

# Juvenile Idiopathic Arthritis: An Update

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## ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common chronic arthropathy of childhood. Previous terminology identified this entity as juvenile rheumatoid arthritis. The 7 subsets of JIA identified under the new classification system are discussed, as are current treatments. A differential diagnosis of JIA is included as this condition continues to be diagnosed by exclusion. Recent studies, which discuss the outcome of adults with previous childhood arthritis, are reviewed.

## INTRODUCTION

Many different types of arthritis affect children. Some are acute and self-limiting, such as viral arthritis. Other forms of arthritis represent chronic conditions. The purpose of this article is to review and highlight new developments in chronic arthritis of childhood. The new classification system of juvenile idiopathic arthritis (JIA), formerly juvenile rheumatoid arthritis (JRA), will be discussed. Additionally, information on the occurrence, diagnosis, clinical features, management, and outcome of this disorder will be updated and reviewed.

## EPIDEMIOLOGY

The exact incidence and prevalence of juvenile arthritis (JA) is not known. A recent meta-analysis of 34 epidemiological studies showed wide variability in both the reported incidence and prevalence of JA (inclusive of the different classification systems of JRA, JIA, and juvenile chronic arthritis [JCA]).<sup>1</sup> Incidence numbers varied considerably from 0.008 to 0.226/1000 children per year.<sup>1</sup> Prevalence numbers varied even more widely and ranged from 0.07 to 4.01/1000 children.<sup>1</sup> No specific study has been performed to address the incidence and prevalence of juvenile arthritis in Wisconsin.

## DIFFERENTIAL DIAGNOSIS AND CLINICAL FEATURES

Juvenile idiopathic arthritis is diagnosed by the presence of a chronic persistent arthritis of at least 6 weeks duration in children or adolescents who are under age 16. The diagnosis of JIA also requires the exclusion of other disorders, which may present in a similar manner. The current JIA terminology was developed to achieve international consensus on the diagnosis of persistent childhood arthritis, as it has been difficult to compare studies of children with JRA in the United States with those of JCA in Europe. The terminology was also changed in the recognition that children under 16 infrequently have true "rheumatoid arthritis" with nodules, erosive synovitis, and rheumatoid factor positivity. Rheumatoid factor positive polyarthritis represents only 1 of the 7 subsets of JIA. The remaining 6 subtypes include systemic, oligoarthritis (persistent or extended), polyarticular arthritis (RF negative), psoriatic arthritis, enthesitis related arthritis, and other arthritis.<sup>2</sup> The clinical features and associations of these different subtypes of JIA will be discussed.

As JIA is an exclusionary diagnosis, it is important to be familiar with the alternative diagnoses. The required 6 weeks duration of arthritis is an important first step in excluding common childhood conditions such as viral arthritis and trauma. This time frame also excludes acute vasculitic syndromes, such as Kawasaki's disease or Henoch-Schoenlein purpura. The requirement for persistent joint involvement helps identify arthritic syndromes, which present with different patterns of joint involvement. One example would be the arthritis of acute rheumatic fever, which is both severely painful and migratory. Some arthritides, such as Lyme arthritis, may present with an episodic pattern of involvement, providing a clinical clue and facilitating the diagnosis. Orthopedic conditions such as Legg-Calve-Perthes disease or slipped capital femoral epiphysis cause hip or knee pain. Recognition that hip involvement, as an initial presentation of JIA, is unusual can direct one toward an appropriate evaluation of

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these disorders. Septic arthritis needs to be considered when there is a monoarticular arthritis accompanied by fever, severe pain, and exquisite tenderness.

Perhaps one of the most concerning aspects of the diagnosis of JIA is the recognition that some childhood malignancies, such as leukemia and neuroblastoma, may present with musculoskeletal pain or arthritis. The severity of pain, lack of morning stiffness, nocturnal nature of the pain, and the ability to localize the site of pain to the bones on palpation are clinical measures that can direct the examiner to the consideration of a malignancy. In a series of 12 children with leukemia who initially were presumed to have JRA, Wallendahl found that there were no differences in white count, hemoglobin or platelet count that enabled these children to be diagnosed with malignancy. Elevated lactate dehydrogenase was the only test where differences were noted in some children.<sup>3</sup> It is important to consider and exclude the diagnosis of malignancy, if appropriate, as immunosuppressive treatment for arthritis may impact the response of leukemia to future chemotherapy.

Arthritis also occurs in the context of other chronic childhood rheumatic diseases including systemic lupus erythematosus, mixed connective tissue disease, and juvenile dermatomyositis. These conditions tend to have more multisystem features than JIA. Localized scleroderma, which occurs more often than systemic sclerosis in children, may present with a joint contracture.

Arthritis on examination is recognized by the presence of joint effusions or the combination of limited motion with pain at the extremes of range of motion. The documentation of arthritis on examination helps exclude a variety of pain syndromes that may occur in childhood. The joint examination in a child with growing pains is normal. Children with growing pains have nocturnal lower extremity pain that can be relieved by comfort measures, such as massage. Children with joint hypermobility have a higher incidence of arthralgia. Exercise often exacerbates their symptoms and joint laxity can be documented on physical examination. Children and adolescents with fibromyalgia have a history of fatigue, disordered sleep and demonstration of tender points on physical examination.

The most common subtype of JIA is oligoarthritis, previously pauciarticular JRA. Children with this type of JIA present with involvement of 1-4 joints in the first 6 months of disease. Over time, children with limited arthritis progress to a polyarticular course. It is for this reason that the new classification system for JIA distinguishes between persistent oligoarthritis and ex-

tended oligoarthritis. Extended oligoarthritis occurs when 5 or more joints are involved after the first 6 months of illness. This type of arthritis is female predominant and its peak occurrence is in toddlers and preschoolers. Most of these children appear healthy. They may have morning stiffness and want to be carried in the morning. Later in the day, their activity and ambulation may appear normal. Pain complaints may be minimal as the children limit their joint movement to the area of pain-free range of motion. This may result in the development of joint contractures. The joint involvement may be asymmetric and lead to leg length discrepancies. The affected leg often overgrows and has accelerated maturation because of the increased vascularity that accompanies inflammation.

One of the most well recognized associations of JIA is for children with oligoarticular arthritis to develop a chronic, frequently asymptomatic iritis. This occurs in approximately 15%-20% of children with oligoarticular arthritis.<sup>4</sup> Antinuclear antibodies detected by Hep-2 cell substrate have been detected in 55% of children with both iritis and JIA.<sup>5</sup> It is well known that this chronic iritis may be asymptomatic, particularly in early disease. Because of the lack of symptoms, clinical guidelines for routine ophthalmologic screening have been developed and published by the American Academy of Pediatrics.<sup>6</sup>

Children with involvement of 5 or more joints in the first 6 months of illness are classified as having polyarticular disease and, as previously mentioned, these subtypes are differentiated by the presence or absence of rheumatoid factor. Generally, polyarticular disease tends to be more symmetric and is more likely to involve the small joints of the hands and feet. Local growth disturbances can occur. Some are distinctive, such as the micrognathia, which can develop from arthritis of the temporomandibular joint. Cervical spine involvement may occur in the polyarticular and systemic subtypes and be characterized by posterior fusion of the vertebrae.

Systemic arthritis is the least common subtype of JIA. It is also the most dramatic in its presentation, as children have high spiking fevers that accompany the arthritis. The differential diagnosis of this type of arthritis often involves an initial extensive diagnostic work-up for the wide range of disorders that can present as a fever of unknown origin. This type of arthritis is considered when the fever has been present at least 2 weeks. Frequently, a rheumatoid rash may be present. This rash is characteristically intensified by fever or heat. It is evanescent by nature and has a tendency for Koebner's

phenomenon. This is the occurrence of typically linear skin lesions at a site of previously uninvolved skin after trauma or scratching. Serositis, anemia of chronic disease, hepatosplenomegaly, and lymphadenopathy all may be seen. Children with systemic arthritis typically have both negative rheumatoid factors and antinuclear antibody (ANA) serology. A prominent leukocytosis and thrombocytosis are seen. While rare, there is a life-threatening syndrome that can occur in systemic arthritis, known as macrophage activation syndrome. Following a history of intercurrent illness or recent medication change, these children often develop sustained (not spiking) fevers along with marked pancytopenia, coagulopathy, hepatic involvement, and hypoalbuminemia. Despite the severity of these symptoms, the erythrocyte sedimentation rate may fall into the normal range, presumably from impairment of the acute phase response due to liver dysfunction. These children require emergent treatment with corticosteroid medications or immunosuppressive therapy. It is thought that this syndrome is related to other hemophagocytosis syndromes and recent investigations have shown abnormalities of natural killer cell function.<sup>7</sup>

While systemic arthritis is unique in its febrile presentation, the number and pattern of joint involvement, as well as the presence or absence of rheumatoid factor, distinguish the other 6 types of JIA. Two of the subtypes of JIA, psoriatic arthritis and enthesitis-related arthritis, have previously been included under the generic terminology of spondyloarthropathy. These conditions share features of arthritis, enthesopathy (tenderness at ligamentous attachment sites to bone) and the tendency to be associated with HLA-B27. Historically, it has been recognized that school age children, particularly boys, may have presented with features of pauciarthritic JIA and then followed a course more consistent with one of the spondyloarthropathy syndromes. These disorders may be associated with back or sacroiliac joint involvement. They may also develop an iritis, which often presents as the acute red eye. Other conditions, generally thought to occur in the spondyloarthropathy spectrum, such as reactive arthritis associated with enteric or chlamydia infections and the arthropathy of inflammatory bowel disease, are not included in this classification system as they are not considered to be "idiopathic."<sup>2</sup> However, it is important for clinicians to consider these disorders, as the arthritis may be an initial manifestation of a different systemic disease.

#### TREATMENT AND MANAGEMENT

The care of children with arthritis has seen definite ad-

vances over the last several years. Initial management of children with arthritis includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain, enhance mobility, and reduce morning stiffness. The armamentarium of approved NSAIDs for childhood arthritis is limited, compared to the availability of these agents for the adult population, and includes ibuprofen, naproxen, and tolmetin. A review of the clinical trials of these agents by the Pediatric Rheumatology Collaborative Study Group showed that 65% of children responded to a particular agent by 1 month, but that some children were late responders and could take up to 3 months to respond to a particular agent.<sup>8</sup> Aspirin therapy is not routinely used because of alternatives with reduced frequency of dosing schedules, less frequent liver enzyme elevation, and concerns of Reye's syndrome in children exposed to viral infections, particularly varicella or influenza. While selective COX-2 inhibitors have been approved for adults with arthritis, these agents have not yet received FDA approval for pediatric use.

Systemic corticosteroids are not routinely utilized in the care of children with JIA because of side effects, primarily osteopenia and growth retardation, which are already concerns for children because of their underlying disease process. Steroid medications are reserved for life-threatening or severe manifestations, such as macrophage activation syndrome, pericarditis, or severe anemia of chronic illness. They may be used to maintain ambulation if other strategies have failed, or treat severe sight-threatening iritis, but these cases are rare. Steroid medications are preferable as a local measure. Examples include the use of topical ophthalmic drops for iritis or the use of intra-articular triamcinolone hexacetonide. Studies of triamcinolone hexacetonide have shown a sustained local response to this agent. In 60% of children, this response lasts 6 months and in 45% the response may last a year.<sup>4</sup> Unfortunately, this steroid preparation, which has been the most studied and has shown the most sustained responses, has been unavailable due to commercial shortages of this agent.

While a variety of second line agents have been used, methotrexate administered once a week has become the agent of choice for persistent disease. A controlled clinical trial of this agent showed improvement in 72% of children.<sup>9</sup> It is recognized that there may be improved efficacy of this agent with subcutaneous rather than oral administration of this agent. Use of this medication requires ongoing monitoring of blood counts and transaminases. A recent advance in the care and treat-

ment of children with JRA has been the arrival of etanercept. This drug, which represents a new generation of cytokine modifying agents, works by blocking the tumor necrosis factor receptor. In a controlled study of patients with severe JRA whose disease did not respond to methotrexate, 74% patients improved at 3 months.<sup>12</sup> Subsequent studies have now shown sustained improvement for as long as 2 years.<sup>13</sup> In the primary care of children receiving these agents, it is important to recognize that they are receiving immunosuppressive treatment as they are evaluated for fevers and intercurrent illnesses. Live virus vaccines should be avoided while these children are on immunosuppressive therapy. Other cytokine modifying drugs have recently been approved for use in adult rheumatoid arthritis, but have not yet received pediatric approval. Occasionally, other agents such as sulfasalazine have been utilized.

Children with JIA are known to have an increased risk of osteopenia from their disease. It has now been shown that this risk exists independent of the use of corticosteroid medications.<sup>14</sup> Strategies to minimize the consequences of osteopenia should be employed. Encouragement of physical activity is important. Klepper has shown that children with JIA are less physically fit than children without JIA and that most children with JIA can exercise without exacerbating the symptoms of their disease.<sup>15,16</sup> The provision of adequate calcium either by diet or with calcium supplementation is important. A standard age-appropriate multivitamin containing vitamin D is also suggested.

It is important to encourage physical activity to maintain bone density, prevent disuse weakness and muscle atrophy, and minimize contractures. The severity of disease and symptoms experienced by some children may suggest the need for adaptations and modifications. Swimming and bicycling are often well-tolerated activities for individuals with arthritis. Heat may help reduce the accompanying inactivity stiffness. For children experiencing increased disease activity, physical and occupational therapy may be needed. Therapy is often provided to complement a home exercise program performed by the child and supervised by the parents.

In addition to the care of the arthritis, it is important to establish routine ophthalmologic care for children with JIA. Because of the asymptomatic nature of the iritis regularly scheduled, routine slit lamp eye examinations are recommended. The American Academy of Pediatrics has issued guidelines for ophthalmologic examinations for children with JIA. Children at the high-

est risk are recommended to have eye exams at 3-month intervals. Intervals of follow-up differ by the age of the child at onset of arthritis, ANA status, and duration of the disease.<sup>6</sup> Some authors have reported improvements in visual outcome of children with JIA and they speculate that adherence to a regular program of eye screening have led to the reported improvements in outcome.<sup>15</sup>

Children with arthritis may have symptoms that impact their school performance. For example, children with hand involvement may have difficulty with writing and require adaptations. Children with lower extremity involvement may experience difficulties in running and other activities in their physical education courses. Impairments in ambulation may create difficulties changing classes, standing in line, or utilizing stairs. Providers of care may need to work with families to coordinate the needs their children may have in the school setting.

Measures to help the child and their family realize that they are not the only ones coping with the challenge of arthritis can help facilitate their adjustment to the disease. Internet sources such as [www.arthritis.org](http://www.arthritis.org) sponsored by the Arthritis Foundation can provide information and links to the American Juvenile Arthritis Organization (AJAO). There is a Wisconsin chapter of the AJAO, which provides families in the state with an opportunity for information and support. Opportunities for group interaction, such as Camp MASH (Make Arthritis Stop Hurting), coordinated by the Arthritis Foundation, Wisconsin Chapter, allow children to meet other children dealing with similar issues. The American College of Rheumatology has published a position statement on the referral of children and adolescents to pediatric rheumatologists. One of the 5 stated goals in this document is to provide families with specialized input to help the family cope with the disease process, accept treatment plans, allay anxiety, and provide education.<sup>16</sup>

#### OUTCOME

Families faced with the challenge of dealing with arthritis often want to know what the future holds. While unable to predict the future for a specific family, the outcome studies performed on JIA can give some insight. Older studies show that adults with JIA develop more limitations in self-care function as the follow-up interval becomes longer. Patients in Steinbrocker functional class III or IV have marked limitations in self-care activities. Wallace and Levinson showed an increase in functional impairment over time. At 10 years,

9% of patients were in functional class III or IV, but at 15-20 years of follow-up, the numbers increased to 17%.<sup>17</sup>

Recently, a new generation of studies reporting the outcome of adults with JIA have become available. These studies utilize more refined outcome measures than the Steinbrocker classification system. Peterson et al performed a study comparing adults with JIA to a control group. At a mean time of follow-up of 24.7 years, these individuals experienced more disability, pain, fatigue, poorer health perception, and decreased physical function compared to the control group. They also found that educational level, income, insurance status, and rates of pregnancy and childbirth were similar in the cases and controls.<sup>18</sup> Another study by these authors showed an increased mortality rate of 0.27 deaths/100 years of patient follow-up compared to the expected mortality rate of 0.068 deaths/100 years for the general population. In their series, the deaths were all associated with other autoimmune diseases.<sup>19</sup> Thomas et al also reported increased mortality rates for adults with a history of JIA. This Scottish study reported a standardized mortality rate of 3.39 for males and 5.09 for females.<sup>20</sup>

Packham et al reported a series of 246 adults with JIA with a mean disease duration of 28.3 years (a range of 8-73 years) and noted that 56.7% of patients had no signs of active inflammation at follow-up. These authors noted that both male and female heights were decreased compared to the general population. Fifty-one percent of their patient group had required at least 1 joint replacement surgery.<sup>21</sup> Oen et al reported rates of arthroplasty of 23% for rheumatoid factor positive patients and 17% for systemic onset disease. The lower rates may reflect a shorter median duration of follow-up of 10.5 years. These authors also reported on probability of remission at 10 years after onset. The remission rate were as follows: systemic 37%, oligoarticular 47%, polyarticular RF- 23%, and polyarticular RF + 6%.<sup>22</sup>

Foster et al reported on 82 adults with JIA and a mean duration of disease of 21 years. Using the Health Assessment Questionnaire they found that patients with oligoarticular onset disease had less functional impairment compared to patients with systemic or polyarticular disease. They used the SF-36 instrument and found that compared to controls, patients had worse scores for physical function, vitality, pain, general health, social function, and emotional role. Most of the patients included in their study had excellent educational achievement, but despite this had lower rates of employment than the control population.<sup>23</sup> It is impor-

tant to realize that for all the studies of adults with JIA their disease began before the wide availability of newer proven therapies, such as methotrexate and etanercept.

There are some data addressing the outcome of children treated during the methotrexate era, but prior to the use of etanercept. At 5 years after onset, >25% of children with polyarticular onset disease and approximately 50% of children with systemic onset disease had functional limitations that required modifications in their school schedule. These authors noted that over half of the children with systemic onset arthritis required admission to the hospital during the first year of disease. At 5 years, 12% of children with polyarticular disease and 30% of those with systemic disease were in Steinbrocker class III or IV reflecting significant impairments in self-care activities. At 5 years, 67% of children with polyarticular arthritis showed joint space narrowing and the numbers were higher for children with systemic arthritis as 75% of the patients had radiographs showing joint space narrowing.<sup>24</sup>

Hopefully, the newer therapies will show improved long-term results for children now being treated during the age of biologic agents. Currently, many children with JIA will enter adulthood with inactive disease and with good functional outcome. Yet it is clear that there are a significant number of individuals who have had JIA, who did not "outgrow" their disease and have experienced significant impairments continuing into adulthood.

The field of pediatric rheumatology has been a dynamic one in the past several years. Standardization of terminology will enhance comparisons of studies performed throughout the world. Increased awareness should help children receive appropriate therapy early in their disease course. Newer treatments hopefully will improve the outcome and consequences of JIA, which are now being better understood. Research studies also continue to better understand the etiologies of this heterogeneous group of chronic childhood arthritides and hopefully will lead to novel therapies in the future.

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