

Rheumatic illnesses may present in childhood. Some diseases, such as systemic-onset juvenile rheumatoid arthritis and pauciarticular juvenile rheumatoid arthritis, are more common in children than adults. Special considerations apply to childhood illnesses because clinical and treatment decisions are influenced by the child's growth and development; furthermore, the impact of these rheumatic diseases extends beyond the child to the entire family.

## JUVENILE RHEUMATOID ARTHRITIS

Juvenile rheumatoid arthritis (JRA) is the most prevalent rheumatic disease in children. The overall prevalence of JRA is ~30–150 per 100,000 with 70,000–100,000 inactive and active cases of JRA in the United States (1). This is approximately the same number of children as those with juvenile diabetes and at least 4 times as many children as have sickle cell anemia or cystic fibrosis (2). The course of JRA can vary widely, with some children recovering fully and others experiencing lifelong symptoms.

### Classification of JRA

The diagnostic criteria for JRA include disease onset at <16 years of age, defined as persistent arthritis in 1 or more joints for 6 weeks or longer, and exclusion of other types of childhood arthritis (such as reactive arthritis, inflammatory bowel disease, or systemic lupus erythematosus) (3). The disease-onset subtype of JRA is defined by clinical symptoms that appear in the first 6 months of disease. JRA is divided into 3 subtypes: pauciarticular, polyarticular, or systemic.

A recent classification system developed by the International League Against Rheumatism is being used to more rigorously define arthritis (4). The term juvenile idiopathic arthritis is used in this classification system, which separates the idiopathic arthritides of childhood into 8 separate categories: systemic arthritis; oligoarthritis-persistent, with <5 joints involved at any time during the onset or course of disease; oligoarthritis-extended, with arthritis in <5 joints in the first 6 months of disease but affecting a cumulative total of  $\geq 5$  joints after the first 6 months; polyarthritis-rheumatoid factor negative; polyarthritis-rheumatoid factor positive; enthesitis-related arthritis; psoriatic arthritis; and other.

### Pauciarticular JRA

Pauciarticular JRA is defined by involvement of <5 joints after 6 months of disease. It is further subdivided into early-onset or late-onset. Children with early-onset pauciarticular JRA typically are <5 years old, are more often girls, and are more often antinuclear antibody (ANA) positive. A positive ANA is associated with an increased risk of uveitis. Early-onset pauciarticular JRA has the highest prevalence of uveitis, with eye involvement reported in 30–50% (5). The uveitis usually begins in the anterior chamber of the eye and is usually not associated with any

systemic symptoms. If the uveitis progresses, children may suffer from serious complications, including cataracts, glaucoma, and cystoid macular edema. Ophthalmologic screening for children diagnosed before age 7 with a positive ANA is recommended every 3 months. If children <7 years old at diagnosis have had normal eye exam results for 7 years, or were diagnosed at  $\geq 7$  years and have normal eye examination results for 4 years, the frequency of eye exams can be decreased to once every 12 months (6).

Late-onset pauciarticular JRA is more common in boys and 50% are HLA-B27 positive. These children are more likely to have enthesitis or tendinitis. The arthritis typically involves the large joints, such as the hips, knees, or ankles. The differential diagnosis includes the spondyloarthropathies (including ankylosing spondylitis), arthritis secondary to inflammatory bowel disease, and psoriatic arthritis. Eye involvement is less common than in early-onset JRA and, in contrast, is usually associated with significant pain, photophobia, and sudden onset.

### Polyarticular JRA

Polyarticular JRA is defined as involvement of >5 joints after 6 months of illness. It is the second most common subtype of JRA with a prevalence of 30–40%. There is a bimodal distribution of age of onset, with the first peak at 2–5 years and the second peak at 10–14 years. Girls are more commonly affected than boys. Two distinct subgroups of children can be defined based on the presence or absence of rheumatoid factor (RF). RF-positive children are usually older (>8 years) with a female predominance. Children with RF are at increased risk of developing joint erosions and rheumatoid nodules, because disease manifestations are similar to those found in adult RA.

### Systemic-Onset JRA

Systemic-onset JRA accounts for ~10% of cases. It is characterized by daily or twice-daily fever spikes  $>101^{\circ}\text{F}$  (quotidian fever) as well as a salmon-colored, blanching, nonpruritic rash. The rash and joint symptoms may wax and wane during febrile episodes. The rash of systemic-onset JRA is often present on the trunk and proximal extremities and may involve the palms and soles. Superficial trauma or pressure to the skin may cause eruption of the rash. Children may initially present with significant arthralgias, rather than frank arthritis, at the onset of systemic JRA. Serositis, pleuritis, pericarditis, hyperbilirubinemia, elevated liver enzyme levels, leukocytosis, and anemia may be part of the initial presentation, making exclusion of infectious or hematologic causes of fever and systemic symptoms critical.

### Complications of JRA

Linear growth retardation is seen in children with active JRA, particularly with systemic or polyarticular-onset. The degree of linear growth retardation depends on the severity and duration of inflammation as well as the use of corticosteroids. Pauciarticular JRA may lead to localized growth

abnormalities, such as leg-length discrepancy. Leg-length measurements should be recorded at each visit and if discrepancies are noted, orthotic shoe inserts should be used to avoid a compensatory scoliosis. Early in the course of disease, bony development is accelerated due to increased blood flow to the growth plate, and the affected leg may appear longer. However, later in the course of the illness, after the epiphyseal junction has fused, the opposite may be true. Micrognathia and malocclusion are also common sequelae of localized growth defects in the temporomandibular joint in JRA. Orthodontic consultation is recommended.

Osteopenia, or low bone mass for age, may be seen in children with JRA. Both the cortical appendicular skeleton and axial trabecular bone may be involved. The degree of osteopenia correlates with disease activity and severity. Medications, such as corticosteroids, may also contribute to osteopenia. Therapy includes weight-bearing exercises, appropriate nutrition, as well as calcium and vitamin D supplementation.

Cardiac involvement may occur in up to one-third of systemic-onset JRA patients. Pericarditis, myocarditis, or endocarditis may occur, with pericarditis being the most common. Chest pain, dyspnea on exertion, or a friction rub on examination should prompt further testing, including x-ray or echocardiography. These episodes may last for weeks to months and are generally associated with arthritis flares. Treatment includes antiinflammatory medications, including corticosteroids.

Adequate nutritional status is critical for children with JRA to minimize growth abnormalities. Protein stores, iron, selenium, vitamin C, and zinc have been reported to be low in children with JRA. In addition, some patients may have mechanical problems with feeding due to jaw involvement. Medications may also impact nutritional status. For example, corticosteroids may increase appetite, elevate blood sugar, and lead to excessive weight gain.

## Treatment of JRA

The optimal treatment of JRA involves physical, social, and pharmacologic strategies. Physical modalities include range-of-motion exercises for involved joints and splints to minimize joint deformity or to correct joint contractures. Active participation in physical and occupational therapy is often essential for maintaining joint mobility and physical functioning in JRA.

Social programs should involve the entire family, as family factors greatly influence a child's ability to cope with this chronic illness. Some studies have concluded that there is an increased risk of psychosocial problems in children with JRA and that chronic family difficulties predicted these problems more so than disease severity. Positive family factors also influence adherence to medications. A highly cohesive family structure that stresses individual freedom with eventual self-mastery of medications seems best suited to transition the pediatric patient into adulthood. The Arthritis Foundation and the American Juvenile Arthritis Organization are excellent resources for educational programs in family coping skills.

Pharmacologic therapy is tailored to disease severity. In pediatrics, the dose of the medicine is based on the weight of the child, with the maximum being the standard adult dose. This applies for all medicines, but has particular importance for cytotoxic medications in which the risk of side effects is high.

Often in patients with mild arthritis, such as pauciarticular JRA, nonsteroidal antiinflammatory drugs (NSAIDs) alone are sufficient. Treatment requires a full antiinflammatory dose, which is often larger than that needed for pain control alone (7). Methotrexate, at dosages of 10 mg/m<sup>2</sup>, is used primarily for treatment of polyarticular or systemic-onset JRA. Approximately 70% of patients show clinical improvement while taking methotrexate, although the rate of response is lower in systemic-onset JRA patients with significant systemic symptoms (8).

In patients who do not respond to methotrexate at dosages of 10 mg/m<sup>2</sup>, higher dosages of up to 1 mg/kg/week (maximum of 50 mg/week) have been shown to be well tolerated and beneficial. At doses >20 mg/m<sup>2</sup>, oral absorption of methotrexate may be unpredictable and subcutaneous parenteral administration is recommended (9). Therapeutic benefit of methotrexate may not be evident for 3–4 weeks and the maximal response is not reached for 3–6 months. Methotrexate side effects include nausea, oral ulcers, decreased appetite, and abdominal pain. The gastrointestinal side effects may be minimized with subcutaneous administration or oral folate administration.

Tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) antagonists have also been used effectively in JRA. In a randomized, prospective, placebo-controlled trial in children with methotrexate-resistant polyarticular JRA, treatment with etanercept resulted in a clinically significant improvement in joint exam, sedimentation rate, and C-reactive protein (10). Infliximab, another TNF $\alpha$  antagonist, has been shown to be effective for treatment of the uveitis associated with JRA (11). Other biological agents, including an interleukin-1 (IL-1) receptor antagonist, have also been studied in JRA. In children with systemic-onset JRA, investigators have demonstrated increased IL-1 in peripheral blood mononuclear cells (12). In systemic-onset patients who had failed to receive benefit with methotrexate and TNF-receptor antagonists, treatment with an IL-1 receptor antagonist resulted in dramatic improvement in systemic symptoms and arthritis.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a diverse array of presentations. As in adults, SLE in children can involve any organ system. The American College of Rheumatology criteria for the classification of SLE applies to children; however, the natural history of disease may be quite variable (13). Pediatric SLE may present insidiously, making diagnosis difficult, or may present acutely with rapid progression, leading to death.

SLE accounts for 10% of patients with pediatric rheumatic diseases, with an estimated prevalence of 5,000–10,000 children in the United States (14). SLE is much more common in adolescent girls. Girls are affected 5 times more frequently than boys, and disease prevalence is higher in African Americans, Asians, and Hispanics. The disease is rare in children younger than 5 years; before menarche, the female-to-male ratio is equal.

Although available immunologic tests have made the diagnosis of SLE easier, a high index of suspicion is required for obtaining the necessary tests. Early symptoms of pediatric SLE, including fever, fatigue, anorexia, and weight loss, may be quite nonspecific and can mimic viral syndromes. Infants may also develop an SLE-like syndrome. SS-A antibody of the IgG class may pass from the mother across the placenta to the fetus, leading to positive serologies and diagnosis of neonatal SLE. Infants present with rash, thrombocytopenia, hemolytic anemia, or congenital heart block. With the exception of congenital heart block, the symptoms of neonatal SLE are transient and resolve over a few months as the antibodies are cleared.

Cutaneous manifestations of SLE occur in ~80% of pediatric patients at some time in the course of disease. The malar rash (butterfly rash) can be seen in one-third of patients and presents with erythema, with possible whitish scale and sparing of the nasolabial folds. Alopecia can occur in 20% of patients and may present as patchy, scaling areas on the scalp, leading to scarring and permanent baldness. Mucocutaneous ulcerations in the oral or nasal cavity can also be seen in pediatric SLE.

SLE arthritis is usually more transient and episodic compared with that seen in JRA. Jaccoud arthropathy in SLE is a nondeforming,