

Rational approach to the child with juvenile idiopathic arthritis

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Introduction

Musculoskeletal symptoms are common among children. However, only a minority has arthritis. Incidence of arthritis in United Kingdom is 1 in 10,000¹ and prevalence 1 in 1000¹. Arthritis can be defined as inflammation of joints. Inflammation is recognized by its cardinal manifestations viz. pain, redness, warmth, swelling and loss of function. These features are not prominent in some children, particularly those with pauciarticular juvenile idiopathic arthritis (JIA) characterized by low grade inflammation, which could result in delayed diagnosis. Therefore, in children, we use the following criteria to diagnose arthritis²:

1. Swelling or effusion arising from joint even in absence of other features of inflammation.
2. In absence of swelling –
 - Tenderness over a joint / painful movement.
 - Limited range of movements.
 - Warmth.
 - Muscle spasm around a joint.

Three of the above 4 criteria should be fulfilled to diagnose arthritis.

Definition of JIA

JIA is defined as a heterogeneous group of diseases characterized by persistent arthritis lasting more than 6 weeks, commencing before 16 years of age, in the absence of a defined diagnosis (e.g. systemic lupus erythematosus).

Diagnosis of JIA could be difficult in some children and delayed in the majority as it takes many days or weeks for characteristic features to appear. Diagnosis is essentially clinical as there are no pathognomonic or diagnostic laboratory tests. Furthermore, some

children present with atypical features such as limping, torticollis or upper limb dysfunction for e.g. lack of use in playing. In certain situations children present with non specific features like fever, lethargy, irritability and poor appetite. Therefore, clinicians should have a high index of suspicion to minimise delay in diagnosis which may result in muscle wasting and ankylosis of joints.

Classification

Juvenile arthritis is a heterogeneous group of diseases of unknown aetiology, many of which are clinically and genetically distinct from chronic arthritis in adults. There has been long standing confusion about differences between JCA (Europe) and JRA (North America). JIA is the new term proposed to unify these previous classifications to facilitate research and further knowledge and understanding of biologically significant and clinically homogenous disease entities. The new classification^{3,4} given below is predominantly clinical, requires prospective validation and will evolve further with greater understanding of the aetiopathogenesis of these diseases.

(1) *Systemic*

Arthritis with or preceded by fever of at least 2 weeks, documented to be quotidian for at least 3 days, accompanied by one or more of the following:-

- Transient, erythematous rash
- Hepatomegaly / splenomegaly
- Generalised lymphadenopathy
- Serositis

(2) *Pauciarticular*

Arthritis affecting 1-4 joints during first 6 months of disease. Children with a family history of psoriasis or a positive rheumatoid factor are excluded from this group.

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- *Persistent pauciarticular* - Affect up to 4 joints throughout course of disease.
- *Extended pauciarticular*- Affect up to 4 joints during first 6 months, but progresses to 5 or more joints after 6 months.

(3) *Polyarthritis*

Arthritis affecting 5 or more joints during first 6 months of disease. Children with a family history of psoriasis are excluded.

- *Rheumatoid factor negative*
- *Rheumatoid factor positive* - associated with positive rheumatoid factor tests on 2 occasions at least 3 months apart.

(4) *Enthesitis related arthritis*

Arthritis and/or enthesitis with at least 2 of the following:

- Sacroiliac tenderness / inflammatory spinal pain
- HLA B27
- Acute anterior uveitis
- Onset in males over eight years
- Family history of HLA B27 related medical conditions

At present children with antinuclear antibody, rheumatoid factor or inflammatory bowel disease are excluded from this group.

(5) *Psoriatic arthritis*

Arthritis and psoriasis or arthritis with two of the following:

- Family history of psoriasis
- Dactylitis
- Nail abnormalities - pitting, onycholysis

Children with positive rheumatoid factor are excluded from this group.

(6) *Other*

Children with arthritis of unknown cause not fulfilling above categories or who develop more than one category.

Investigations

Laboratory tests help to exclude other diagnoses and to monitor disease activity, detect complications and predict outcome.

- *Elevated ESR* and *C- reactive protein* indicate active inflammation.
- *Full blood count* Characteristic changes are normochromic normocytic anaemia, neutrophil leucocytosis and thrombocytosis, most marked in systemic JIA.
- *Synovial fluid analysis* is mandatory in assessment of children with a single hot, swollen joint.
- *Antinuclear antibodies (ANA)* are positive in 50% patients with JIA, but are also found in viral illness, non rheumatic disease and healthy children. They are not diagnostic and must be carefully interpreted in clinical context. However, in presence of JIA. ANA indicate risk of chronic asymptomatic uveitis.
- *Rheumatoid factor* is a poor diagnostic test but its presence in a child with polyarticular JIA indicates a guarded prognosis.
- *Radiographs* are useful in excluding malignancy, osteomyelitis and trauma (including suspected non-accidental injury). In early JIA radiographs may show only an effusion or periarticular osteopenia; erosions may not appear for months or years

Differential diagnosis

(A) *Life threatening conditions*

- Malignancy (leukaemia, lymphoma, bone tumour)
- Sepsis (septic arthritis, osteomyelitis)
- Non-accidental injury

(B) *Joint pain with no swelling*

- Hypermobility syndromes
- Idiopathic pain syndromes (reflex sympathetic dystrophy, fibromyalgia)
- Orthopaedic syndromes (slipped capital femoral epiphysis, Osgood Schlatter disease)
- Metabolic (hypothyroidism)

(C) Joint pain with swelling

- Juvenile idiopathic arthritis
- Trauma
- Infection related
 - septic arthritis - bacterial, mycobacterial
 - reactive arthritis - post enteric
 - rheumatic fever
- Inflammatory bowel disease
- Connective tissue diseases
 - systemic lupus erythematosus
 - scleroderma
 - dermatomyositis
 - vasculitis
- Sarcoidosis
- Metabolic
 - osteomalacia
- Haematological
 - haemophilia
 - haemoglobinopathy
- Crystal arthropathy
- Tumour
 - benign
 - malignant
- Developmental
 - spondylo - epiphyseal dysplasia

Prognosis

JIA is not a self limiting disease process. Remission rate for different types of JIA after 10 years in one large series is given below⁵.

- Systemic 57%
- Polyarticular RF + 0%
- Polyarticular RF - 60%
- Persistent pauciarticular 70%
- Extended pauciarticular 65%

Management

Optimal management requires accurate diagnosis and early intervention by an experienced, well coordinated multidisciplinary team involving physiotherapist, occupational therapist, nurses, paediatric rheumatologist, psychologist, social worker, ophthalmologist, dentist and orthopaedic surgeon. The primary aim of management is to preserve joint position, function and vision.

Non Pharmacological Measures

- Education of patient and family
 - booklets, video tapes

- Nutrition
 - adequate amounts of calories, calcium and protein
- Dental hygiene
- Psychological support
- Family life
- Physiotherapy / occupational therapy
 - monitoring and recording of range of movements of joints
 - exercises to increase the range of movements of joints
 - exercises to increase the bulk of muscles
 - hydrotherapy
 - splinting - nocturnal (resting), working splints, serial splints to correct deformities
- Relief of pain / muscle spasm
 - ice packs, hot packs, electrotherapy

Drug Therapy

Optimization of outcome requires early recognition and treatment of disease and its complications, and frequent surveillance over many years. Increasingly aggressive therapies are available to treat inflammatory arthritis in children, but it is a major challenge to find accurate and early prognostic indicators to target those with severe disease and avoid exposing those with mild diseases to potentially toxic therapies.

Simple analgesics, such as paracetamol, are extremely useful to minimize pain when used together with regular anti-inflammatory drugs. This can be given early morning, even on an empty stomach, as inflammatory features are most marked on awakening.

Non-steroidal anti-inflammatory drugs (NSAIDs) are indicated in all children with active synovitis. These drugs take about 2-4 weeks to act effectively. Therefore changing NSAIDs frequently (unless due to side effects) is not recommended. Combination of NSAIDs should be avoided as it leads to addition of side effects. Children tolerate higher doses of NSAIDs as liver metabolism is efficient. Recommended doses⁵ of commonly used NSAIDs are given below.

- Ibuprofen 30-50 mg/kg/day
- Naproxen 10-20 mg/kg/day
- Diclofenac 2-3 mg/kg/day
- Indomethacin 12 mg/kg/day
- Piroxicam 0.2-0.3 mg/kg/day

Slow-release preparations and long acting NSAIDs such as piroxicam are extremely useful to counteract morning stiffness when given in the night. Cox-2 inhibitors are still not licensed for use in children and adolescents.

Methotrexate⁶ is now considered the drug of choice among disease modifying drugs. This is started at a dose of 0.3 mg/kg/week initially and increased to a maximum of 1 mg/kg/week at monthly intervals (10-15 mg/m²/week). Mode of action is complex as it has inhibitory effects on folate, antibody synthesis and inflammatory mediators, in addition to cellular effects. This is given together with folic acid 5 mg/week 2 days after methotrexate which seem to improve the tolerability. Live vaccines should be avoided while a child is on methotrexate. Adolescents should be warned against taking alcohol as the hepatotoxicity is additive.

Long term studies have shown that methotrexate is useful in polyarticular and pauciarticular disease unresponsive to intra-articular steroids. However, its role in systemic JIA is unclear⁶. It is imperative that children on methotrexate need regular blood tests to monitor efficacy and safety. It takes about 3 months for full effect of methotrexate to manifest.

Sulfasalazine (50 mg / kg / day) is used in enthesitis related arthritis or pauciarticular JIA.

Steroids have a useful role to play in management of JIA. Intra-articular⁷ route is preferred as it is associated with minimal side effects. It is highly beneficial in pauciarticular disease in controlling synovitis and helps to minimize fibrosis and ankylosis of joints. Intra-articular steroids are given under sedation or general anaesthesia for young children.

High dose oral prednisolone⁵ (1-2 mg/kg/day) is used to treat systemic features of JIA. Pulsed IV methyl prednisolone 30 mg/kg/day (1-3 days) is a safe but more expensive alternative in this instance.

In practice, low dose (<0.5 mg/kg/day) oral prednisolone is used to treat polyarticular JIA who do not respond well to NSAIDs. This is useful as a disease remitting agent while starting methotrexate therapy which can take several months to be effective. When using oral steroids, complications can be minimized by giving them as a single morning dose. Risk of osteopenia associated with long-term steroids can be minimized by giving supplemental calcium and vitamin D therapy.

For children with resistant JIA, various drugs had been used in new combinations and new schedules. For resistant systemic JIA⁸ encouraging results had been shown with a combination of pulsed methyl prednisolone (30 mg/kg/day) for 3 days with oral cyclophosphamide 0.4g/m² on day 3 together with oral

methotrexate 10 mg/m² weekly. In this regime these pulses are used every 3 months up to one year.

Intravenous immunoglobulins⁸ have been found to be beneficial in polyarticular JIA if given early. It is given at a dose of 1.5-2.0 g/kg twice a month for 2 months and then continued monthly for a period of 6 months.

New biological therapies⁹ are available for patients not responding to methotrexate⁸. Etanercept and infliximab have been used with dramatic and sustained improvement in this setting. Use of these agents is restricted because of limited availability and high cost.

Use of gene therapy⁸ is still at experimental level. Candidate genes encoding for anti-inflammatory, immunosuppressive, chondro-protective and chondro-reparative proteins, may be incorporated into synovial lining cells so that their products are secreted directly into joint space.

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