Juvenile Idiopathic Arthritis

Educational Gap

Juvenile idiopathic arthritis affects around 294,000 children in the United States. In 2001, a new classification of the disorder and its subtypes was created. Current therapies, including the use of biologic medications, have improved the prognosis of this condition significantly.

Objectives  After completing this article, readers should be able to:

1. Understand the pathophysiology of juvenile idiopathic arthritis (JIA).
2. Recognize the clinical features of the different types of JIA.
3. Be aware of the complications of JIA.
4. Know the treatment of JIA.

Introduction

Juvenile idiopathic arthritis (JIA) is a broad term used to describe several different forms of chronic arthritis in children. All forms are characterized by joint pain and inflammation. The older term, juvenile rheumatoid arthritis, has been replaced by JIA to distinguish childhood arthritis from adult-onset rheumatoid arthritis and to emphasize the fact that arthritis in childhood is a distinct disease. JIA also includes more subtypes of arthritis than did juvenile rheumatoid arthritis.

JIA is the most common rheumatologic disease in children and is one of the more frequent chronic diseases of childhood. The etiology is not completely understood but is known to be multifactorial, with both genetic and environmental factors playing key roles. Without appropriate and early aggressive treatment, JIA may result in significant morbidity, such as leg-length discrepancy, joint contractures, permanent joint destruction, or blindness from chronic uveitis.

Definition

Arthritis is defined as joint effusion alone or the presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased warmth in one or more joints. JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age. JIA is a diagnosis of exclusion. A number of conditions, such as infections, malignancy, trauma, reactive arthritis, and connective tissue diseases such as systemic lupus erythematosus (SLE), must be excluded before a diagnosis of JIA can be made (1) (Table 1).

JIA is subdivided into seven distinct subtypes in the classification scheme established by the International League of Associations for Rheumatology in 2001 (Table 2). The subtypes differ according to the number of joints involved, pattern of specific serologic markers, and systemic manifestations present during the first 6 months of disease. These categories were established to reflect similarities and differences among the different subtypes so as to facilitate communication among physicians worldwide, to facilitate research, and to aid in understanding prognosis and therapy. (2)

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
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<tr>
<td>ARF</td>
<td>acute rheumatic fever</td>
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<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>JIA</td>
<td>juvenile idiopathic arthritis</td>
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<tr>
<td>MAS</td>
<td>macrophage activation syndrome</td>
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<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>RF</td>
<td>rheumatoid factor</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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*The Steven and Alexandra Cohen Children’s Medical Center of New York, North Shore Long Island Jewish Health System, New Hyde Park, NY.
Epidemiology

It has been estimated that JIA affects ~294,000 children between the ages of 0 and 17 years in the United States. The incidence and prevalence of JIA vary worldwide. This difference likely reflects specific genetic (eg, HLA antigen alleles) and environmental factors in a given geographic area. The incidence rate has been estimated as 4 to 14 cases per 100,000 children per year, and the prevalence rates have been reported as 1.6 to 86.0 cases per 100,000 children. JIA tends to occur more frequently in children of European ancestry, with the lowest incidence rates reported among Japanese and Filipino children.

In white populations with European ancestries, oligoarticular JIA is the most common subtype. In children of African American descent, however, JIA tends to occur at an older age and is associated with a higher rate of rheumatoid factor (RF)-positive polyarticular JIA and a lower risk of uveitis.

Different subtypes of JIA vary with respect to age and gender distributions (Table 2). Oligoarticular JIA, for example, occurs more frequently in girls, with a peak incidence in children between 2 and 4 years of age. Polyarticular JIA also occurs more frequently in girls and has a bimodal age of onset; the first peak is from 1 to 4 years of age and the second peak occurs at 6 to 12 years of age.

Table 1. Differential Diagnosis of Arthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>Reactive</td>
<td>Poststreptococcal Rheumatic fever Serum sickness “Reiter syndrome”</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Juvenile idiopathic arthritis Inflammatory bowel disease Sarcoidosis</td>
</tr>
<tr>
<td>Infection</td>
<td>Septic joint Postinfectious: toxic synovitis Viral (eg, Epstein–Barr virus, parvovirus) Lyme disease Osteomyelitis Sacroilitis, bacterial Discitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Systemic lupus erythematous Henoch–Schönlein purpura Serum sickness Dermatomyositis Mixed connective tissue disease Progressive systemic sclerosis Periodic fever syndromes Psoriasis Kawasaki disease Behçet disease</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Leukemia Neuroblastoma Malignant bone tumors (eg, osteosarcoma, Ewing sarcoma, rhabdosarcoma)</td>
</tr>
<tr>
<td>Benign bone tumors</td>
<td>Osteoid osteoma Osteoblastoma</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
</tbody>
</table>


Pathogenesis

The cause of JIA is not well understood, but is believed to be influenced by both genetic and environmental factors. Twin and family studies strongly support a genetic basis of JIA; concordance rates in monozygotic twins range between 25% and 40%, and siblings of those affected by JIA have a prevalence of JIA that is 15- to 30-fold higher than the general population.

Strong evidence has been reported for the role of HLA class I and II alleles in the pathogenesis of different JIA subtypes. HLA-B27 has been associated with the development of inflammation of the axial skeleton with hip involvement, and often is positive in patients who have enthesitis-related arthritis. HLA-A2 is associated with early-onset JIA. The class II antigens (HLA-DRB1*08, 11, and 13 and DPB1*02) are associated with oligoarticular JIA. HLA-DRB1*08 is also associated with RF-negative poly JIA.

Clinical features of systemic-onset JIA mostly resemble autoinflammatory syndromes, such as familial Mediterranean fever, and there is a lack of an association between systemic-onset JIA and HLA genes. As a result, many conclude that systemic-onset JIA should be considered a separate entity, distinct from the other JIA subtypes.

Cell-mediated and humoral immunity play a role in the pathogenesis of JIA. T cells release proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and IL-1, which are found in high levels in patients who have polyarticular JIA and systemic-onset JIA. Evidence for the role of T cells in JIA comes from studies that show oligoclonal expansion of T cells and a high percentage of activated T cells in the synovium of patients who have JIA.
<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Frequency (% of all JIA)</th>
<th>Age of Onset</th>
<th>Sex Ratio</th>
<th>Susceptibility Alleles</th>
</tr>
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<tbody>
<tr>
<td>Systemic onset juvenile idiopathic arthritis (JIA)</td>
<td>Arthritis in one or more joints with or preceded by fever of at least 2 weeks’ duration that is documented as daily (“quotidian”) for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, (4) serositis</td>
<td>4%–17%</td>
<td>Childhood</td>
<td>F=M</td>
<td>HLA-DRB1*11</td>
</tr>
<tr>
<td>Oligo JIA</td>
<td>Arthritis affecting one to four joints during the first 6 months of disease</td>
<td>27%–56%</td>
<td>Early childhood; peak at 2–4 years</td>
<td>F&gt;&gt;M</td>
<td>HLA-DRB1<em>08, HLA-DRB1</em>11, HLA-DQA1<em>04, HLA-DQA1</em>05, HLA-DQB1*04, HLA-A2 (early onset)</td>
</tr>
<tr>
<td>Persistent</td>
<td>Affects no more than four joints throughout the disease course</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Extended</td>
<td>Affects more than four joints after the first 6 months of disease</td>
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<tr>
<td>Polyarthritis (RF-negative)</td>
<td>Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative</td>
<td>11%–28%</td>
<td>Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years</td>
<td>F&gt;&gt;M</td>
<td>HLA-DRB1*0801</td>
</tr>
<tr>
<td>Polyarthritis (RF-positive)</td>
<td>Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart</td>
<td>2%–7%</td>
<td>Late childhood or adolescence</td>
<td>F&gt;&gt;M</td>
<td>HLAB1*04, HLA-DR4</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, (3) family history of psoriasis in a first-degree relative</td>
<td>2%–11%</td>
<td>Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years</td>
<td>F&gt;M</td>
<td>HLA-B27 IL23R (new association)</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
<td>Arthritis or enthesitis with at least two of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27 antigen, (3) onset of arthritis in a male &gt;6 years old, (4) acute anterior uveitis, (5) family history in a first-degree relative of HLA-B27–associated disease</td>
<td>3%–11%</td>
<td>Late childhood or adolescence</td>
<td>M&gt;F</td>
<td>HLA-B27 ERAP1 (new association)</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>Arthritis that fulfills criteria in no category or in two or more of the above categories</td>
<td>11%–21%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


Recently, inflamed joints in patients who have JIA have been shown to have high levels of IL-17–producing T cells; IL-17 induces the production of other interleukins and matrix metalloproteinases that are all involved in joint damage. The role of humoral immunity in JIA pathogenesis is supported by the increased level of autoantibodies, such as antinuclear antibodies (ANAs) and immunoglobulins, by complement activation, and by the presence of circulating immune complexes. (5)

Other possible factors that have been implicated in the pathogenesis of JIA include immunologic dysregulation, psychological stress, trauma, hormonal abnormalities, and infectious triggers.

Clinical Features
JIA is divided into seven subtypes defined by clinical features during the first 6 months of disease. The International League of Associations for Rheumatology classification of JIA includes the following subtypes: (1) Systemic-onset arthritis, (2) oligoarticular arthritis, (3) polyarticular RF-positive arthritis, (4) polyarticular RF-negative arthritis, (5) psoriatic arthritis, (6) Enthesitis-related arthritis, and (7) undifferentiated arthritis, or “other.” Each subtype varies with respect to clinical presentation, pathogenesis, treatment outcomes, and prognosis. All subtypes of JIA, however, share common symptoms, such as morning stiffness or “gelling phenomenon” (stiffness after a joint remains in one position for a prolonged period) that improves throughout the day, limp, swollen joints, limitation of activities because of pain, and periods characterized by disease remission interspersed with disease flares.

There is no diagnostic test for JIA; therefore, other causes of arthritis must be excluded carefully before the diagnosis is made.

Systemic-Onset JIA
Systemic-onset JIA is distinct compared with the other subtypes in that it is characterized by the presence of high-spiking fevers of at least 2 weeks’ duration in addition to arthritis. The disease affects 10% to 15% of children who have JIA, and tends to affect boys and girls equally, with a peak age of onset between 1 and 5 years. Early in the disease course, patients can present with fatigue and anemia. The fever in systemic JIA is characterized by temperatures >39°C that occur daily or twice daily, with a rapid return to baseline or below baseline (quotidian pattern). Fever spikes usually occur in the late afternoon or evening. Children often appear ill during febrile periods and look well when the fever subsides.

The rash in systemic JIA is described typically as an evanescent, salmon-colored macular rash that accompanies febrile periods (Fig 1). The rash generally is nonpruritic and occurs most commonly on the trunk and proximal extremities, including the axilla and inguinal areas. (2) Other extra-articular manifestations that can be seen in systemic JIA include hepatosplenomegaly, lymphadenopathy, pulmonary disease, such as interstitial fibrosis, and serositis, such as pericarditis. The febrile period and other systemic features may precede the onset of arthritis by weeks to months. A definite diagnosis of JIA, however, cannot be made until arthritis is detected on physical examination. (6)

Laboratory abnormalities typically observed in systemic JIA include anemia, leukocytosis, thrombocytosis, elevated liver enzymes, and acute-phase reactants, such as erythrocyte sedimentation rate, C-reactive protein, and ferritin. ANA titer is usually negative and is not helpful in making the diagnosis.

Complications of systemic JIA include infection from immunosuppressive therapy, growth disturbances, osteoporosis, cardiac disease, amyloidosis (rare in North America compared with other parts of the world), and macrophage-activation syndrome (MAS) (Table 3). MAS occurs in about 5% to 8% of children who have systemic JIA and is characterized by persistent fever, pancytopenia, hepatosplenomegaly, liver dysfunction, coagulopathy, and neurologic symptoms. Bone marrow examination
in patients who have MAS reveals phagocytosis of hematopoietic cells by macrophages. (2) Triggers of MAS include viral infections and certain changes in medications.

Laboratory abnormalities include pancytopenia, prothrombin time and partial thromboplastin time, and elevated levels of D-dimer, triglycerides, and ferritin. Contrary to what would be expected, the erythrocyte sedimentation rate typically falls in MAS because of the low fibrinogen levels resulting from a consumption coagulopathy and hepatic dysfunction. Because MAS carries a significant mortality rate of approximately 20% to 30%, early recognition and treatment of MAS with corticosteroids or cyclosporine is important to prevent multisystem organ failure. (6)

Diagnosis of systemic JIA involves the exclusion of other conditions, such as infections, malignancy, collagen vascular diseases, and acute rheumatic fever (ARF). Infections tend to have less-predictable fever patterns than systemic JIA. Children who have leukemia tend to have leukopenia, thrombocytopenia, and elevated lactic dehydrogenase levels. In ARF, the fever tends to be persistent, the arthritis is migratory and asymmetric, cardiac involvement often is associated with endocarditis, and the rash (referred to as erythema marginatum) is associated with an expanding margin. Antistreptolysin O titers can be elevated in any inflammatory condition; however, the more specific antibodies for streptococcal infection, such as antideoxyribonuclease β, antistreptokinase, and antihyaluronidase, would be elevated only in ARF, indicating a recent group A streptococcal infection.

The prognosis of systemic JIA depends on the severity of the arthritis. Most systemic symptoms resolve over months to years, and mortality, which is <0.3% in North America, is associated mainly with MAS and infections secondary to immune suppression. (6)

### Oligoarticular JIA

Oligoarticular JIA is defined as arthritis that affects four or fewer joints in the first 6 months of disease. This subtype accounts for ~50% of cases of chronic arthritis in children and can be subdivided further into persistent oligoarthritis (affecting four or fewer joints throughout the disease course) or extended oligoarthritis (affecting more than four joints after the first 6 months of disease). The peak age of onset is between 2 and 4 years, with a female-to-male ratio of ~3:1.

Children who have oligoarticular JIA generally are well appearing and typically present with arthritis that affects the lower extremities (Fig 2). In 30% to 50% of cases, one joint is affected at presentation, with the knee being the most commonly affected joint (~89%). (2) The hip joint is affected rarely in oligoarticular JIA. The typical presentation is that of a child who presents with a limp and is found to have a warm and swollen joint that is not very painful or tender. The pain tends to be worse in the morning or after being in one position for an extended period of time (the “gelling phenomenon”).

Growth disturbance may result from prolonged arthritis in a joint, resulting from increased blood flow to the

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**Table 3. Macrophage Activation Syndrome**

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Bruising, purpura, mucosal bleeding</th>
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<tbody>
<tr>
<td>Laboratory findings</td>
<td>Elevated: AST, ALT, PT, PTT, fibrin degradation products, ferritin, triglycerides</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Active phagocytosis by macrophages and histiocytes</td>
</tr>
<tr>
<td>Treatment</td>
<td>Intravenous glucocorticoid, cyclosporine</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time; PTT = partial thromboplastin.

growth plate at sites of inflammation, which leads to overgrowth. This complication is most common with knee arthritis and it leads to a leg length discrepancy. Later in the disease course, growth disturbances can result also from growth plate damage or premature fusion of the epiphyseal plates, leading to undergrowth of an affected extremity. (6)

One of the most serious complications of JIA is iritis. Approximately 15% to 20% of children who have oligoarticular JIA are found to have iritis. The iritis tends to be a chronic, anterior, nongranulomatous inflammation affecting the iris and ciliary body and often is asymptomatic. This complication tends to occur in girls affected with oligoarticular JIA at a young age who have positive ANA titers. Appropriate ophthalmologic screening evaluation is imperative in all children who have JIA, especially those who have oligoarticular JIA and are ANA-positive (Table 4). If left untreated, complications include corneal clouding, cataracts, band keratopathy, synechiae, glaucoma, and visual loss (Fig 3). The outcome depends on early diagnosis and treatment. (2)

The differential diagnosis of a child with oligoarthritis includes trauma, septic arthritis, Lyme disease, postinfectious arthritis, and malignancy. In a child who presents with features of an infectious illness, synovial fluid analysis and cultures are important to distinguish inflammatory from infectious processes. In a septic joint, for example, there usually are more than 100,000 white blood cells/mm³, with 90% being polymorphonuclear neutrophils. Lyme arthritis can occur weeks to months after the initial infection, and children typically will present with acute onset of a large, swollen joint, typically the knee.

In children who have oligoarticular JIA, laboratory evaluation may be normal or indicate a mild increase in inflammatory markers. Tests for RF often are negative, and tests for ANA may be positive in low titers in 70% to 80% of children who have oligoarthritis, especially girls and those who have iritis. (2)

Among children who have JIA, those with oligoarthritis have the best prognosis. Children who develop a more complicated disease, characterized by joint space narrowing, bone erosions, and flexion contractures, are more likely to be those who have a polyarticular course.

Polyarticular JIA

Children affected by arthritis in five or more joints during the first 6 months of disease are diagnosed as having polyarticular JIA. Polyarticular JIA can be either RF-positive (seropositive) or RF-negative (seronegative). RF-positive disease affects approximately 5% to 10% of patients who have JIA and mainly affects girls in late childhood or early adolescence. Seropositive patients tend to develop an arthritis similar to adult rheumatoid arthritis, having a more aggressive disease course. There tends to be symmetric, small joint involvement of both the hands and feet and the cervical spine and temporomandibular joints also may be affected (Fig 4). Rheumatoid nodules and a more severe erosive disease characterized by joint deformities (ie, Boutonnière and Swan neck contractures) also may occur in patients who are RF-positive. (1) Patients with RF-negative arthritis tend to have involvement of fewer joints and have a better overall functional outcome.

Children who have polyarticular JIA may present with morning stiffness, joint swelling, and limited range of motion of the affected joints. In addition, they also may experience fatigue, growth disturbances, elevated inflammatory markers, and anemia of chronic disease. Iritis may develop, although less frequently than in patients who have oligoarticular disease.

The differential diagnosis of patients presenting with polyarthritis includes infection, malignancy, and other collagen vascular disorders such as SLE. Polyarthritis in an adolescent girl could be an initial manifestation of SLE; serologic tests for lupus must be sent.

Table 4. American Academy of Pediatrics Guidelines for Screening Eye Examinations

<table>
<thead>
<tr>
<th>Juvenile Idiopathic Arthritis (JIA) Subtype</th>
<th>Risk of Iritis</th>
<th>Examination Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarticular or polyarticular, onset &lt;7 years of age and antinuclear factor +</td>
<td>High risk</td>
<td>Every 3–4 months</td>
</tr>
<tr>
<td>Oligoarticular or polyarticular and antinuclear antibody (−) regardless of age</td>
<td>Medium risk</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Onset &gt;7 years of age regardless of antinuclear antibody status</td>
<td>Medium risk</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Systemic onset JIA</td>
<td>Low risk</td>
<td>Every 12 months</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis
Juvenile psoriatic arthritis is characterized as an asymmetric arthritis that can affect both large and small joints and typically has an onset in mid childhood. The condition is defined more specifically by the presence of arthritis and the typical psoriatic rash, or any two of the following if the rash is absent: family history of psoriasis in a first-degree relative, dactylitis (diffuse swelling of fingers extending beyond the joint margin), and nail pitting (Fig 5). Children who have psoriatic arthritis may develop iritis and should therefore undergo slit-lamp evaluations every 6 months. These children also may be found to be ANA-positive and HLA-B27-positive, especially when there is inflammation of the axial skeleton. (1)

Enthesitis-Related Arthritis
Children affected by enthesitis-related arthritis generally are boys >8 years of age. This type of arthritis is characterized by the presence of enthesitis, or inflammation at the sites of tendon insertions onto bone. Most patients afflicted with this type of arthritis are HLA-B27-positive. Patients typically complain of pain, stiffness, and loss of mobility of the lower back, and can present with arthritis in lower extremity joints. Unlike other JIA subtypes, the sacroiliac joints can be involved at presentation. Children with this subtype may experience anterior or acute iritis, which is characterized by injected, erythematous conjunctiva, photophobia, and pain. Many patients who have this type of arthritis have a positive family history of an HLA-B27-related disease, such as IBD, psoriasis, or ankylosing spondylitis (AS). (2)

Patients who have enthesitis-related arthritis may develop AS, reactive arthritis, or IBD-associated arthritis. Children who have AS typically present with limitation and pain of the lumbar spine and may have evidence of sacroiliac joint inflammation on imaging. AS is most common in boys, with a male-to-female ratio of 7:1, and 90% of patients are found to be positive for HLA-B27. Reactive arthritis often occurs after a genitourinary or gastrointestinal infection and often is associated with conjunctivitis and urethritis. Patients who have IBD may present initially with an asymmetric arthritis involving joints of the lower extremities. Flares of IBD also may be associated with episodic arthritis. (1)

Undifferentiated Arthritis
Children diagnosed as having an undifferentiated arthritis generally do not meet inclusion criteria for any other category, or they may meet criteria for more than one. (2)
Complications

One of the more common and devastating complications associated with JIA is iridocyclitis, a form of chronic anterior uveitis. The condition occurs in approximately 15% to 20% of patients who have JIA and can lead to permanent blindness. (6) It is critical that children who have JIA be screened routinely for iritis because the uveitis can be diagnosed early in the course only with a slit lamp examination by an ophthalmologist. The frequency of required examinations is determined by the child’s age and his or her ANA status. Children < 6 years of age who have a positive ANA titer are at highest risk and require evaluation every 3 to 4 months (Table 4). Only the systemic subtype has a minimal risk of iritis and therefore does not require routine screening.

Growth disturbances (ie, leg length discrepancy) must be considered and monitored in growing children who have chronic arthritis. Prolonged arthritis affecting a knee can result in accelerated growth of the affected leg. Prolonged arthritis in ankles or feet and wrists or hands usually results in local growth retardation. Arthritis of the temporomandibular joint can be particularly devastating because of the growth plate’s close proximity to the joint space, resulting in micrognathia.

Osteopenia and osteoporosis, permanent joint damage, and persistent arthritis leading to significant disability and functional limitations are other complications of prolonged uncontrolled arthritis. Psychosocial factors, such as anxiety and school absenteeism, also can occur in children who have a more prolonged disease course. (1)

Treatment

Treatment of JIA relies on a multidisciplinary approach that includes physical and occupational therapy, pharmacologic therapy, and psychosocial interventions. The goal is to implement therapy early in the disease course to prevent the morbidity associated with JIA, such as pain, joint limitation, contractures, and growth disturbances. There is no cure for JIA at present, but current therapies, including the use of biologic medications, have improved the prognosis of this condition significantly. (7) Readers should be aware that some of the drugs used to treat JIA have not been approved by the Food and Drug Administration (FDA) for that indication, including methotrexate, infliximab, anakinra, rilonacept, and rituximab. Clinicians can check the current approval status at the time they are considering the use of any specific agent.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment for patients who have JIA. The most commonly used NSAIDs in children include ibuprofen, naproxen, and indomethacin. NSAIDs may be sufficient to control cases of mild arthritis. Most children tolerate NSAIDs well, but a few develop adverse effects, such as abdominal pain; hematologic, renal, hepatic, and neurologic adverse effects can occur also. Pseudoporphyria cutanea tarda, a rash manifested by small blisters in fair-skinned children occurring after sun exposure, may occur with naproxen. Cox-2 inhibitors, such as celecoxib, occasionally are used in patients who have severe gastrointestinal complaints. In children who have IBD, traditional NSAIDs should be avoided because these can cause a flare in the bowel symptoms. Cox-2 inhibitors would be the choice in this condition.

Intra-articular corticosteroid injections may be very effective in controlling arthritis in patients who have limited disease, such as persistent oligoarthritis. Triamcinolone hexacetonide is used commonly and may lead to rapid resolution of inflammation that may last for a prolonged time and replace the need for oral therapy. Oral or intravenous (IV) corticosteroids are used mainly for systemic manifestations of JIA and, in some cases, for severe polyarthritis. Patients may be given low doses of prednisone to obtain symptomatic relief of pain and stiffness while waiting for a second-line agent to become effective. High-dose solumedrol or a “pulse” (30 mg/kg with a maximum of 1 g) may be given in systemic-onset JIA that is refractory to oral corticosteroids or to gain control over the disease rapidly with fewer adverse effects than high-dose oral corticosteroids. Adverse effects of corticosteroids are seen most commonly at higher dosages (eg, >20 mg/d) and include immunosuppression, adrenal suppression, increased appetite and weight gain, acne, mood changes, osteoporosis and avascular necrosis, cataracts and increased intraocular pressures, cushingoid features, and diabetes. (2)

Disease-modifying antirheumatic drugs are agents that slow the radiologic progression of disease and are required by two-thirds of children. These agents include sulfasalazine, azathioprine, hydroxychloroquine, leflunomide, cyclosporin, and methotrexate. Methotrexate, a folate antagonist, is the disease-modifying antirheumatic drug most commonly prescribed in children who have more aggressive arthritis. Methotrexate is given once weekly in either the oral or subcutaneous route. The effects of this medication generally are seen within 6 to 12 weeks. Adverse effects mainly include gastrointestinal manifestations, such as oral ulcers, abdominal pain, nausea, decreased appetite, and hepatic dysfunction (ie, elevation of liver enzymes). Folic acid can be administered to decrease these gastrointestinal side effects.

Pulmonary toxicity is a known adverse effect that rarely occurs in children. There is an increased risk of
immunosuppression while on methotrexate and patients should not receive any live virus vaccines such as measles-mumps-rubella, varicella, and intranasal flu vaccines. A child taking methotrexate who develops a fever or is unwell should be examined by the pediatrician and have studies sent (complete blood count, blood and urine cultures) to exclude an underlying bacterial infection. An increased risk of lymphoproliferative malignancies also is reported in children who take methotrexate, but this effect has not been proven clearly. Blood counts and liver enzymes are monitored every 4 to 8 weeks while a child is taking methotrexate. The treatment period is not defined clearly, but generally, a child is treated with methotrexate for at least 1 year after achieving disease remission. Overall, methotrexate is a very safe and effective drug and is now considered a “gold-standard” therapy for children who have JIA. (2)(8)

Use of biologic agents has improved the morbidity associated with JIA significantly. Biologic drugs are medications, such as monoclonal antibodies, soluble cytokine receptors, and receptor antagonists, that target specific proteins involved in the inflammatory cascade. All biologics are given through the IV or subcutaneous route. All of these agents carry a risk of immunosuppression and cytopenias; therefore, a child taking a biologic agent must be followed closely with detailed physical examinations and laboratory studies.

As with methotrexate, a child taking a biologic who develops a fever or appears unwell even without a fever (biologics such as anti-TNFs can block the febrile response despite active infection) must be examined and have blood work to exclude a serious bacterial infection. Biologics should not be given while a child is acutely ill. Also, children on biologics should not be given live vaccines. Reactivation of tuberculosis is another potential complication, and patients are screened for tuberculosis before the start of therapy and then yearly while on these medications. (8)

Elevated levels of TNF-α are found in patients who have JIA. Etanercept, infliximab, and adalimumab are biologic agents that block TNF-α. Etanercept is a soluble TNF receptor that binds and inhibits TNF-α and was approved by the FDA in 1999 for the treatment of JIA in children >2 years of age. The drug has been shown to be highly effective in patients who have extended oligoarthritis or polyarticular JIA who were not responsive to treatment with NSAIDs or methotrexate. In addition to the risk of immunosuppression, headache, upper respiratory tract infections, and injection site reactions are other common adverse effects.

Infliximab, a chimeric monoclonal antibody to TNF-α that is given through the IV route, has been shown to be efficacious in the treatment of JIA and uveitis. Adalimumab, a humanized monoclonal antibody to TNF, was the second biologic agent to be approved by the FDA in 2008 for moderate to severe JIA in children >4 years of age. Unlike etanercept, which is given once weekly, adalimumab is given once every 2 weeks and has been shown to be effective in patients who have polyarticular JIA. Elevated levels of IL-1 and IL-6 are found in the sera and synovial fluid of patients who have JIA. These levels are particularly elevated in children who have systemic-onset JIA. Recently, anakinra, an anti-IL-1 receptor antagonist, and tocilizumab, an anti-IL-6 monoclonal antibody, which is now approved by the FDA, have demonstrated promising results in the treatment of patients who have systemic JIA. Abatacept, a recombinant fusion protein that down-regulates T-cell stimulation, was approved by the FDA in 2008 for moderate to severe polyarticular JIA in children >6 years old. Other therapies, such as rituximab (an anti-CD20 B-cell-depleting monoclonal antibody) and rilonacept (an IL-1 blocking agent), are being studied for the treatment of JIA. The duration of treatment with biologics is at least for 1 year after disease remission is achieved. (2)(7)(8)

Treatment of uveitis depends largely on the ophthalmologist’s recommendations. Typically, dilating agents and topical corticosteroids are used first. If inflammation persists or the patient is unable to taper off corticosteroid ophthalmic drops, often methotrexate is started. Infliximab and adalimumab also have been found to be quite beneficial in the treatment of uveitis. (9)

**Autologous Stem Cell Transplantation**

Patients who have JIA that is refractory to the previously described medical interventions may undergo autologous stem cell transplantation. Autologous stem cell transplantation involves using immunosuppression to remove autoreactive lymphocytes followed by stem cell transplantation. This procedure would be considered only for a small subset of patients who have JIA that is refractory to all other treatments. (7)

**Other Considerations**

Other treatment considerations must include physical therapy and occupational therapy to improve mobility of affected joints and maintain muscle strength. Monitoring physical and psychological functioning must be assessed routinely, and counseling or psychotherapy offered when needed. Leg-length discrepancies may require treatment if they become significant and orthopedic referrals should be made when appropriate.

**Prognosis**

Approximately 50% of children who have JIA continue to have active disease into adulthood. In patients who have
active disease into adulthood, there can be significant disability, such as joint deformity, growth abnormalities, visual disturbance caused by uveitis, functional limitations because of pain, and so forth. Factors affecting disease outcome include disease duration, presence of polyarticular disease, and use of systemic corticosteroid treatment. The mortality rate in JIA based on reports from the United States and Canada is 0.29 per 100 patients, and most deaths occur in patients who have systemic JIA. (1)

Summary

- Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood.
- JIA is a chronic disease that is associated with periods of disease flares and periods of disease inactivity.
- Early, aggressive treatment with nonsteroidal anti-inflammatory drugs, intra-articular corticosteroid injections, or methotrexate, has significantly improved the outcome of most children who have JIA.
- Biologics have been shown to be both safe and effective for the treatment of more aggressive forms of arthritis and for uveitis. Long-term safety data of biologics is still uncertain.
- In the near future, it is hoped that genetic testing will allow earlier diagnosis of JIA as well as help predict the disease course of children who have JIA. Genetic analysis also may allow physicians to target therapies more effectively.
- It is hoped that development of more specific therapies will decrease overall immunosuppression and other associated toxicities.

References


PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take Pediatrics in Review quizzes and claim credit online only. No paper form will be printed in the journal.

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1. You are evaluating a 10-year-old girl for joint pain that has been present for ~2 months. She has no fever but complains of pain and swelling in her hands and feet, which is worse in the morning. On physical examination, she has evidence of symmetric swelling of all proximal interphalangeal joints in her hands and feet and pain over her temporomandibular joint. The remainder of the examination is normal. Which of the following is the most likely diagnosis?
   A. Enthesitis-related arthritis
   B. Oligoarticular juvenile idiopathic arthritis (JIA)
   C. Polyarticular JIA
   D. Psoriatic arthritis
   E. Systemic-onset JIA

2. After determining the diagnosis in the patient mentioned above, you decide to initiate therapy for her arthritis. Which of the following medications is the most appropriate first medication to begin?
   A. Celecoxib
   B. Infliximab
   C. Methotrexate
   D. Naproxen
   E. Prednisone

3. Which of the following statements regarding JIA is true?
   A. African American children more often have systemic-onset JIA than other subtypes.
   B. Association with HLA-B27 positivity is typical in enthesitis-related arthritis.
   C. Oligoarthritis occurs most commonly in adolescents.
   D. Polyarthritis occurs most commonly in male subjects.
   E. Psoriatic arthritis is not associated with ophthalmologic disease.

4. Which of the following patients who have JIA is most likely to develop iritis?
   A. A 15-year-old boy who has enthesitis-related arthritis, antinuclear antibody (ANA)-negative
   B. A 3-year-old girl who has oligoarticular subtype, ANA-negative
   C. A 6-year-old girl who has oligoarticular subtype, ANA-positive
   D. A 12-year-old girl who has polyarticular subtype, ANA-positive
   E. A 5-year-old boy who has systemic onset subtype, ANA-negative

5. A 7-year-old girl has developed a limp and complains of pain in her right knee, which is warm and swollen. Although she is afebrile in the office, her parents say she had a fever at home. You suspect oligoarticular JIA but have concerns about infection. Which of the following tests would give you a definitive answer?
   A. ANA
   B. Erythrocyte sedimentation rate
   C. Rheumatoid factor
   D. Synovial fluid analysis
   E. White blood cell count