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Rheumatic diseases

result from autoimmune processes that lead to inflammation of target organs. Because many different organs may be affected, rheumatic diseases must be considered for a wide range of presenting complaints. Rarely, children develop ***overlap syndrome*s** with manifestations fulfilling criteria for more than one rheumatic disease.

Mixed connective tissue disease is sometimes used to describe an overlap syndrome, especially among adult females, characterized by fever, Raynaud phenomenon, skin rash, arthritis, and myositis. Children may also have **undifferentiated connective tissue disease** in which manifestations strongly suggest but do not meet diagnostic criteria for a specific rheumatic disease.

ETIOLOGY AND PATHOGENESIS.

Rheumatic diseases are characterized by **autoimmune responses.** The immune system normally responds to viruses, bacteria, and other non-self molecules but does not mount reactions to self molecules. This property of **tolerance** to self is lost in rheumatic diseases.

Two possible explanations

(1) similarity between foreign and self molecules that are recognized by immune cells, particularly T lymphocytes,

(2) viral or other infections that incite, exaggerate, or prolong otherwise self-limited immune responses.

Certain genetic factors, such as specific HLA alleles, may influence susceptibility to developing disease, whereas other factors, such as those that influence levels of baseline immune activities, may affect disease severity.

Many rheumatic diseases are characterized by a series of abnormal cellular and molecular events. T lymphocytes recognize viruses and other foreign antigens that rest in the groove of the HLA molecule on the surfaces of antigen-presenting cells. Molecular signals are released that

activate other cells such as macrophages, which produce inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), and IL-6. These cytokines cause tissue damage through direct effects and by attracting additional inflammatory cells to the affected site. Further tissue damage is sometimes mediated by B lymphocytes that are activated by helper T cells to produce excessive antibody, including autoantibodies that bind to self antigens. Normal cells in target organs can be destroyed also by complement-mediated cytolysis, direct or indirect effects of TNF-α, or effects of natural killer or cytolytic T lymphocytes.

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA) is a common, rheumatic disease of children and a major cause of chronic disability. It is characterized by a synovitis of the peripheral joints manifesting in soft tissue swelling and effusion. In the Classification Criteria of the American College of Rheumatology (ACR), JRA is regarded not as a single disease but as a category of diseases with three principal types of onset: (1) oligoarthritis or pauciarticular disease, (2) polyarthritis, and (3) systemic-onset disease.

Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joints
Duration of disease: ≥ 6 wk
Onset type defined by type of articular involvement in the 1st 6 mo after onset:
Polyarthritis: ≥5 inflamed joints
Oligoarthritis: ≤4 inflamed joints
Systemic disease: arthritis with a characteristic intermittent fever
Exclusion of other forms of juvenile arthritis

ETIOLOGY.

The etiology of this type of chronic arthritis in children is unknown. At least two necessary events are postulated: immunogenetic susceptibility and an external, presumably environmental, trigger. Specific HLA

subtypes confer varying degrees of susceptibility, or indeed protection, depending on the age of the child. Possible external triggers include viruses (parvovirus B19, rubella, Epstein-Barr virus), host hyperreactivity to specific self antigens (type II collagen), and enhanced T-cell reactivity to bacterial or mycobacterial heat shock proteins

EPIDEMIOLOGY.

The incidence of JRA is ≈13.9/100,000 children/yr among white children ≤15 yr of age, with a prevalence of ≈113/100,000 children. Different racial and ethnic groups have varying frequencies of the subtypes of JRA. African-American children may be older at onset and less likely to have elevated antinuclear antibody (ANA) titers or develop chronic uveitis.

PATHOGENESIS.

The synovitis of JRA is characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the subsynovial tissues. Vascular endothelial hyperplasia is prominent and characterized by infiltration of mononuclear and plasma cells. **Pannus formation,** which is an inflammatory exudate over the synovial lining, occurs in advanced uncontrolled disease and results in progressive erosion of articular cartilage and contiguous bone.

CLINICAL MANIFESTATIONS.

Initial symptoms may be subtle or acute, and often include morning stiffness and gelling, easy fatigability, particularly after school in the early afternoon, joint pain later in the day, and objective joint swelling. The involved joints are often warm, resist full range of motion, are painful on motion, but are not usually erythematous.

Oligoarthritis (pauciarticular disease) predominantly affects the joints of the lower extremities, such as the knees and ankles . Often, only a single joint is involved at onset. Isolated involvement of upper extremity large joints is not characteristic of this type of onset. Involvement of the hip is almost never a presenting sign of JRA. Hip disease may occur later, particularly in polyarticular JRA, and is often acomponent of a deteriorating functional course .

Polyarthritis (polyarticular disease) is generally characterized by

involvement of both large and small joints of both upper and lower extremities. As many as 20–40 joints may be affected in the more severely involved child, although inflammation of only ≥5 joints is required as a criterion for classification of this type of onset. Polyarticular disease may resemble the characteristic presentation of adult rheumatoid arthritis and the HLA profile is often similar. **Rheumatoid nodules** on the extensor surfaces of the elbows and over the Achilles tendons, while unusual, are associated with a more severe course. **Micrognathia** reflects chronic temporomandibular joint disease. Cervical spine involvement of the apophyseal joints occurs frequently with a risk of atlantoaxial subluxation and potential neurologic sequelae.

Systemic-onset disease is characterized by arthritis and prominent visceral involvement that includes hepatosplenomegaly, lymphadenopathy, and serositis, such as a pericardial effusion. It is characterized by a quotidian fever with temperatures to ≥39°C, sometimes followed by mildly hypothermic temperatures for ≥2 wk. Each febrile episode is frequently accompanied by a characteristic faint, erythematous, macular rash; these evanescent **salmon-colored lesions** may be linear or circular, from 2–5 mm in size, and are often distributed in groups with a linear distribution most commonly over the trunk and proximal extremities. This rash is not pruritic. Its most diagnostic feature is its transient nature, with a group of lesions usually lasting <1 hr. The **Koebner phenomenon,** which is cutaneous hypersensitivity to superficial trauma resulting in a localized recurrence of the rash, is suggestive, but not diagnostic, of systemic-onset disease. Heat, such as a warm bath, also evokes a reappearance of the rash.

DIAGNOSIS.

The diagnosis is greatly aided by the ACR Classification Criteria and its subclassification of course of the disease, and by the meticulous clinical exclusion of other articular diseases. There is often no one pathognomonic finding for these disorders. The classic intermittent fever in association with the typical rash and objective arthritis is highly suggestive of systemic-onset JRA. The diagnosis is based on a history compatible with inflammatory joint disease and a physical examination that confirms the presence of arthritis. Some children have persistent arthralgia despite repeated normal physical examinations. Although they do not fulfill the diagnostic criteria for JRA initially, that diagnosis may become evident as late as ≥2 yr after the initial presentation. Laboratory abnormalities characteristic of inflammation include elevated erythrocyte

sedimentation rate (ESR) and C-reactive protein (CRP), leukocytosis, thrombocytosis, and the anemia of chronic disease, which support the diagnosis.

DIFFERENTIAL DIAGNOSIS.

Arthritis can be the presenting manifestation for any of the rheumatic diseases of childhood, including

- systemic lupus erythematosus (SLE) ,
- juvenile dermatomyositis ,
- sarcoidosis ,
- the vasculitic syndromes . In scleroderma, swelling along the digits early in the disease is not confined to the joints and subsequent loss of motion may occur without any articular swelling.
- **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, a remittent fever, and polyarthritis that is usually migratory.
- Autoimmune hepatitis can be associated with an acute arthritis.
- **Lyme disease** should be considered in children living in or visiting endemic areas who present with oligoarthritis. Although a history of tick exposure, preceding flu-like illness and subsequent rash should be sought, these are not always present.
- Monarticular arthritis unresponsive to anti-inflammatory treatment may be the result of chronic mycobacterial or other infection; the diagnosis is often established only by synovial biopsy. Joint pain and swelling of a single joint suggests trauma or infection; correlation with history, laboratory, and radiologic findings helps exclude these possibilities.

LABORATORY FINDINGS.

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell and platelet counts and decreased hemoglobin concentration and mean corpuscular volume. The ESR and CRP usually mirror these findings, along with elevated serum immunoglobulins. It is not unusual for the ESR to be normal in some children with chronic arthritis. Because platelets are an acute-phase reactant, a high ESR and neutropenia with a low platelet count may be a clue to leukemia as a cause of periarticular swelling and pain.

Elevated ANA titers are present in at least 40–85% of children with oligoarticular or polyarticular JRA, but are unusual in children with systemic-onset disease.

ANA seropositivity is associated with increased risk for the development of **chronic uveitis** in a child with limited joint disease.

Rheumatoid-factor (RF) seropositivity may be associated with onset of polyarticular involvement in an older child (≈8%) and the development of rheumatoid nodules, and with a poor overall prognosis with eventual functional disability. Both ANA and RF seropositivity occur in association with transient events during childhood, such as viral infections, particularly Epstein-Barr virus.

Bone mineral metabolism and skeletal maturation are often abnormal in children with JRA with a history of active synovitis, relatively independent of onset type or course subtype, and predominantly affect appendicular cortical bone, with less effect on the normal age-related development of trabecular bone. Increased levels of cytokines such as IL-6 may decrease bone formation (reflected by decreased serum levels of osteocalcin and bone-specific alkaline phosphatase) to a greater extent than bone resorption (which may also be decreased, as reflected by decreased levels of tartrate-resistant acid phosphatase). Abnormalities of skeletal growth become most prominent during the pubertal growth spurt and in postpubertal children (Tanner stages IV–V) and lead to failure of the child to achieve acceptable peak bone mass (osteopenia).

Early radiographic changes of arthritis include soft tissue swelling, regional osteoporosis, and periosteal new-bone apposition about affected joints. Regional epiphyseal closure may be stimulated, and local bone growth decreased. In large joints, linear growth may be accelerated and limb length discrepancy, especially with involvement of a knee, becomes prominent. Continued active disease may lead to subchondral erosions and narrowing of cartilage space, especially in small tubular bones, with varying degrees of bony destruction and, potentially, fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-3 may progress to atlantoaxial subluxation. MRI studies may be helpful to evaluate both joint and soft tissues and are more sensitive to early, minimal changes than is plain radiography .

TREATMENT.

The long-term treatment of children with JRA is initiated and subsequently modified if necessary according to disease subtype, severity of the disease, specific manifestations of the illness, and responses to therapy. The objectives of treatment are to establish the child in a pattern of adaptation that is as normal as possible and to accomplish this goal with minimal risk of adverse effects .

- Most children with oligoarthritis respond to nonsteroidal anti-inflammatory drugs (NSAIDs) with relief of pain and amelioration of the signs of inflammation.
- Most children with polyarticular disease or with systemic-onset disease, however, require additional anti-inflammatory therapy.
- One approach is to use combination therapy beginning with the least toxic medications, proceeding through methotrexate and possibly etanercept or infliximab .
- Medications that place the child's present and future health most at risk, such as azathioprine and cyclophosphamide, are reserved for the few children who do not respond to less aggressive therapy.
- TNF-α blockers may prove to be more specific for synovial inflammatory disease and potentially less toxic than other immunosuppressive medications.
- Glucocorticoids are recommended only for management of overwhelming inflammatory or systemic illness, for bridge therapy early in disease in lower doses for the child who has not yet responded to conventional therapy, and for ocular control of uveitis and intra-articular use in persistent limited joint disease. Steroids are effective anti-inflammatory drugs, perhaps the most efficacious in current use for systemic disease, but they impose on the child the risk of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia.

Methotrexate is considered the safest, most efficacious, and least toxic of the currently available second-line agents for initial adjunctive therapy with an NSAID. It is given either orally or subcutaneously once weekly.

A program of management must include periodic slit-lamp ophthalmologic examinations of all patients to monitor for asymptomatic uveitis; dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake; and physical and occupational therapy. A social worker and nurse clinician can be an invaluable resource for families to recognize stresses imposed by illness, identify

appropriate community resources, and maintain compliance with the treatment protocol.

PROGNOSIS.

Although the course of JRA in an individual child is unpredictable, some prognostic generalizations can be made based on the type of onset and course subtype . Studies from the United States indicate that, based on management in the pre-TNF-α era, ≈45% of JRA patients have active disease persisting into early adulthood, often with severe limitations of physical function.