, chondrocytes, and osteoclasts, mediate cartilage and bone destruction. It has been established that the recruitment, activation, and effector function of each of these contributor lineages are directed principally by a network of cytokines (Fig. 1).

Antigen-specific T cells appear to play a central role in the pathogenesis of arthritis subtypes within JRA. T-cell infiltrates are composed predominantly of T helper 1 (Th1) cells, which
 fluids or tissues in a majority of JRA patients. These cytokines are detected in synovial phages, and synovial fibroblasts likely have primary roles in the pathogenesis of JRA. Collectively, these dual actions seem to lead to joint damage. Indeed, fibroblasts from producing tissue inhibitors of metalloproteinases.

Th1 cells stimulate B cells, monocytes, macrophages, and synovial fibroblasts to produce immunoglobulins and inflammatory mediators. Activated B cells produce immunoglobulins, including RF and antinuclear antibodies (ANAs). The precise pathogenic role of RF remains unknown, but it may involve the activation of complement through the formation of immune complexes. ANAs, which are mainly associated with early-onset oligoarthritis, have been reported to react against different nuclear targets, none of which are specific for JRA. Activated macrophages, lymphocytes, and fibroblasts, as well as their products including vascular endothelial growth factor (VEGF) and osteopontin, can stimulate angiogenesis. VEGF is highly expressed in synovial tissue, whereas osteopontin is raised in synovial fluid and tissue, and correlates with new vascularisation.

TNF-α and IL-1 produced by activated monocytes, macrophages, and synovial fibroblasts likely have primary roles in the pathogenesis of JRA. These cytokines are detected in synovial fluids or tissues in a majority of JRA patients, and are known to stimulate mesenchymal cells, such as synovial fibroblasts, osteoclasts, and chondrocytes, to release tissue-destroying matrix metalloproteinases. TNF-α and IL-1 also inhibit synovial fibroblasts from producing tissue inhibitors of metalloproteinases. Collectively, these dual actions seem to lead to joint damage. Indeed, data from animal models strongly suggest TNF-α and IL-1 play roles in JRA. For instance, transgenic mice that expressed a deregulated human TNF-α gene spontaneously developed an inflammatory and destructive polyarthritis similar to JRA. Moreover, blocking TNF-α with either a soluble TNF-receptor fusion protein or monoclonal antibodies also ameliorated disease activity in mice with type II collagen-induced arthritis. Injection of IL-1 into the knee joints of rabbits has been demonstrated to result in the degradation of cartilage, whereas the injection of antibodies against IL-1 ameliorated collagen-induced arthritis in mice and decreased the damage to cartilage.

IL-6 is a multifunction cytokine that has a wide range of biological activities in various target cells and regulates immune responses, acute phase reactions, hematopoiesis, and bone metabolism. Circulating levels of IL-6 are markedly elevated in patients with JRA, and are associated with laboratory and clinical variables of disease activity. IL-6 stimulates hepatocytes and induces the production of several acute-phase proteins, such as C-reactive protein (CRP). Thus, elevated levels of IL-6 in serum correlate with CRP levels in JRA patients with active disease.

IL-17 is produced by Th17 cells, and induces a massive tissue reaction due to the broad distribution of the receptors to this cytokine. Recent evidence suggests that IL-17-producing Th17 cells have a crucial role in autoimmune inflammation. In particular, IL-17 promotes a proinflammatory cytokine environment in the joint, stimulating macrophage production of TNF-α and IL-1, and synergizes with these cytokines to increase IL-6 and IL-8 production. In addition, IL-17 contributes directly to joint destruction by upregulating matrix metalloproteinases and stimulating osteoclastogenesis through receptor activation of nuclear factor-κB ligand (RANKL) induction. IL-17 is increased in JRA patients with active disease compared with levels in individuals in remission. Data from animal models also suggest IL-17 has a role in cartilage degradation. For instance, IL-17-deficient mice were demonstrated to be resistant to induction of collagen-induced arthritis. Moreover, joint inflammation and cartilage and bone destruction were suppressed after administration of anti-IL-17 antibodies in mice with collagen-induced arthritis.

3. Unique inflammatory profile of systemic onset disease

The pathogenesis of systemic onset disease differs from that of other types of JRA in several respects, such as the lack of association with HLA type and the absence of autoantibodies and autoreactive T cells. Thus, patients with systemic onset disease do not show signs of lymphocyte-mediated antigen-specific immune responses. Instead, the typical clinical signs of systemic onset disease are associated with granulocytosis, thrombocytosis, and upregulation of acute-phase reactants, which indicate an uncontrolled activation of the innate immune system. During both the initial manifestation and the flares of systemic onset disease, there is a perivascular infiltration of neutrophils and
monocytes producing proinflammatory cytokines involved in the pathogenesis of this disease\textsuperscript{46}. The predominant role of the innate immune system in systemic onset disease is also underscored by the high expression and serum concentrations of the calcium-binding proteins S100A8, S100A9, and S100A12, which are specifically secreted during activation of neutrophilic granulocytes and monocytes\textsuperscript{47}. The extraordinarily high serum concentrations of these proteins are closely associated with the disease activity of systemic onset disease, and are not found in patients with other forms of inflammatory arthritis or other autoimmune or infectious disease\textsuperscript{48, 49}. S100 proteins exhibit proinflammatory effects on leukocytes and endothelial cells, and are thus likely to be directly involved in the inflammatory process of systemic onset disease\textsuperscript{50, 51}.

Recent data indicate that IL-1 has a prominent role in systemic onset disease. Treatment with IL-1 receptor antagonist has been shown to reduce the clinical and laboratory features of disease activity in patients with systemic onset disease who show resistance to anti-TNF-\(\alpha\) treatment\textsuperscript{52}. In addition, activated monocytes from patients with systemic onset disease secrete significantly higher amounts of IL-1 in comparison with secreted levels from monocytes of healthy controls, whereas release of TNF-\(\alpha\) and IL-6 is not significantly different between these groups. Another member of the IL-1 cytokine family, IL-18, was found to be extremely elevated in patients with adult-onset Still’s disease compared with levels in healthy controls, whereas release of TNF-\(\alpha\) and IL-6 is not significantly higher than levels in the healthy controls\textsuperscript{53}. An equally dramatic rise in IL-18 concentration has been found in serum from children with systemic onset disease, whereas levels in children with polyarticular or oligoarticular disease were not significantly higher than levels in the healthy controls\textsuperscript{54}. Moreover, IL-18 concentrations are significantly higher in patients with either serositis or hepatosplenomegaly than in patients without these manifestations.

The circulating concentration of IL-6 is noticeably increased in patients with systemic onset disease and correlates with the extent of joint involvement\textsuperscript{55, 56}. In addition, IL-6 concentration is significantly higher in the synovial fluid of patients with systemic onset disease than in patients with other JRA subtypes\textsuperscript{57}. The overproduction of IL-6 may explain many of the extra-articular manifestations of this disease, including microcytic anemia\textsuperscript{58} and growth impairment\textsuperscript{59}. Treatment with a monoclonal antibody directed against the IL-6 receptor is associated with pronounced clinical improvement and the reestablishment of normal levels of acute-phase reactants in patients with systemic onset disease\textsuperscript{60}.

The clinical and pathologic manifestations of macrophage activation syndrome (MAS) are thought to result from the activation and uncontrolled proliferation of T-lymphocytes and well-differentiated macrophages, which leads to an unrestricted release of inflammatory cytokines, such as TNF-\(\alpha\), IL-1, and IL-6. However, the cause of the immunologic derangement associated with MAS is unknown. Recently, studies have revealed markedly decreased natural killer cell function and, in some cases, depressed perforin expression in patients with systemic onset disease; it has been suggested that these abnormalities may explain the distinctive susceptibility of these patients to developing MAS\textsuperscript{61, 62}.

4. Anti-inflammatory mediators in JRA

The two most well-known anti-inflammatory cytokines associated with JRA are IL-10 and IL-4. IL-10 has been shown to reverse cartilage degradation mediated by antigen-stimulated mononuclear cells in adult patients with arthritis\textsuperscript{63}. In addition, a single nucleotide polymorphism connected to lower production of IL-10 is associated with a more severe type of arthritis\textsuperscript{64}. IL-4 inhibits the activation of Th1 cells, which in turn decreases the production of TNF-\(\alpha\) and IL-1 and inhibits cartilage damage\textsuperscript{65}. IL-4 and IL-10 cooperate to inhibit the production of inflammatory cytokines, including IL-6 and IL-8\textsuperscript{66}. Higher levels of IL-4 and IL-10 mRNA within a joint are allied with a milder oligoarticular course and non-erosive disease\textsuperscript{67}.

Foxp3+CD4+CD25+ regulatory T cells (Tregs) are important for controlling inflammatory processes\textsuperscript{68}. In humans, an X-linked genetic defect in Foxp3 is the underlying cause of a condition that presents with multiple autoimmune conditions, which is named the immuno-dysregulation, polyendocrinopathy, enteropathy (IPEX) syndrome\textsuperscript{69}. Less serious defects in Treg function have also been put forward as a cause of failed tolerance in several human autoimmune diseases. However, there is currently no evidence suggesting defects in Treg function in JRA, although the number of synovial Tregs is significantly lower in patients with extended oligoarthritis compared with the number in patients with a milder course of the disease\textsuperscript{70}. Moreover, a higher number of Tregs have been found within joints of JRA patients compared with the number in peripheral blood\textsuperscript{71}, which indicates an enrichment of Tregs within the inflamed joints. However, it appears that high numbers of regulatory cells in the joint fail to moderate the local inflammatory process. This finding may be related to effector T cell resistance, suppression at the site of inflammation\textsuperscript{72}, or the attenuation of Treg function by local dendritic cell-derived cytokines, such as IL-6\textsuperscript{73}.

Clinical manifestations

1. Arthritis

An arthritic joint exhibits a number of cardinal signs of inflam-
mation, such as swelling, erythema, heat, pain, and loss of function (Fig. 2, 3). Involved joints are often warm, but are not typically erythematous. Children with arthritis may not complain of pain while at rest, but active or passive motion typically elicits pain. Joint tenderness is usually maximal at the joint line or just over the hypertrophied, inflamed synovium. Of note, bone pain or tenderness is not characteristic of JRA and may instead indicate the possibility of a malignancy involving bone. Morning stiffness and gelling following inactivity are common manifestations of joint inflammation, but young children infrequently describe these symptoms. Often, young children do not complain of pain and instead refuse to use the affected joint entirely.

Any joint can be affected by JRA, but large joint are more frequently involved than smaller joints. However, small joints of the hands and feet are also affected, particularly in polyarticular onset disease. Of note, cricoarytenoid arthritis is unusual but may be responsible for acute airway obstruction. Inflammation of the synovial joints in the middle ear has also been detected by tympanometric studies. The temporomandibular joint and the cervical, thoracic, and lumbar spine should also be examined in the case of JRA. JRA often affects the cervical spine, and the most common changes in the upper cervical spine are anterior atlantoaxial subluxation and impaction. Subluxation of the atlantoaxial joints may also occur, rendering the affected child at risk of injury in an accident or upon attempted intubation prior to receiving general anesthesia. Scoliosis, which possibly reflects asymmetric thoracolumbar apophyseal joint inflammation, may also occur in children with JRA. Small outpouchings of synovium are not uncommon in individuals with JRA and are particularly evident at the extensor hood of the proximal interphalangeal joint and around the wrist or ankle. A synovial cyst in the antecubital area or anterior to the shoulder may be the initial or sole presentation of JRA.

Oligoarticular disease develops in at least 50% of children with JRA during the first 6 months of disease. This subtype is the only form of JRA without an adult equivalent. Oligoarticular disease affects up to 4 joints at presentation, with the knee joints mostly affected, followed by the ankles. In contrast, this subtype almost never affects the hips, and rarely the smaller joints of the hands and feet. Oligoarticular disease is characterized by asymmetric arthritis, early onset (before 6 years of age), female predilection, high frequency of positive ANAs, and a high risk of iridocyclitis. The ILAR classification distinguishes 2 further categories within the oligoarthritis subtype: persistent oligoarthritis, in which the disease is confined to 4 or fewer joints, and extended oligoarthritis, in which the arthritis extends to more than 4 joints after the first 6 months of disease. Up to 50% of oligoarticular patients develop extended disease, and 30% will do so in the first 2 years after diagnosis. The risk factors for extended disease include involvement of an upper limb joint and elevated erythrocyte sedimentation rate (ESR) at onset.

Polyarticular disease is defined as the presence of arthritis in 5 or more joints during the first 6 months of disease. The arthritis may be symmetrical and usually involves the large and small joints of the hands and feet, although the axial skeleton, including the cervical
spine and the temporomandibular joints, may also be affected. This subtype includes children with both RF-negative and RF-positive diseases. Both types affect girls more frequently than boys. RF-negative patients often develop polyarthritis in early childhood, whereas RF-positive patients instead develop arthritis during late childhood and adolescence. Three distinct subsets of RF-negative polyarthritis have been identified. The first subset is a form that resembles early-onset oligoarticular disease, except for the number of joints affected in the first 6 months of disease. The second subset is similar to adult-onset RF-negative rheumatoid arthritis, and is characterized by overt symmetric synovitis of large and small joints, onset during school age years, increased ESR, negative ANA, and variable outcome. Finally, the third subset is a form known as dry synovitis, which shows negligible joint swelling but stiffness and flexion contractures\(^{80}\). RF-positive patients are primarily adolescent girls with symmetric small joint involvement and early-onset erosive synovitis. Approximately a third of these patients develop subcutaneous nodules (non-tender, firm lesions over pressure points and tendon sheaths), typically in the board of the forearm and elbow. The HLA associations in these patients are the same as in adult seropositive rheumatoid arthritis patients and likely represent the early expression of adult rheumatoid arthritis.

2. Systemic extra-articular manifestations

Systemic involvement may precede the development of overt arthritis by weeks, months, or rarely years. In the right clinical setting, with characteristic fever and classic rash, the diagnosis of probable systemic onset disease may be made, and confirmation of the diagnosis can follow when persistent arthritis develops\(^{81}\). The arthritis associated with systemic onset disease is usually polyarticular affecting both large and small joints. Asymmetric, oligoarticular arthritis is less common. The systemic pattern is prominent during the first 4-6 months of disease and rarely occurs for the first time during the later course of disease.

The most prominent feature of systemic involvement is a high spiking fever\(^{82}\). Specifically, the temperature of an individual typically rises to 39°C or higher on a daily or twice-daily basis, followed by a rapid return to the baseline temperature or below (Fig. 4). Although this quotidian pattern is highly suggestive of systemic onset disease, patients may not present this fever pattern. Fever may occur at any time of the day, but characteristically presents in the late afternoon to evening in conjunction with the rash. Moreover, the temperature may be subnormal in the morning. During episodes of fever, an affected child commonly appears ill when chills are present, but then appears well when the fever breaks. Fever associated with systemic onset disease often responds poorly to the commonly prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), even at high doses.

In the case of systemic onset disease, intermittent fever is almost always accompanied by the classic rash\(^{82}\). The classic rash is evanescent (usually coming and going with the fever spikes) and consists of discrete, circumscribed, salmon-pink macules (2-mm to 10-mm in size) that may be surrounded by a ring of pallor or may develop central clearing (Fig. 5). Lesions are most common on the trunk and proximal extremities, including the axilla and inguinal areas, but can also develop on the face, palms, or soles of affected individuals. The rash tends to be migratory and is strikingly evanescent: individual lesions last for up to a few hours and leave no residua. Moreover, the rash may be much more persistent in children who are systemically very ill, and may reappear with each systemic exacerbation. Such rash also occurs very rarely in children with polyarticular onset disease, and likely never occurs in those with classic oligoarthritis. Individual lesions may be elicited either by rubbing and/or scratching the skin (the so-called Koebner\(^{35-41}\)
response), by a hot bath, or by psychological stress. The rash is occasionally pruritic but is never purpuric.

Pericarditis and pericardial effusions are especially common in children with systemic onset disease. Pericarditis may precede the development of arthritis or may occur at any time during the course of disease, and is usually accompanied by a systemic exacerbation of disease. Pericarditis tends to occur in older children, but it is not related to sex, age at onset, or severity of joint disease. Most pericardial effusions are asymptomatic, although some children have dyspnea or precordial pain that may be transferred to the back, shoulder, or neck. In many cases, pericardial effusions develop insidiously, may not be accompanied by obvious cardiomegaly or electrocardiographic changes, and escape recognition except by echocardiography. Examination of affected patients may disclose diminished heart sounds, tachycardia, cardiomegaly, and a pericardial friction rub, usually at the left lower sternal border. Pneumonitis or pleural effusions may also occur with carditis, or may be asymptomatic and detected only as incidental findings on chest radiographs. Pulmonary rheumatoid nodules that are described in adult rheumatoid arthritis are rare in childhood.

Another characteristic of systemic onset disease is enlargement of lymph nodes and spleen, either alone or in combination. Marked symmetric lymphadenopathy is particularly common in the anterior cervical, axillary, and inguinal areas, and may suggest the diagnosis of lymphoma. Mesenteric lymphadenopathy may cause abdominal pain or distention and lead to an erroneous diagnosis of an acute surgical abdomen. Splenomegaly is generally most prominent within the first years after onset of systemic onset disease. The degree of splenomegaly may be extreme, but it is uncommonly associated with Felty’s syndrome (splenic neutropenia). Hepatomegaly is less common than splenomegaly. Furthermore, moderate to severe enlargement of the liver is often associated with only mild derangement of function and relatively nonspecific histopathologic changes. However, massive enlargement of the liver is usually accompanied by abdominal distention and pain. Progressive hepatomegaly is characteristic of secondary amyloidosis, which refers to the tissue deposition of the fibrillar protein amyloid.

MAS is a rare but life-threatening complication of systemic onset disease that is characterized by demonstration of histiophagocytosis in bone marrow. The main manifestations of MAS include fever, hepatosplenomegaly, lymphadenopathy, severe cytopenias, serious liver disease, and disseminated intravascular coagulation. The pathognomonic feature of MAS is often found in bone marrow, which includes numerous, well-differentiated macrophages phagocytosing hematopoietic elements. It has been estimated that MAS develops in at least 10% of patients with systemic onset disease, although the true incidence of MAS might be much higher since there are no validated diagnostic criteria for this syndrome and mild instances are not always recognized. MAS bears close resemblance to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH). Triggers of MAS include a preceding viral illness and the addition of or a change in medications, especially including NSAIDs, intramuscular gold injections, sulfasalazine, and more recently etanercept.

3. Uveitis

Chronic, anterior, nongranulomatous uveitis (iritidocyclitis) develops in up to 21% of patients with oligoarticular disease and 10% of patients with polyarticular disease. However, no patients with systemic onset disease have been diagnosed as having uveitis to date. The only known independent risk factor for developing uveitis is a positive ANA test. The onset of chronic uveitis is typically insidious and often entirely asymptomatic, although up to one half of affected children have symptoms attributable to uveitis (e.g., pain, redness, headache, photophobia, change in vision) later in the course of their disease. Uveitis may be present at the time of diagnosis, may develop during the course of JRA, or may be an initial manifestation of JRA that is usually detected in the course of routine ophthalmologic examination. JRA patients should be screened routinely to prevent delay in diagnosis of uveitis. The earliest signs of uveitis on slit-lamp examination are the presence of inflammatory cells and increased protein concentration in the aqueous humor of the anterior chamber of the eye. In addition, deposition of inflammatory cells on the inner surface of the cornea (keratopunctate deposits) may develop later during the course of disease. Complications of uveitis include posterior synechiae, cataracts, band keratopathy, glaucoma, and visual impairment.

References

1. Phelan J, Thompson S. Genomic progress in pediatric arthritis: recent work and future goals. Curr Opin Rheumatol 2006;18:482-9.
2. Førre O, Smerdel A. Genetic epidemiology of juvenile idiopathic arthritis. Scand J Rheumatol 2002;31:123-8.
3. Murray K, Thompson SD, Glass DN. Pathogenesis of juvenile chronic arthritis: genetic and environmental factors. Arch Dis Child 1997;77:530-4.
4. Adams A, Lehman TJ. Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis. Curr Opin Rheumatol 2005;17:612-6.
5. Wilkinson N, Jackson G, Gardner-Medwin J. Biologic therapies for juvenile arthritis. Arch Dis Child 2003;88:186-91.
proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977;20:195-9.

7) European League Against Rheumatism. EULAR Bulletin No. 4: nomenclature and classification of arthritis in children. Basel (Switzerland): National Zeitung AG, 1977.

8) Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997. J Rheumatol 1998;25:1991-4.

9) Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis—why does it vary so much? J Rheumatol 2002;29:1520-30.

10) Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta Paediatri Jpn 1997;39:242-4.

11) Saurenmann RK, Rose JB, Tyrrell P, Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta Paediatri Jpn 1997;39:242-4.

12) Moroldo MB, Tague BL, Shear ES, Glass DN, Giannini EH. Juvenile rheumatoid arthritis in affected sib-pairs. Arthritis Rheum 1997;40:1962-6.

13) Glass DN, Giannini EH. Juvenile rheumatoid arthritis as a complex genetic trait. Arthritis Rheum 1999;42:2261-8.

14) Prahalad S. Genetics of juvenile idiopathic arthritis: an update. Curr Opin Rheumatol 2004;16:588-94.

15) Thomson W, Donn R. Juvenile idiopathic arthritis genetics—what’s new? Arthritis Rheum 2002;47:186-90.

16) Hinks A, Barton A, John S, Bruce I, Hawkins C, Griffiths CE, et al. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. Arthritis Rheum 2005;52:1694-9.

17) Rosen P, Thompson S, Glass D. Non-HLA gene polymorphisms in juvenile rheumatoid arthritis. Clin Exp Rheumatol 2003;21:650-6.

18) Wedderburn LR, Robinson N, Patel A, Varsani H, Woo P. Selective recruitment of polarized T cells expressing CCR5 and CXCR3 to the inflamed joints of children with juvenile idiopathic arthritis. Arthritis Rheum 2000;43:765-74.

19)Gattorno M, Prigione I, Moranti F, Gregorio A, Chiesa S, Ferlito F, et al. Phenotypic and functional characterization of CCR7+ and CCR7- CD4+ memory T cells homing to the joints in juvenile idiopathic arthritis. Arthritis Res Ther 2005;7:R256-67.

20) Scola MP, Imagawa T, Boivin GP, Glass DN, Hirsch R, Grom AA, et al. Expression of angiogenic factors in juvenile rheumatoid arthritis: correlation with revascularization of human synovium engrafted into SCID mice. Arthritis Rheum 2001;44:794-801.

21) Gattorno M, Gregorio A, Ferlito F, Gerloni V, Parafioriti A, Felici E, et al. Synovial expression of osteopontin correlates with angiogenesis in juvenile idiopathic arthritis. Rheumatology 2004;43:1091-6.

22) Grom AA, Murray KJ, Luynik L, Emery H, Passo MH, Glass DN, et al. Patterns of expression of tumor necrosis factor α, tumor necrosis factor β, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. Arthritis Rheum 1996;39:1703-10.

23) Kutukculer N, Caglayan S, Aydogdu F. Study of pro-inflammatory (TNF-α, IL-1α, IL-6) and T-cell-derived (IL-2, IL-4) cytokines in plasma and synovial fluid of patients with juvenile chronic arthritis: correlations with clinical and laboratory parameters. Clin Rheumatol 1998;17:288-92.

24) Shingu M, Nagai Y, Isayama T, Naono T, Nobunaga M, Nagai Y. The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. Clin Exp Immunol 1993;94:145-9.

25) Kefler J, Probert L, Cazaliers H, Georgopoulos S, Kaslaris E, Kioussis D, et al. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J 1991;10:4025-31.

26) Wooley PH, Dutcher J, Widmer MB, Gillis S. Influence of a recombinant human soluble tumour necrosis factor receptor Fc fusion protein on type II collagen-induced arthritis in mice. J Immunol 1993;151:6602-7.

27) Williams RO, Feldmann M, Maini RN. Anti-tumour necrosis factor ameliorates joint disease in murine collagen-induced arthritis. Proc Natl Acad Sci U S A 1992;89:9784-8.

28) Pettipher ER, Higgs GA, Henderson B. Interleukin 1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint. Proc Natl Acad Sci U S A 1986;83:8749-53.

29) Joosten LAB, Helsen MMA, van de Loo FAJ, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice: a comparative study using anti-TNFα, anti-IL-1α/β, and IL-1Ra. Arthritis Rheum 1996;39:797-809.

30) Nishimoto N, Kishimoto T. Interleukin 6 from bench to bedside. Nat Clin Pract Rheumatol 2008;4:619-26.

31) Manghe H, Kenzian H, Gallisal S, Neuwirth G, Liebmann P, Kaufersch W, et al. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. Arthritis Rheum 1995;38:211-20.

32) Ou LS, See LC, Wu CJ, Kao CC, Lin YL, Huang JL. Association between serum inflammatory cytokines and disease activity in juvenile idiopathic arthritis. Clin Rheumatol 2002;21:52-6.

33) Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990;265:621-36.

34) Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy KM. Th17: an effector of CD4 T cell lineage with regulatory T cell ties. Immunity 2006;24:677-88.

35) Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, Zhang M, et al. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-15 and TNF-α, by human macrophages. J Immunol 1998;160:3513-21.

36) Chabaud M, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. J Immunol 1998;161:409-14.

37) Katz Y, Nadiv O, Beer Y. Interleukin-17 enhances tumor necrosis factor α-induced synthesis of interleukins 1, 6, and 8 in skin and synovial fibroblasts: a possible role as a “fine-tuning cytokine” in inflammation processes. Arthritis Rheum 2001;44:2176-84.

38) Chabaud M, Garnero P, Dayer JM, Guerne PA, Fossiez F, Miossec P. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. Cytokine 2000;12:1092-9.

39) Sato K, Saematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cells subset that links T cell activation and bone destruction. J Exp Med 2006;203:2673-82.

40) Kotake S, Udagawa N, Takahashi N, Matsuoki K, Itoh K, Ishiyama S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest 1999;103:1345-52.
41) De Jager W, Hoppenreijis EP, Wulffraat NM, Wedderburn LR, Kuis W, Prakken BJ. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. Ann Rheum Dis 2007;66:589-98.

42) Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. J Immunol 2003;171:6173-7.

43) Lubberts E, Konders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LA, et al. Treatment with a neutralizing anti-murine IL-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction and bone erosion. Arthritis Rheum 2004;50:650-9.

44) Nepom BS, Glass DN. Juvenile rheumatoid arthritis and HLA: report of the Park City III workshop. J Rheumatol Suppl 1992;33:70-4.

45) Ravalli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.

46) Frosch M, Metze D, Foell D, Vogl T, Sorg C, Sunderkötter C, et al. Early activation of cutaneous vessels and epithelial cells is characteristic of acute systemic onset juvenile idiopathic arthritis. Exp Dermatol 2005;14:259-65.

47) Foell D, Roth J. Proinflammatory S100 proteins in arthritis and autoimmune disease. Arthritis Rheum 2004;50:3762-71.

48) Frosch M, Vogl T, Seeliger S, Wulffraat N, Kuis W, Viemann D, et al. Expression of myeloid-related proteins 8 and 14 in systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 2003;48:2622-6.

49) Foell D, Wittkowski H, Hammerschmidt I, Wulffraat N, Schmeling I, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum 2004;50:1286-95.

50) Roth J, Vogl T, Sorg C, Sunderkötter C. Phagocyte specific S100 proteins: a novel group of proinflammatory molecules. Trends Immunol 2003;24:155-8.

51) Viemann D, Strey A, Janning A, Jurk K, Klimmek K, Vogl T, et al. Myeloid-related proteins 8 and 14 induce a specific inflammatory response in human microvascular endothelial cells. Blood 2005;105:2955-62.

52) Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-17 (IL-17) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 2005;201:1479-86.

53) Kawaguchi Y, Terajima H, Harigai M, Hara M, Kamatani N. Interleukin-18 expression in human microvascular endothelial cells. J Rheumatol 2002;29:1101-8.

54) Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003;299:1057-61.

55) Pasare C, Medzhitov R. Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. Science 2003;301:755-8.
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74) Hahn YS, Kim JG. A clinical study on pauciarticular juvenile rheumatoid arthritis. J Korean Pediatr Soc 1995;38:386-96.
75) Hahn YS, Park JS, Kim JG. A clinical study on polyarticular juvenile arthritis: III. Polyarticular type. J Korean Rheum Assoc 1997;4:70-81.
76) Siamopoulos-Mavridou A, Asimakopoulos D, Mavridis A, Skevas A, Moutsopoulos HM. Middle ear function in patients with juvenile chronic arthritis. Ann Rheum Dis 1990;49:620-3.
77) Laiho K, Savolainen A, Kauhtainen H, Kekki P, Kauppi M. The cervical spine in juvenile chronic arthritis. Spine J 2002;2:89-94.
78) Barkin RE, Stillman JS, Potter TA. The spondylitis of juvenile rheumatoid arthritis. N Engl J Med 1955;253:1107-10.
79) Guillaume S, Prieur AM, Coste J, Job-Deslandre C. Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. Arthritis Rheum 2000;43:1858-65.
80) Ostrov BE. What is the significance of dry synovitis? Pediatr Rheumatol Online J 2004;2:114-8.
81) Schaller JG. Juvenile rheumatoid arthritis. Pediatr Rev 1980;2:163-74.
82) Kim JG, Jung JY, Yoon BY, Hahn YS. Clinical Observations on Juvenile Rheumatoid Arthritis: I. Systemic Type. J Korean Rheum Assoc 1994;1:73-82.
83) Goldenberg J, Ferraz MB, Pessoa AP, Fonseca AS, Carvalho AC, Hilario MO, et al. Symptomatic cardiac involvement in juvenile rheumatoid arthritis. Int J Cardiol 1992;34:57-62.
84) Bernstein B, Takahashi M, Hanson V. Cardiac involvement in juvenile rheumatoid arthritis. J Pediatr 1974;85:313-7.
85) Toomey K, Hepburn B. Felty syndrome in juvenile arthritis. J Pediatr 1985;106:254-5.
86) Schaller J, Beckwith B, Wedgwood RJ. Hepatic involvement in juvenile rheumatoid arthritis. J Pediatr 1970;77:203-10.
87) Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: A potentially fatal complication of rheumatic disorders. Arch Dis Child 2001;85:421-6.
88) Behrens EM, Beukelman T, Paessler M, Cron RQ. Occult macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Rheumatol 2007;34:1133-8.
89) Athreya BH. Is macrophage activation syndrome a new entity? Clin Exp Rheumatol 2002;20:121-3.
90) 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.
91) Schneider R, Passo MH. Juvenile rheumatoid arthritis. Rheum Dis Clin North Am 2002;28:503-30.
92) Bowyer SL, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace C, et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003;30:394-400.