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Juvenile Idiopathic Arthritis: Diagnosis and Management

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the archetypal, and the commonest, pediatric rheumatological disease in clinical practice.[1-3] It encompasses a diverse group of inflammatory disorders of agnogenic origin characterised by chronic inflammation of joints involving increased pro-inflammatory cytokines mediated via innate and adaptive immune responses. Despite advances in diagnosis and newer treatment modalities, JIA continues to be misdiagnosed causing delays in initiation of appropriate treatment leading to permanent damage of joints and functional disability.

CLASSIFICATION CRITERIA

Since, the 1970's when researchers in the US and Europe proposed the initial definitions of JIA, there has been a paradigm shift in the classification criteria with emphasis on the clinical phenotype and underlying immunology. The most commonly used classification criteria for JIA is the one proposed by the 'International League of Associations for Rheumatology' (ILAR).[1] It defines JIA as arthritis that persists > 6 weeks in children < 16-years (Figure 1).

However, the ILAR classification criteria are not without controversy because of the heterogeneous clinical phenotype of each type of JIA, and the ever-evolving understanding of the immunopathogenesis of JIA. The 'Pediatric Rheumatology International Trials Organization' (PRINTO) has recently proposed a newer classification criteria to address these aspects (Table 1).[2]

Table 1: PRINTO Classification criteria for JIA.

Arthritis	Remarks
ANA positive early onset arthritis	Only seen in children
RA factor associated arthritis	Pediatric counterpart of Rheumatoid arthritis in adults
Systemic JIA	Similar to Adult-onset Still's disease
HLAB27 associated arthritis	Seropositive spondyloarthritis
Others (Psoriatic arthritis, RA factor negative polyarticular JIA)	Seronegative spondyloarthritis
Undifferentiated	Not fitting into any group

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CLINICAL FEATURES

1. Systemic JIA

a) Prominent systemic features, especially fever.
b) It is seen across all age groups.
c) Equally seen in boys and girls.
d) Accounts for 5-15% of patients with JIA.
e) Interval between onset of systemic signs and appearance of arthritis may >10-years.
f) They are at risk to develop macrophage activation syndrome, a rheumatological emergency, characterized by continuous fever, pancytopenia, prominent hepatomegaly and transaminitis, hypertriglyceridemia, hyperferritinemia, coagulopathy, hypofibrinogenemia, decreased ESR, increased CRP, and hemophagocytosis in bone marrow examination.

2. Oligoarticular JIA

a) Asymmetric arthritis.
b) Young age of onset (< 6-years of age).
c) More common in girls.
d) High likelihood of developing chronic anterior uveitis, particularly when ANA is positive, and it is usually asymptomatic in early stages.
e) Knee joint is most commonly involved.
f) Accounts for 30-60% of patients with JIA.

3. Polyarticular JIA (RF negative)

a) Two clinical patterns
   - Younger age of onset, asymmetric involvement, positive ANA, female preponderance, higher chance of uveitis.
   - Common in school-going children, symmetric involvement, negative ANA, guarded prognosis.
b) Accounts for 10-25% of patients with JIA.

4. Polyarticular JIA (RF positive)

a) Similar to adult rheumatoid arthritis
b) More common in girls
c) Usually presents in adolescence

d) Accounts for 3-7% of patients with JIA

5. Psoriatic arthritis

a) Bimodal distribution of age (2-4 years, and 9-11 years)

b) Asymmetric arthritis

c) More common in girls

d) Two clinical patterns

- Similar to oligoarticular JIA, presence of dactylitis, involvement of distal interphalangeal joint.
- Similar to enthesitis related arthritis and/or adult spondyloarthritis.

e) Accounts for 3-10% of patients with JIA

6. Enthesitis related arthritis

a) Seen more commonly in adolescent boys

b) Lower limb joints are affected: knee, midfoot, ankle, and hip joints

c) Usually asymmetric

d) HLAB27 is positive in 50-90% of cases

e) Acute asymmetric symptomatic uveitis is seen in 7-10% of patients

f) Accounts for 5-10% of patients with JIA

Assessment

(A) Laboratory tests: Currently, there is no gold standard investigation for the diagnosis of JIA.

- Complete blood count: normocytic anaemia, thrombocytosis, leucocytosis, elevated ESR and CRP.
- Specific tests based on clinical phenotype: ANA (oligoarthritis), RF (polyarthritis), HLAB27 (enthesitis related arthritis)
- Liver function test and renal function test to rule out organ dysfunction.
- Infection screening: tuberculosis, HIV, hepatitis B, hepatitis C (since immunosuppressive drugs may need to be initiated).

(B) Radiological investigations: assessment of joint damage, monitoring diseases progression and ruling out other joint conditions

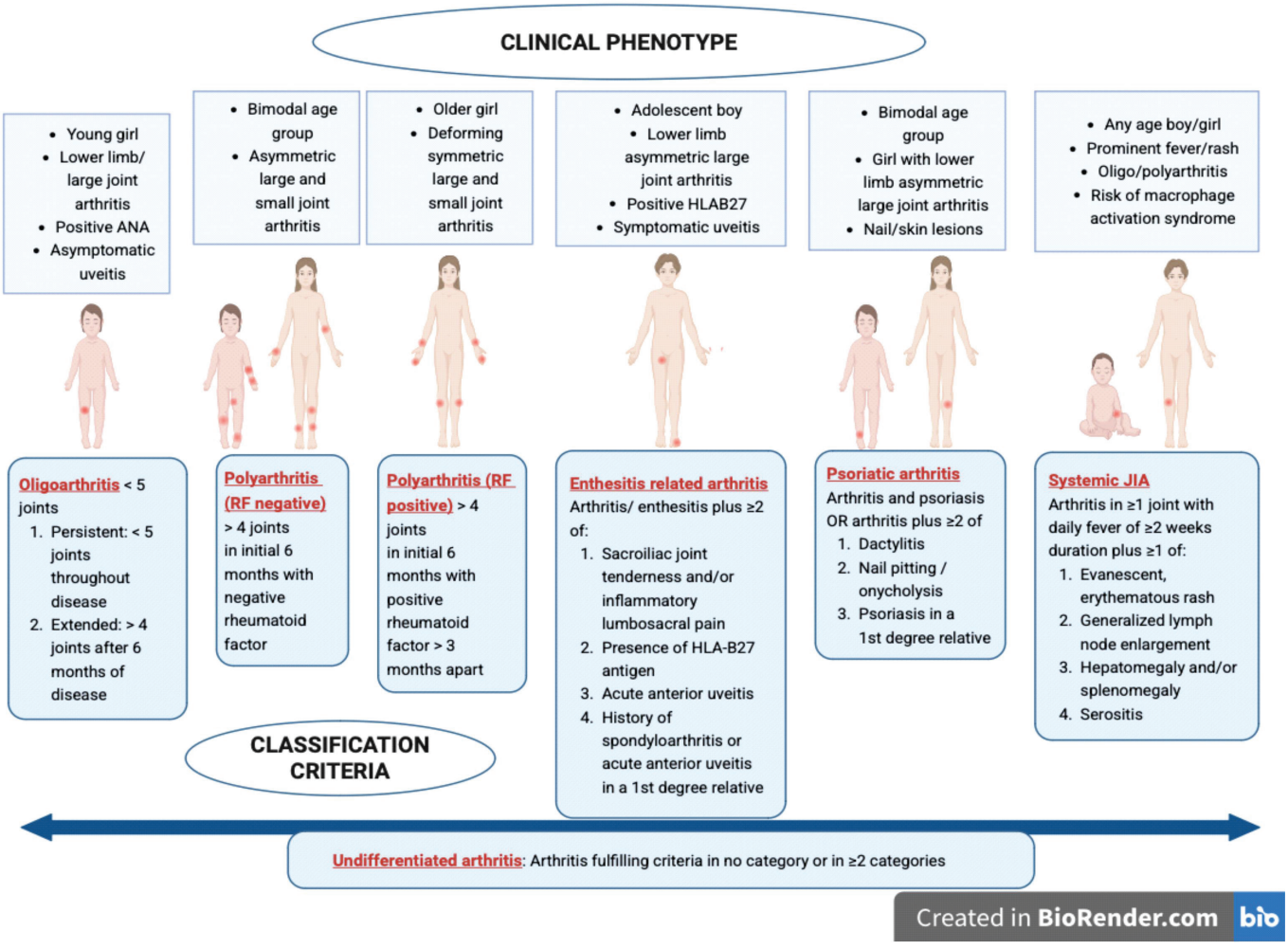

Figure 1: Classification criteria and clinical phenotype of Juvenile idiopathic arthritis. Created in BioRender.com.

- X-ray: may be normal in early stages; findings include swelling and increased density of soft tissues, peripheral osteoporosis, reduction of joint space, bony erosion and ankylosis in advanced stages.
- Musculoskeletal ultrasonography: non-invasive, cost-effective, and non-radiating imaging modality in JIA; allows dynamic assessment of joints, and can help identify synovial changes and bony erosions.

High-risk assessment (for prognostication and need for intensive therapy):

1. Axial involvement
2. Ankle, wrist, hip and temporo-mandibular joint involvement
3. Persistent elevated inflammatory markers
4. Positive ANA
5. Positive RF
6. Delay in diagnosis
7. Presence of erosive disease

Treatment: A multidisciplinary approach is recommended

(A) Pharmacological therapy

1. **Non-steroidal anti-inflammatory drugs (NSAID):** In children, naproxen is the first-line and most widely used drug due to its safety profile.
2. **Steroids**
   a. Intra-articular steroid (triamcinolone acetonide or triamcinolone hexacetonide) is preferred in oligoarthritis (may lead to rapid resolution of symptoms; however, not to be repeated in the same joint within 6 months)
   b. Systemic steroid is used predominantly as a short course bridge therapy
3. **Disease modifying anti-rheumatic drugs (DMARD)**
   - Methotrexate (15-20 mg/m^2/week) [subcutaneously] is the backbone of therapy in children with JIA.
   - Sulfasalazine (30-50 mg/kg/day) is preferred in enthesitis related arthritis.
   - Other less frequently used DMARDs include leflunomide and hydroxychloroquine.
4. **Biologics**

   Commonly used drugs include:
   - Anti-TNF - Adalimumab, Infliximab, Etanercept
   - IL-6 inhibitor - Tocilizumab
   - IL-1 inhibitor - Anakinra [not available in India currently]

There is usually no preferred biologic in JIA; however, tocilizumab/anakinra works better in systemic JIA, and anti-TNF in enthesitis related arthritis (especially in sacroiliitis).

Management of JIA-associated uveitis

1. Topical glucocorticoid steroid for 3 months
2. Systemic glucocorticoids when no response to topical therapy and in high-risk group
3. DMARDs (methotrexate) with glucocorticoid
4. If there is no response to methotrexate, to start with adalimumab
5. Refractory cases: Tocilizumab, rituximab

(B) Non-pharmacological therapy

1. Pain management: cognitive behavioral therapy, aquatic exercises, interferential current therapy.
2. Management of muscle/joint weakness: orthotics, isometric exercises.
3. Psychological rehabilitation: cognitive behavioral therapy, patient support programmes, family-centered interventions.

CONCLUSION

In India, JIA continues to present with joint complications due to delay in diagnosis. Understanding the typical clinical phenotype can help delineating JIA from other joint conditions. Over the past 20-years, significant progress has been made in the management of JIA, and introduction of biologics has dramatically improved its prognosis. A multidisciplinary approach is essential to enhance the standard of living of children with JIA.

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