pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 24, No. 3, June, 2017
https://doi.org/10.4078/jrd.2017.24.3.131

Review Article

Differential Diagnosis of Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is a broad spectrum of disease defined by the presence of arthritis of unknown etiology, lasting more than six weeks duration, and occurring in children less than 16 years of age. JIA encompasses several disease categories, each with distinct clinical manifestations, laboratory findings, genetic backgrounds, and pathogenesis. JIA is classified into seven subtypes by the International League of Associations for Rheumatology: systemic, oligoarticular, polyarticular with and without rheumatoid factor, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis. Diagnosis of the precise subtype is an important requirement for management and research. JIA is a common chronic rheumatic disease in children and is an important cause of acute and chronic disability. Arthritis or arthritis-like symptoms may be present in many other conditions. Therefore, it is important to consider differential diagnoses for JIA that include infections, other connective tissue diseases, and malignancies. Leukemia and septic arthritis are the most important diseases that can be mistaken for JIA. The aim of this review is to provide a summary of the subtypes and differential diagnoses of JIA. **(J Rheum Dis 2017;24:131-137)**

Key Words. Juvenile idiopathic arthritis, Subtype, Differential diagnosis, Children

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term for a group of chronic arthritides. The term chronic is defined as lasting more than 6 weeks, idiopathic is an unknown etiology, and juvenile is defined as an onset of arthritis at 16 years of age or younger [1,2]. The concept that inflammatory polyarthritis occurred in childhood suggested in 1864 by Cornil. George Frederick Still, an English pediatrician, presented the classic description of chronic childhood arthritis in 1897 while he was a medical registrar at the Hospital for Sick Children, Great Ormond Street, London [1,3,4]. In the past, childhood arthritis was called juvenile rheumatoid arthritis by the American College of Rheumatology criteria have been widely used in the United States and was called juvenile chronic arthritis by the European League Against Rheumatism in Europe. In 1993, the Pediatric Committee of the International League of Associations for Rheumatology (ILAR) proposed a classification of idiopathic arthritis of childhood [5]. JIA is the most common chronic rheumatic disease of childhood, the most frequent chronic illness of children, and an important cause of long-term disability [1].

The incidence has varied from 2 to 23 per 100,000 and the prevalence rates have varied from 4 to 400 per 100,000 children [6].

The International League of Associations for Rheumatology classified JIA into seven subtypes based on distinct clinical and laboratory findings: systemic, oligoarticular, polyarticular with and without rheumatoid factor, enthesitis-related arthritis (ERA), psoriatic arthritis, and undifferentiated arthritis (Table 1) [1,4,7].

A remarkable different rate in the frequency of JIA has been noticed in different geographical areas and ethnic groups. In Western countries, oligoarthritis is the most common subtype, while polyarthritis predominates in Costa Rica, India, and New Zealand [1,7]. In Asia, systemic arthritis accounts for a greater proportion of childhood arthritis [8]. In India, Mexico, and Canada, a greater

Received : February 26, 2017, **Revised :** April 2, 2017, **Accepted :** April 14, 2017

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Table 1. International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA)

Subtype	Diagnostic criteria
Systemic arthritis	Fever of at least 2 weeks' duration and arthritis in ≥1 joint
	Plus one or more of the following:
	Erythematous rash
	Lymphadenopathy
	Serositis
	Hepatomegaly and/or splenomegaly
	Exclusions: a, b, c, d
Oligoarthritis	Arthritis affecting ≤4 joints during the first 6 months of disease
	There are 2 subcategories:
	Persistent: affect 4 or fewer joints throughout the disease course
	Extended: affect more than 4 joints after the first 6 months of disease
	Exclusions: a, b, c, d, e
RF(−) polyarthritis	Arthritis affecting ≥5 joints during the first 6 months of disease
	Test for RF is negative
	Exclusions: a, b, c, d, e
RF(+) polyarthritis	Arthritis affecting ≥5 joints during the first 6 months of disease
	Two or more test for RF at least 3 month apart during the first 6 months of disease are positive
	Exclusions: a, b, c, e
ERA	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
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
Unclassified arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories

RF: rheumatoid factor, ERA: enthesitis-related arthritis, HLA: human leukocyte antigen. 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; a) Psoriasis or a history of psoriasis in the patient or first-degree relative; b) Arthritis in an HLA-B27-positive male beginning after the sixth birthday; c) Ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease or acute anterior uveitis, or a history of one of these disorders in a first-degree relative; d) The presence of immunoglobulin M rheumatoid factor and at least two occasions at least 3 months a part; e) The presence of systemic JIA in the patient.

incidence of ERA has been registered, reflecting, at least in part, the high frequency of the human leukocyte antigen (HLA)-B27 in these populations [1]. Rheumatoid factor (RF)-positive polyarthritis is the least common subtype overall.

Each subtype has a different manifestation and requires different treatments. Therefore, it is important to diagnose the exact subtype.

As mentioned above, JIA is an umbrella term for a group of chronic arthritides of unknown etiology that excludes other known conditions. The clinical symptoms of JIA can be quite variable. As a result, the differential diagnosis of suspected JIA may be difficult, especially at onset or early in the course of the disease. 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 arthritides of known etiologies. Late treatment due to excessive delay of diagnosis can cause severe damage to joints and other organs, inducing leg length discrepancy and visual loss.

Therefore, early detection of JIA is critical to ensure prompt treatment and to prevent short- and long-term complications in childhood.

MAIN SUBJECTS

Subtypes of JIA

Systemic JIA accounts for 5%～15% of children with JIA in North America and Europe [1,9]. Systemic JIA is defined as the presence of arthritis accompanied or preceded by a daily intermittent fever more than 39°C, lasting more than 2 weeks, and at least one of the following: characteristic evanescent rash, generalized lymphadenopathy, serositis, hepatomegaly, or splenomegaly [10]. The fever has a typical pattern of one or two daily spikes of more than 39°C. The characteristic evanescent rash usually appears with fever and is non-fixed, erythematous, salmon pink, and macular [1]. The arthritis is often symmetrical and polyarticular, but could be absent at onset, developing later in the disease course [2]. Although there are no specific laboratory findings, systemic inflammatory signs are always present. Laboratory findings show leukocytosis with neutrophilia, thrombocytosis, elevated erythrocyte sedimentation rate (ESR), and elevated C-reactive protein. Microcytic anemia is also a common lab finding [7]. In patients with systemic JIA, the presence of pancytopenia, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, and increased serum transaminase suggest the occurrence of macrophage activation syndrome (MAS) (Table 2) [11]. MAS is the most devastating complication of systemic JIA and occurs in 5%～8% of systemic JIA [1,2].

RF-negative polyarthritis accounts for 17% of children with JIA [1,7]. RF-negative polyarthritis is defined as an arthritis affecting five or more joints during the first 6 months of disease and an absence of immunoglobulin (Ig)M RF. This is a heterogeneous subtype that may manifest with at least three distinct subsets [1,2,7]. The first subset is a form that resembles early-onset oligoarthritis, but differs in the number of joints affected in the first 6 months of disease. The second subset is more similar to RF-negative rheumatoid arthritis (RA) of adults, and is characterized by symmetric arthritis of large and small joints, later onset, and negative anti-nuclear antibody (ANA). The third subset, known as "dry synovitis", exhibits negligible joint swelling but prominent stiffness and flexion contractures. This subset is often poorly responsive to treatment and may pursue a destructive course [12].

RF-positive polyarthritis accounts for 3% of children with JIA [1]. RF-positive polyarthritis is defined as an arthritis that affects five or more joints during the first 6 months of disease with the presence of an IgM RF on at least two occasions that are more than 3 months apart. RF-positive polyarthritis is the same as adult RF-positive RA but occurs mainly in adolescent girls. The typical finding is a symmetrical polyarthritis that affects the small joints of the hands and feet. Also present are rheumatoid nodules which are rarely seen in the other subtypes of JIA [1].

Oligoarthritis accounts for 50% to 80% of all children with JIA [1]. Oligoarthritis is defined as an arthritis that affects four or fewer joints during the first 6 months of disease. In the ILAR classification, children satisfying the following criteria are excluded from the oligoarthritis subtype: psoriasis, a family history of psoriasis, a HLA-B27-associated disease in a first-degree relative, a positive RF test, or disease occurring in a male patient older than 6 years [2,4].

Oligoarthritis is subdivided as persistent or extended oligoarthritis. Persistent oligoarthritis is confined to four or fewer joints involved during the whole disease course, while extended oligoarthritis spreads to more than four joints after the initial 6 months of disease [1]. Wrist and ankle arthritis and high ESR at onset have been identified as predictors for an extended course [13,14]. Most children with oligoarthritis show typical findings not seen in adults, such as asymmetric arthritis, early disease onset (<6 years), female predilection, high frequency of positive ANA, and high risk of iridocyclitis [1,7]. Oligoarthritis predominantly affects the joints of the lower extremities, with the knee joint most commonly affected, followed by the ankle joint. The worst complications of oligoarthritis are leg length discrepancy and visual loss. Iridocyclitis is

Table 2. New classication criteria of macrophage activation syndrome from Ravelli in 2016

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classied as having macrophage activation syndrome if the following criteria are met:
Ferritin >684 ng/mL
and any 2 of the following:
Platelet count $\leq 181 \times 10^9$/L
Aspartate aminotransferase >48 units/L
Triglycerides >156 mg/dL
Fibrinogen ≤360 mg/dL

a characteristic feature of oligoarthritis and affects about 20% to 30% of patients with oligoarthritis. ANA-positive patients have the highest risk of Iridocyclitis [1,15-17]. The onset of iridocyclitis is insidious and asymptomatic, in contrast to the painful iridocyclitis seen in ERA. Iridocyclitis in oligoarthritis is observed in less than 10% of patients before the onset of arthritis, with most cases developing 5 to 7 years following the onset of arthritis [2,18]. Since iridocyclitis is asymptomatic at onset, children with oligoarthritis should be screened periodically by slit-lamp examination [1].

ERA accounts for 1% to 7% of all children with JIA [1]. ERA is defined as either both arthritis and enthesitis of at least 6 weeks duration in a child younger than 16 years, or arthritis or enthesitis plus two of the following: sacroiliac tenderness or inflammatory spinal pain, HLA-B27 positivity, onset of arthritis in a male older than 6 years, or family history of HLA-B27-associated disease [19]. The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon, plantar fascia, and tarsal area. The arthritis commonly affects the joints of the lower extremities. Unlike other subtypes of JIA, hip involvement is common at disease presentation of ERA [2]. ERA belongs to the group of spondyloarthropathies, however ERA differs from ankylosing spondylitis in adults. Patients with ERA appear to have more peripheral joint involvement and more root joint involvement (hips and shoulders) than axial involvement [20]. There are no diagnostic laboratory findings for ERA. ANA and RF are typically negative but HLA-B27 is strongly associated with ERA [7].

Juvenile psoriatic arthritis (JPsA) accounts for 7% of all children with JIA [1]. JPsA is defined as the simultaneous presence of arthritis and a typical psoriatic rash, or, if a rash is absent, the presence of arthritis and any two of the following: family history of psoriasis in a first-degree relative, dactylitis (sausage-like swelling of one or more fingers that extends beyond the joint margin), and nail pitting or onycholysis [2]. Exclusions include systemic JIA, positive RF, and HLA-B27 disease in first-degree relatives of the child. There is increasing evidence that JPsA is not a homogeneous disease entity, but rather includes at least two distinct subgroups: one shares the same characteristics as early-onset ANA-positive JIA, and the other belongs to the spectrum of spondyloarthropathies [21].

Undifferentiated arthritis accounts for 10% of all children with JIA [1]. Undifferentiated arthritis is defined as chronic arthritis that cannot be classified as one of the above subtypes. This includes patients who do not meet the criteria for any subtype, or who meet the criteria for more than one. Depending on new manifestations, the diagnosis of undifferentiated arthritis can change [22,23].

The characteristics of each subtype of JIA are listed in Table 3 [24].

Differential diagnosis

Childhood arthralgia arises from several causes including JIA, infection, tumor, growing pains, transient synovitis of the hip, etc. [25,26]. There are many illnesses that can mimic JIA (Table 4) [27,28].

Septic arthritis (SA) is the most frequent cause of arthritis in hospitalized children, followed by JIA [26]. SA usually occurs in childhood as a complication of bacteremia and is considered a true clinical emergency [27,29]. The most common infectious organism of SA is *Staphylococcus aureus*. Other important organisms are the *Streptococcus* species, *Pseudomonas aeruginosa*, pneumococci, *Neisseria meningitidis*, *Escherichia coli*, *Klebsiella* species. [27]. Early

Table 3. Characteristic findings of the juvenile idiopathic arthritis subtypes

Variable	Oligoarthritis	RF(−) polyarthritis	RF(+) polyarthritis	Systemic	ERA	Psoriatic arthritis
Peak age	1～3 years	Dual peaks	Teenage	2 years	Teenage	Dual peaks
Sex	F>M	F>M	F>M	Equal	M>F	F>M
Fever	No	No	No	Yes	No	No
Uveitis	Silent	Silent	Rare	Rare	Acute	Silent
Enthesitis	No	No	No	No	Yes	Rare
Dactylitis	Rare	No	No	No	Yes	Yes
RF+	No	No	Yes	No	No	No
ANA+	Majority	Majority	Rare	Rare	Rare	Majority
HLA-B27+	No	No	No	No	Typically	Rare

Unclassified juvenile idiopathic arthritis meet criteria for none or for two or more of the categories listed in the table. RF: rheumatoid factor, ERA: enthesitis related arthritis, F: female, M: male, ANA: antinuclear antigen, HLA: human leukocyte antigen.

Table 4. Differential diagnosis of juvenile idiopathic arthritis (JIA) in children

Monoarticular JIA	Polyarticular JIA	Systemic JIA
Acute monoarthritis	SLE	Infection
Arthritis related to infection	Arthritis related to infection	Inflammatory bowel disease
Septic arthritis	Lyme disease	Connective tissue diseases
Reactive arthritis	Reactive arthritis	SLE
Malignancy	Other	Juvenile dermatomyositis
Leukemia	Sarcoidosis	Vasculitis
Neuroblastoma	Mucopolysaccharidoses	Castleman's disease
Hemophilia		Familial mediterranean fever
Trauma		Hyper IgD syndrome
Chronic monoarthritis		
Tuberculosis		

SLE: systemic lupus erythematosus, Ig: immunoglobulin.

Table 5. Clinical predictors of septic arthritis (based on Kocher and Caird)

1. Refusal to bear weight
2. A history of fever (an oral temperature $>38.5^{\circ}C$)
3. Serum white blood cell count $>12,000/mm^3$
4. Erythrocyte sedimentation rate >40 mm/hr
5. C-reactive protein level >1.0 mg/dL

differentiation between SA and JIA is essential in management, as children with SA require urgent treatment including surgical joint drainage and intravenous antibiotics [30]. In comparison, children with JIA require nonurgent treatment, including non-steroidal anti-inflammatory drugs and/or intra-articular injections of triamcinolone hexacetonide and/or biologic agents [31]. Onset of fever, malaise, and prominent localizing signs such as erythema, local heat, and significant pain at the affected joint are all suggestive of a septic joint. The gold standard for the diagnosis of SA is isolation of the causative agent from joint fluid or blood, but this is not always possible, especially in children. Joint drainage and immobilization may delay appropriate treatment of JIA if it is misdiagnosed, resulting in additional disease progression and increased joint erosion and disability [32].

Transient synovitis of the hip is a benign, self-limiting synovial inflammatory condition and occurs most commonly in boys between 3 to 8 years old. Pains in the hip and thigh may be of sudden onset and can last for 6 days. There is also loss of internal rotation of the hip. The C-reactive protein, ESR, and total white cell count are normal. Radiologic tests show normal findings or widening of the joint spaces [33]. Transient synovitis is the most common cause of arthritis and commonly involves a well child with a history of recent mild upper respiratory infection presenting with a painful limp [27]. Management involves symptomatic treatment, with no role for surgical therapy. Transient synovitis of the hip is a diagnosis of exclusion and septic arthritis of the hip is the most important disease that must be distinguished. The Kocher criteria is a useful tool in the differentiation of septic arthritis from transient synovitis in the child with a painful hip (Table 5).

Malignancies, including leukemia, lymphoma, neuroblastoma, osteosarcoma, and Ewing's sarcoma can present as joint pain. The symptoms of arthritis, sometimes with a migratory pattern, can precede the hematologic features of malignancy [34]. Considerable findings that point to the diagnosis of a malignancy are pallor, bruising, lymphadenopathy, hepatosplenomegaly, and bony tenderness.

Recurrent hemarthrosis is a hallmark of hemophilia A, which is one of the most important X-linked recessive coagulopathic diseases. Hemarthrosis can occur before the child starts walking, and the frequency of hemarthrosis increases during childhood. The most commonly affected joints are the knees, ankles, and elbows [1,35].

Kawasaki disease (KD) is a systemic vasculitis that may cause coronary artery complications. It is known as one of the most common causes of acquired cardiac diseases in children from developed countries, especially Japan and Korea [36]. Arthritis was observed in 7.5% of patients with KD, and characterized as 55% oligoarticular and 45% polyarticular. The most commonly affected joints are the knees, ankles, wrist, and elbows [1].

CONCLUSION

JIA is an umbrella term that describes a clinically heterogeneous group of arthritides of unknown cause, lasting for at least 6 weeks, and with onset before the age of 16 years. JIA is classified into seven subtypes based on distinct clinical findings and laboratory findings: systemic, oligoarticular, polyarticular with and without rheumatoid factor, ERA, psoriatic arthritis, and undifferentiated arthritis. Each subtype has a different manifestation and requires different treatments, and therefore it is important to diagnose the exact subtype. To make a clinical diagnosis of JIA, it is important to exclude arthritis of known etiologies including septic arthritis, transient synovitis, hemophilia, and malignancy.

ACKNOWLEDGMENTS

This work was supported by grant of the Inje University (20121021).

The authors are grateful to Prof. Woojin Cho, M.D., Ph.D. for valuable contribution in reviewing this manuscript.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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