Early intervention is key in juvenile idiopathic arthritis

How should children be examined?

What investigations should be carried out?

What are the evidence-based treatment options?

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FIGURE 1
Knee joint MRI of a child with JIA (psoriatic arthritis) showing a very large effusion extending into the supra-patellar region and considerable synovial thickening

JUVENILE IDIOPATHIC ARTHRITIS (JIA) IS ONE OF THE MOST COMMON CHRONIC DISEASES OF childhood. JIA is defined as arthritis of unknown cause, beginning before the age of 16, that persists for at least six weeks. The annual incidence in the UK is 1 in 10,000 children and the prevalence is 1 in 1,000. JIA occurs in all races and geographical areas and is more common in girls.[1] The age of onset peaks between three and six and then again around adolescence.

As most children with JIA will first present to primary care, GPs have an important role in diagnosis and management. It is important that a thorough assessment is carried out, if the diagnosis is suspected on clinical grounds, to allow referral as early as possible to a paediatric rheumatologist and ophthalmologist. After confirmation of the diagnosis, the GP will be involved in monitoring the condition using blood tests to assess disease activity and side-effects of treatment. This can be very helpful in bringing poor disease control to the attention of secondary care physicians. JIA has emotional and psychosocial implications for both the child and the family and GPs may be involved in supporting the family through this often difficult time.

PRESENTATION

The most recent and widely accepted classification system is that proposed by the International League of Associations for Rheumatology (ILAR), revised in 2001.[2] This lists seven subtypes (see box 1, right). Juvenile chronic arthritis and juvenile rheumatoid arthritis are outdated terms and should no longer be used.

Each subtype of JIA varies in presentation. Arthritis may present as swelling or reduced range of movement of a joint accompanied by features of inflammation such as warmth, pain or tenderness. Often pain is not a significant feature and children may simply present with a swollen joint.

Oligoarticular JIA

Oligoarticular JIA is the most common form of the disease accounting for around 50% of all cases. It affects one to four joints (mainly large joints, especially knees) during the first six months of the disease but may progress to involve more joints over time.[3] RF positivity is an exclusion criteria for the diagnosis of oligoarticular JIA.

Polyarticular JIA

Polyarticular JIA affects five or more joints within the first six months of the disease.[2] The mean age of onset is »

Box 1

Subtypes of JIA (ILAR classification)

- Oligoarticular JIA (≤ 4 joints)
- Polyarticular JIA (≥ 5 joints) with negative rheumatoid factor (RF)
- Polyarticular JIA (≥ 5 joints) with positive RF
- Systemic onset JIA (previously known as Still's disease)
- Enthesitis related arthritis
- Juvenile psoriatic arthritis
- Undifferentiated arthritis

six and a half with peaks in the pre-school and pre-adolescent years. Patients may be positive or negative for RF. For a diagnosis of polyarticular JIA with positive RF to be made, a positive result for RF needs to be obtained on two occasions at least three months apart.[3]

Systemic onset JIA

Previously known as Still's disease, systemic onset JIA causes arthritis accompanied, or preceded, by fever in a quotidian pattern for at least three days. The fever spikes to over 39°C once or twice a day and returns to below 37°C in between. Other features include an evanescent, salmon pink erythematous rash that tends to occur with the spikes of fever and may only be apparent in the axillae, generalised lymphadenopathy, hepatomegaly and/or splenomegaly and serositis such as pericarditis, pleuritis or peritonitis.

Enthesitis related arthritis

Enthesitis related arthritis (ERA) usually manifests as a combination of arthritis and enthesitis (inflammation of tendon insertions, ligaments or joint capsule).

Juvenile psoriatic arthritis

Juvenile psoriatic arthritis is a combination of arthritis and psoriasis.

Undifferentiated arthritis

Arthritis that does not meet the inclusion criteria for any of the above categories, or fulfils criteria for more than one category is termed undifferentiated arthritis.[3]

DIAGNOSIS

The diagnosis of JIA is made clinically in combination with the judicious use of investigations. When a child presents in primary care with a painful/swollen joint that has not been caused by trauma, the GP should obtain a thorough history from the child and/or the parents/carer. It is important to examine 'every joint, every time' as it is often difficult for children to localise pain and stiffness. This also helps avoid unnecessary joint aspiration for suspected sepsis when an oligo/polyarthritis is evident.

At the initial visit, a full examination should be performed to look for any rash, nail changes, mouth ulcers, hepatosplenomegaly and respiratory or cardiac abnormalities. The differential diagnosis of JIA encompasses a wide range of conditions which should be considered during assessment (see table 1, below). A paediatric gait, arms, legs and spine (pGALS) examination is a useful screening tool[4] that can be used in general practice (see table 2, opposite).

As no diagnostic test exists for JIA, investigations are used to support the diagnosis, see table 3, opposite. Inflammatory markers and FBC can be helpful in supporting the diagnosis when deciding to refer. After discussion with a paediatric rheumatologist it may be appropriate to obtain further investigations which form a routine part of the secondary care assessment. This includes x-rays, autoimmune profile (C3, C4, dsDNA, immunoglobulins) and parameters for classifying the disease (RF, ANA, HLA B27). In early disease, joint x-rays are usually normal but may show a joint effusion, peri-articular osteoporosis or soft tissue swelling. Occasionally alternative diagnoses such as fracture, osteomyelitis or malignancy are seen on plain x-rays. Ultrasound is increasingly used and may show joint effusions and synovitis. MRI demonstrates joint anatomy in excellent detail, see figure 1 p19, and can reveal early pre-erosive changes in the articular cartilage.

In monoarthritis, arthrocentesis is required to exclude septic arthritis, even in established JIA, as these joints are at greater risk of infection. In JIA, aspiration of straw-coloured fluid with a high white cell count but no organism on culture is a typical finding. Children, especially younger ones, require sedation before joint aspiration and injection.

Table 1

Differential diagnosis of JIA

Condition	Distinguishing features
Septic arthritis	Usually monoarthritis. Associated fever and systemically unwell, unable to weight bear. Raised ESR and CRP
Osteomyelitis	Fever, bone pain beyond joint margins
Reactive arthritis	History of recent infections: gastroenteritis or other viral infection (measles, parvovirus)
Trauma	History of trauma may not be recalled in young children. May need to consider possible non-accidental injury
Mechanical	Possibly related to joint hypermobility syndrome, Perthe's disease, slipped upper femoral epiphysis
Inflammatory bowel disease	May first present with arthritis. Weight loss and failure to thrive. Mouth ulcers, family history of HLA B27 related disease
Malignancy	Night pain, back pain, non-articular bone pain, systemic features. Leukaemia, lymphoma, neuroblastoma, Ewing's sarcoma
Autoimmune connective tissue disease	May be features of systemic lupus erythematosus, Juvenile dermatomyositis, Henoch-Schonlein purpura or sarcoidosis
Pain syndromes	Features of complex regional pain syndrome such as autonomic dysfunction
Rheumatic fever	Diagnosis made using Duckett-Jones criteria. Often migratory polyarthritis
Lyme disease	Travel to endemic areas, history of tick bite may be elicited. Large joint oligoarthritis preceded by erythema chronicum migrans

Box 2

Complications of JIA

- Poor dentition
- TMJ dysfunction
- Osteoporosis
- Growth failure
- Infections
- Blindness due to anterior uveitis
- Amyloidosis
- Macrophage activation syndrome
- Joint contractures

Box 3

Specialties involved in JIA

- GP and primary healthcare team
- Paediatric rheumatologist
- Paediatric rheumatology nurse specialist
- Physiotherapist
- Occupational therapist
- Ophthalmologist
- Orthotist
- Musculoskeletal radiologist
- Psychologist
- Dietician
- Social worker
- Paediatric orthopaedic surgeon
- Maxillofacial surgeon

REFERRAL

All children with possible JIA should be referred urgently to a paediatric rheumatologist as soon as possible in order to confirm the diagnosis and consider early institution of DMARD therapy. Once the diagnosis is confirmed, any child with JIA should be considered at risk of uveitis and subsequent blindness and therefore immediate referral to a paediatric ophthalmologist is mandatory.

In areas where specialised paediatric rheumatologists or ophthalmologists are not available there are often consultants with an interest in managing the paediatric cases of their specialty. The child should be referred to such specialists first before accessing tertiary referral centres.

COMPLICATIONS

Complications can arise as a result of the disease itself or as a consequence of its treatment. Anterior uveitis occurs in 8-30% of JIA patients overall, increasing to 45-57% in young female patients with oligoarticular disease who are antinuclear antibody positive.[5]

Uveitis may be silent, requiring slit-lamp examination for diagnosis. If left untreated it can result in permanent visual impairment through the development of cataracts, glaucoma and macular oedema. However with regular screening and early detection this can be prevented.[6,7] The initial ophthalmology assessment should occur as soon as possible and certainly within six weeks of disease onset.[8] Other complications and comorbidities are listed in box 2, opposite. Osteoporosis and growth failure are related to glucocorticoid use and the severity of disease. Psychosocial problems may be a particular concern in adolescents and can include depression, anxiety and difficulty with peers. Schooling and education may suffer.

PHARMACOTHERAPY

Children with JIA are best managed by a multidisciplinary team, see box 3, opposite. The focus of treatment has changed in recent years with the overriding aim now being complete suppression of inflammation with early, intensive intervention.

NSAIDS and steroids

Once the diagnosis is suspected, symptomatic treatment with simple

Table 2

Paediatric GALS examination

Screening questions	
● Do you (or does your child) have any pain or stiffness in your (their) joints, muscles or back?	
● Do you (or does your child) have any difficulty getting yourself (him/herself) dressed without any help?	
● Do you (or does your child) have any problem going up and down stairs?	
Screening manoeuvres	
Observe the child standing (from front, back and sides)	'Put your hands behind your neck'
Observe the child walking and **'Walk on your heels'*** and **'Walk on your tiptoes'**	'Try and touch your shoulder with your ear'
'Hold your hands out straight in front of you'	**'Open wide and put three** (child's own) **fingers in your mouth'**
'Turn your hands over and make a fist'	Feel for effusion at the knee (patella tap, or cross-fluctuation)
'Pinch your index finger and thumb together'	Active movement of knees (flexion and extension) and feel for crepitus
'Touch the tips of your fingers'	Passive movement of hip (knee flexed to 90°, and internal rotation of hip)
Squeeze the metacarpophalangeal joints for tenderness **'Put your hands together palm to palm'** and **'Put your hands together back to back'**	'Bend forwards and touch your toes?'
'Reach up, "touch the sky"' and **'Look at the ceiling'**	

*All items in bold indicate manoeuvres not included in adult GALS

Table 3

Common investigations in JIA

Test	Clinical utility
Full blood count (FBC)	● Anaemia, normocytic normochromic or microcytic ● Normal or mildly raised white cell count with normal differential ● Mildly raised platelets
Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)	● Often raised due to the inflammatory response
Immunology	● RF, anti-double stranded DNA antibodies (dsDNA) and HLA B27 useful in classification ● Consistently raised antinuclear antibody (ANA) suggests increased risk of uveitis. Although ANA is not diagnostic of JIA it is useful in classifying the disease and can inform the likely prognosis
Microbiology/ virology	● Serology for bacterial or viral triggers if reactive arthritis suspected ● Varicella zoster titres to check immunity before starting immunosuppressants

key points

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Juvenile idiopathic arthritis (JIA) is one of the most common chronic diseases of childhood. JIA is defined as arthritis of unknown cause beginning before the age of 16 that persists for at least six weeks. Onset peaks between three and six years of age and again around adolescence.

GPs have an important role in diagnosis and management. It is important that a thorough assessment is carried out, if the diagnosis is suspected on clinical grounds, to allow referral as early as possible to a paediatric rheumatologist and ophthalmologist. After confirmation of the diagnosis, the GP will be involved in monitoring the condition using blood tests to assess disease activity and side-effects of treatment.

Each (of the seven) subtypes of JIA varies in presentation. Arthritis may present as swelling or reduced range of movement of a joint accompanied by features of inflammation such as warmth, pain or tenderness. Often pain is not a significant feature and children may simply present with a swollen joint.

Oligoarticular JIA is the most common form of the disease accounting for around 50% of all cases. It affects one to four joints. Polyarticular JIA affects five or more joints within the first six months of the disease. Systemic onset JIA, previously known as Still's disease, causes arthritis accompanied, or preceded, by fever in a quotidian pattern for at least three days. Other features include: an evanescent salmon-pink, erythematous rash; generalised lymphadenopathy; hepatomegaly and/or splenomegaly; and serositis such as pericarditis, pleuritis or peritonitis.

The diagnosis of JIA is made clinically in combination with the judicious use of investigations. In early disease, joint x-rays are usually normal but may show a joint effusion, peri-articular osteoporosis or soft tissue swelling. In monoarthritis, arthrocentesis is required to exclude septic arthritis.

Anterior uveitis occurs in 8-30% of JIA patients overall, increasing to 45-57% in young female patients with oligoarticular disease who are ANA-positive. If left untreated, it can result in permanent visual impairment through the development of cataracts, glaucoma and macular oedema.

The focus of treatment has changed in recent years with the overriding aim now being complete suppression of inflammation with early, intensive intervention. NSAIDs are helpful in providing symptomatic relief but have no disease-modifying effect. Glucocorticoids are well established in the treatment of JIA and may given either intra-articularly, orally or in severe disease, intravenously. Methotrexate is the first-line DMARD used in JIA. It is safe, reliable and effective in 60-70% of cases. Children who have poorly controlled disease on methotrexate or who are unable to tolerate the drug may be given anti-TNF-α.

analgesics and NSAIDs can be initiated while waiting for a specialist opinion. NSAIDs are helpful in providing symptomatic relief but have no disease-modifying effect.

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DMARDs

Methotrexate is the first-line disease-modifying anti-rheumatic drug (DMARD) used in JIA. It is safe, reliable and effective in 60-70% of cases and may be given orally or subcutaneously. Appropriate counselling and confirmation of varicella immunity are essential before starting treatment with methotrexate.

Children on methotrexate must avoid all live vaccinations and seek advice from the paediatric rheumatology team in the case of acute infection as doses may need to be withheld. Regular monitoring with FBC and LFTs is required to check for toxicity. Other DMARDs which can be used include sulphasalazine especially for ERA and hydroxycholoroquine in conjunction with methotrexate.[3]

Biological therapy

Biological therapy has revolutionised the treatment of inflammatory arthritis. Children who have poorly controlled disease on methotrexate or who are unable to tolerate the drug may be given anti-TNFα treatment. Etanercept and adalimumab are licensed for treatment of JIA. NICE has issued guidance on the use of anti-TNFα in JIA.[9] Studies with these agents have shown high response rates[10,11] which are improved by using combination therapy with methotrexate.[12] Anakinra is a recombinant IL-1 receptor antagonist that may also be useful in systemic onset JIA.[13] A newer biological agent, tocilizumab, (an IL-6 inhibitor) is showing great promise for the treatment of JIA.[14]

Other treatments

Autologous stem cell transplantation is only used in exceptionally severe cases of JIA. Orthopaedic or maxillofacial surgery may be required for joint deformities, contractures and micrognathia. As in adults, joint replacement may be necessary.

PROGNOSIS

Long-term follow up of children with JIA shows that the arthritis persists into adulthood in up to 40% of cases with 30-50% of these patients having severely compromised function.[15] Unemployment rates are three times higher than the general population, regardless of educational capability. The prognosis of JIA is being improved, however, by intensive intervention early in the disease.

CONCLUSIONS

Although JIA is a rare condition, failure to recognise the disorder may have severe long-term consequences for the patient. All children with JIA must be screened for anterior uveitis as failure to detect this may lead to blindness. The shift towards early intensive treatment aims to control disease rapidly to maximise outcome.

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