



Juvenile idiopathic arthritis: Diagnosis and differential diagnosis

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Juvenile idiopathic arthritis (JIA) is comprised of a heterogeneous group of several disease subtypes that are characterized by the onset of arthritis before the age of 16 years and has symptoms lasting at least 6 weeks. The previous classification of JIA included seven different categories, whereas its current classification was compiled by the International League of the Association for Rheumatology, and replaced the previous terms of "juvenile chronic arthritis" and "juvenile rheumatoid arthritis," which were used in Europe or North America, respectively, with the single nomenclature of JIA. As mentioned above, JIA is defined as arthritis of unknown etiology that manifests itself before the age of 16 years and persists for at least 6 weeks, while excluding other known conditions. The clinical symptoms of JIA can be quite variable. Several symptoms that are characteristic of arthritis are not necessarily diagnostic of JIA and may have multiple etiologies that can be differentiated with careful examination of patient history. The disease may develop over days or sometimes weeks, thereby making the diagnosis difficult at the time of presentation. To make a clinical diagnosis of JIA, the first step is to exclude arthritis with known etiologies. Of note, late treatment due to excessive delay of diagnosis can cause severe damage to joints and other organs and impair skeletal maturation. Therefore, early detection of JIA is critical to ensure prompt treatment and to prevent long-term complications including the likelihood of disability in childhood.

Key words: Arthritis, Juvenile Idiopathic, Child, Differential diagnosis

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Introduction

Juvenile idiopathic arthritis (JIA) is comprised of a heterogeneous group of several disease subtypes that are characterized by the onset of arthritis prior to the age of 16 years with symptoms that persist for more than 6 weeks. The occurrence of chronic arthritis

in children has been described since the 1800s. George Frederick Still, an English pediatrician, described 22 children from Hospital for Sick Children, Great Ormond Street that had chronic arthritis¹⁾. It is still believed that 12 of these children had distinctive features of rheumatoid arthritis. Since this report, many additional children have been described with rheumatoid arthritis, and it has become

obvious that the disease we now call JIA or juvenile rheumatoid arthritis (JRA) is a particularly unpredictable and heterogeneous disease group. The previous classification of JIA described 7 categories of the disease²⁾, and the currently used classification was compiled by the International League of Associations for Rheumatology (ILAR). According to the updated ILAR system, the previous terms of “juvenile chronic arthritis (JCA)” and “JRA,” which are used in Europe or North America, respectively, are replaced by the collective term JIA. Moreover, as mentioned above, this system defines JIA as arthritis of unknown etiology beginning before the age of 16 years and persisting for at least 6 weeks, while excluding other known conditions. As a consequence of the

definition, JIA is not diagnosed before 6 weeks of onset, and final classification into one of its 7 subgroups is typically performed after 6 months²⁾.

Classification

The classification of JIA provides an important framework for its research, as well as for assisting with identification of appropriate treatment and prediction of natural disease history. The aim of the ILAR classification system of JIA is to explain relatively homogeneous, mutually exclusive categories of idiopathic childhood arthritis based on predominant clinical laboratory

Table 1. International League of Associations for Rheumatology (ILAR) Classification of Juvenile Idiopathic Arthritis (JIA)²⁾

Category	Diagnostic criteria
Systemic arthritis	Fever of at least 2 weeks' duration (daily for at least 3 days) and arthritis in ≥ 1 joint, plus one or more of the following: Erythematous rash Generalized lymph node enlargement Hepatomegaly and/or splenomegaly Serositis Exclusions: a, b, c, d
Oligoarthritis	Arthritis affecting ≤ 4 joints during the first 6 months of disease There are 2 subcategories: Persistent: affecting not more than 4 joints throughout the disease course Extended: affecting more than 4 joints after the first 6 months of disease Exclusions: a, b, c, d, e
Polyarthritis, RF(-)	Arthritis affecting ≥ 5 joints during the first 6 months of disease Test for RF is negative. Exclusions: a, b, c, d, e
Polyarthritis, RF(+)	Arthritis affecting ≥ 5 joints during the first 6 months of disease 2 or more test for RF at least 3 month apart during the first 6 months of disease are positive. Exclusions: a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: Dactylitis Nail pitting or onycholysis Psoriasis in a first-degree relative Exclusions: b, c, d, e
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of following: The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain The presence of HLA-B27 antigen Onset of arthritis in a male over 6 years of age Acute (symptomatic) anterior uveitis History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative Exclusions: a, d, e
Unclassified arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories

One of the major aims of the ILAR classification is the mutual exclusivity of the subtypes. Therefore, the following list of possible exclusion for each category was defined:

- Psoriasis or a history of psoriasis in the patient or first-degree relative.
- Arthritis in an HLA-B27-positive male beginning after the sixth birthday.
- Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis or a history of one of these disorders in a first-degree relative.
- The presence of IgM rheumatoid factor and at least two occasions at least 3 months apart.
- The presence of systemic JIA in the patient
RF, Rheumatoid factor

features²⁾. The current categories of JIA are shown in Table 1²⁾.

1. Clinical diagnosis and differential diagnosis

The clinical symptoms of JIA can be variable. Several symptoms that indicate arthritis are not necessarily diagnostic of JIA, and may have multiple etiologies that can be differentiated with careful examination of patient history³⁾. Polyarticular joint disease has a multi-factorial etiology, and may present as a viral illness or can be the beginning of a chronic disease. Moreover, its underlying etiological process can be infectious or post-infectious with a rheumatological disease or a manifestation of systemic disease. This disease may evolve over days or sometimes weeks, thereby making the diagnosis difficult at the time of presentation⁴⁾. Thus, to accurately diagnose JIA, the first step is to exclude arthritis with known etiologies⁴⁾ (Table 2).

In a child with acute-onset monoarthritis, the differential diagnosis must include septic arthritis, trauma, and hematologic diseases⁵⁾. A painful joint effusion of short duration may be caused by trauma. It has been suggested that JIA may be the most common cause of chronic oligoarthritis. In a child with oligoarticular JIA, the affected joint is swollen and often warm, but is not typically very painful, tender, or red⁵⁾. Moreover, if a joint is extremely painful and erythematous, or if the child is febrile, septic arthritis is more likely the correct diagnosis⁶⁾. Such patients should undergo a test of prompt joint aspiration to exclude septic arthritis and osteomyelitis. The onset of polyarthritis in a preadolescent or adolescent girl potentially suggests the diagnosis of systemic lupus erythematosus (SLE). The arthritis of SLE may follow that of JIA, but without undertaking serologic studies, its correct diagnosis may be difficult to make until the detection of the more characteristic

clinical symptoms of SLE.

The differential diagnosis of a child suspected of having systemic JIA is often difficult, especially at the onset or early in the course of the disease, when the child may have a high spiking fever with evidence of systemic inflammation but no arthritis or other specific signs that allow for a definitive diagnosis⁷⁾. Children with systemic JIA may first be thought to have an acute infectious disease or septicemia. However, the presence of arthritis and/or a rheumatoid rash helps to establish an accurate diagnosis of systemic JIA. In contrast, laboratory tests may be of little value in diagnosing systemic JIA. Fever in children with infectious diseases is of the septic type; this type of fever is clinically more confusing and typically does not repetitively return to the baseline each day, as does the fever associated with JIA. That is, the diagnostic symptom of systemic JIA is a high spiking fever⁸⁾, which may occur at any time of the day but is commonly present in the late afternoon to evening in conjunction with rash. In contrast, the temperature of an individual affected by JIA may be below normal in the morning. Moreover, JIA-associated fever can frequently accompany chills. Children commonly appear unwell while febrile, but surprisingly well during the rest of the day.

In our experience of assessing patients suspected of having JIA from 1990 to 2000, 51 cases were excluded to other diagnoses, which included arthritis related to infection (61%), malignancy (6%), other rheumatological disorders (26%), and immunodeficiency syndrome (4%)⁹⁾.

2. Laboratory examination

As briefly mentioned above, the diagnosis of JIA is essentially a clinical one. No laboratory test or combination of studies can

Table 2. Differential diagnosis of Juvenile Idiopathic Arthritis in Children

Monoarticular arthritis	Polyarticular arthritis	Systemic onset
Acute onset	Seronegative spondyloarthropathy	Infection
Early rheumatic disease	Juvenile psoriatic arthritis	Inflammatory bowel disease
Oligoarticular JIA	Arthritides of inflammatory bowel disease	Connective tissue diseases
Seronegative spondyloarthropathy	Systemic lupus erythematosus	Systemic lupus erythematosus
Arthritis related to infection	Polyarthritis related to infection	Juvenile dermatomyositis
Septic arthritis	Lyme disease	Vasculitis
Reactive arthritis	Reactive arthritis	Castleman's disease
Malignancy	Other	Familial Mediterranean fever
Leukemia	Sarcoidosis	Hyper IgD syndrome
Neuroblastoma	Familial hypertrophic synovitis	
Hemophilia	Mucopolysaccharidoses	
Trauma		
Chronic		
Oligoarticular JIA		
Juvenile ankylosing spondylitis		
Juvenile psoriatic arthritis		
Villonodular synovitis		
Sarcoidosis		

confirm the diagnosis of JIA. However, the laboratory studies can be used to provide evidence of inflammation, support the clinical diagnosis of JIA, monitor toxicity of therapy, and better understand the pathogenesis of the disease.

Hematologic abnormalities generally reflect the extent of the inflammatory disease. Useful laboratory investigations include count of blood cells (CBC) and inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, the levels of ESR and CRP in active JIA are variable. In general, ESR is a useful measure of active disease at onset and during follow-up visits with a child with JIA, especially in polyarticular or systemic onset. Also, ESR is occasionally helpful in monitoring therapeutic efficacy. A CBC may show anemia of chronic disease if there has been longstanding inflammation. JIA-associated anemia is attributable to chronic disease (low serum iron, low total iron-binding capacity, adequate hemosiderin store), although iron deficiency may also play an important role. It has been established that plasma iron transport and the amount of iron available for erythropoiesis decreases in individuals with systemic disease. Leukocytosis is common in children with active disease, and their platelet count may rise dramatically in cases with severe systemic or polyarticular involvement⁵. The concentrations of the serum immunoglobulins, IgG, IgA, and IgM, were previously determined in 200 patients with juvenile rheumatoid arthritis, which showed abnormality in the distribution of these immunoglobulins in JIA¹⁰. The serum levels of immunoglobulins are reportedly correlated with the activity of the disease and the acute phase response^{10,11}.

In a study of the diagnostic utility of rheumatoid factor (RF) serology in children, RF tests were shown to likely be positive in children with both JIA and diseases other than JIA¹². Thus, evaluation of RFs is not useful as a diagnostic tool for JIA. However, children with high titers of RFs likely represent a subgroup distinctive from the larger number of children with

seronegative disease. A RF test should be performed in patients with polyarthritis, as its presence has prognostic significance¹³. The presence of anti-nuclear antibody (ANA) deliberates risk for the development of asymptomatic uveitis, particularly in those individuals with oligoarticular onset disease, although assessment of ANA should be performed in all JIA patients^{14,15}. Anti-cyclic citrullinated peptide (anti-CCP) antibodies are not routinely tested in JIA patients, but may indicate severe disease¹⁶. Human leukocyte antigen (HLA) B27 should be examined in children who present with symptoms of enthesitis-related arthritis and can indicate susceptibility to the development of axial arthritis. Furthermore, if there is concern that arthritis is part of an underlying connective tissue disease or vasculitis, then it may be useful to test dsDNA, extractable nuclear antigen (ENA), C3, C4, and immunoglobulin levels. Finally, as most of the rheumatological tests lack in desired specificity, results should always be interpreted in the context of a given patient^{4,17,18}.

Conventional radiographs are the most easily available, quick, and inexpensive method of evaluating a joint. Ultrasonography is often the best way of identifying intra-articular fluid, particularly in joints such as the hip and shoulder, where fluid may be difficult to demonstrate clinically¹⁹. Increasing use of standard magnetic resonance (MR) imaging and the advances in more functional MR techniques over the past decade have improved the assessment of joint disease in JIA. Compared to ultrasonography or plain radiography, MR imaging is powerful in detecting inflammatory changes in the joint and cartilage damage. MR imaging is also able to precisely evaluate the later manifestations of JIA, including erosions, loss of joint space, cartilage damage, and ligamentous involvement^{19,20} (Fig. 1). Moreover, bone scans using technetium -99m are also useful for detecting the early stage of inflammatory arthritis²¹ (Fig. 2). Unfortunately, no single modality meets every imaging requirement at this time, but methods for detecting JIA are dramatically improving²².

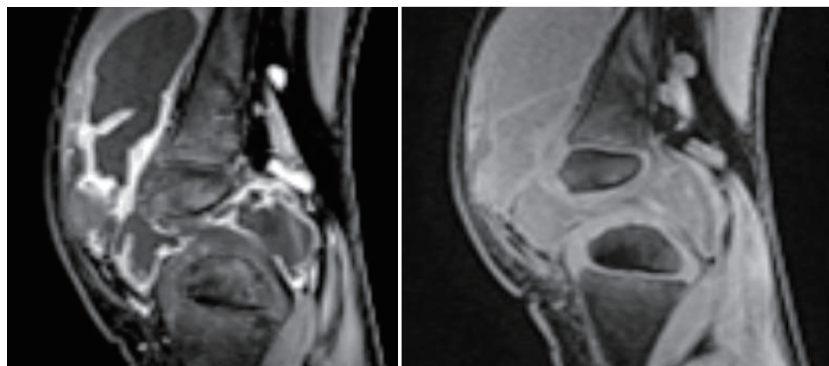


Fig. 1. Magnetic resonance imaging of a patient with juvenile idiopathic arthritis shows synovial proliferation and effusion collection. Thick prominent enhancement along the synovial lining of the knee joint is shown.



Fig. 2. Whole body bone scan using technetium-99m shows increased bone uptake in the lesions of a patient with juvenile idiopathic arthritis.

Conclusion

JIA is the most common rheumatic disease that affects children and is a significant cause of both short- and long-term disabilities. Specifically, JIA is defined as arthritis of unknown etiology and its diagnosis requires clinical exclusion of other known conditions. Excessive delay in instituting advanced treatment for JIA can result in irretrievable damage to joints and other organs and impair skeletal maturation. Thus, early detection of JIA is critical to ensure its prompt treatment and to prevent long-term complications, including the likelihood of disability during childhood.

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