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Juvenile idiopathic arthritis

Background

Juvenile idiopathic arthritis is the most common rheumatic disease in childhood, occurring in approximately 1:500 children. Despite a recent expansion in treatment options and improvement of outcomes, significant morbidity still occurs.

Objective

This article outlines the clinical manifestations, assessment, detection of complications, treatment options and monitoring requirements, with the aid of guidelines recently published by The Royal Australian College of General Practitioners, which provide practical support for general practitioners to ensure best practice care and to prevent lifelong disability in patients with juvenile idiopathic arthritis.

Discussion

General practice plays an important role in the early detection, initial management and ongoing monitoring of children with juvenile idiopathic arthritis. Early detection involves understanding the classification framework for subtypes of juvenile idiopathic arthritis, and being aware of the clinical manifestations and how to look for them, through history, examination and appropriate investigation. The major extra-articular manifestations of juvenile idiopathic arthritis are uveitis and growth disturbance. Treatment options include nonsteroidal anti-inflammatory drugs, methotrexate, biologic agents, and corticosteroids. Management using a multidisciplinary approach can prevent long term sequelae. Unfortunately, approximately 50% of children will have active disease as adults.

Keywords: chronic disease/therapy; arthritis/rheumatic diseases; musculoskeletal diseases; pain



Juvenile idiopathic arthritis (JIA) is characterised by persistent arthritis of unknown cause that begins before 16 years of age and is present for at least 6 weeks after exclusion of other diseases. In Australia, JIA prevalence is between 1 and 4 cases per 1000 children.¹ Almost all children with arthritis report chronic or recurrent pain with 70% restriction in physical activity. Approximately half of those with JIA have limited use of upper limbs or hands and difficulties with hand strength. Long periods of active arthritis impair muscle development, resulting in generalised growth retardation, uneven limb lengths, joint erosion and lower aerobic capacity. Unrecognised, JIA has the potential to cause long term sequelae and leave a lasting impact on the physical function, growth and quality of life of affected children.

General practice plays a pivotal role in the recognition and initial management of JIA as well as in the prompt referral to paediatric rheumatology services. In a collaborative project between The Royal Australian College of General Practitioners (RACGP) Juvenile Idiopathic Arthritis Working Group, The Australian Government Department of Health and Ageing, and the Australian Paediatric Rheumatology Expert Group, guidelines for the diagnosis and management of JIA were developed and recently approved by the National Health and Medical Research Council. These are available at www.racgp.org.au/guidelines/musculoskeletaldiseases.

Classification

The first classification system for arthritis in children was published in 1977.² In 2001, the International League of Associations for Rheumatology developed the most recent classification system³ which describes seven categories of JIA (*Table 1*). The classification system provides an important framework for research in JIA as well as assisting with appropriate treatment and prediction of natural history.

Clinical manifestations

Arthritis is defined as the presence of a joint effusion with reduced range of motion, pain on movement and/or warmth of the joint.



Table 1. International League of Associations for Rheumatology classification of JIA³

Category	Diagnostic criteria
Systemic arthritis (10–20%)	Fever of at least 2 weeks duration (daily for at least 3 days) and arthritis in one or more joints, plus one of the following: <ul style="list-style-type: none">• erythematous rash• generalised lymph node enlargement• hepatomegaly and/or splenomegaly• serositis
Oligoarthritis (50–60%)	Arthritis affecting \leq four joints during the first 6 months of the disease. If after 6 months more than four joints are involved the term extended oligoarthritis is used
Polyarthritis (20–30%) (rheumatoid factor negative)	Arthritis affecting \geq five joints during the first 6 months of the disease with rheumatoid factor negative
Polyarthritis (5–10%) (rheumatoid factor positive)	Arthritis affecting \geq five joints during the first 6 months of disease with rheumatoid factor positive on at least two occasions at least 3 months apart
Psoriatic arthritis (2–15%)	Arthritis and psoriasis or arthritis and at least two of the following: <ul style="list-style-type: none">• dactylitis• nail pitting or onycholysis• psoriasis in a first degree relative
Enthesitis related arthritis (1–7%)	Arthritis and enthesitis or arthritis or enthesitis with at least two of the following: <ul style="list-style-type: none">• presence/history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain and HLA-B27 positive• 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 or acute anterior uveitis in a first degree relative
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in two or more of the above categories

These findings in themselves are not diagnostic of JIA and may have multiple aetiologies which can be differentiated with careful history and examination (*Table 2*).

Clinical manifestations in JIA can be variable. Patients with polyarticular or systemic onset disease often experience fatigue, anorexia, weight loss and growth failure. However, these symptoms are rare in oligoarticular onset JIA. Joint pain is often only experienced on movement and is generally aching in quality and of mild to moderate severity. Children who report extremely severe pain are more likely to have a pain amplification syndrome than JIA.

The child's developmental age will affect how they communicate pain and dysfunction. For example, toddlers may become irritable or simply use affected joints in a different way. They may stop using an affected limb (eg. refusal to weight bear). In such cases, pain is more easily appreciated by examination of the affected joints.

Other common symptoms at presentation include morning stiffness and 'gelling' after inactivity. Parents will often report their child to be 'slow to get moving' in the morning or after a daytime sleep with improvement after a period of time. Quite often children will present with joint swelling after trauma to an affected joint.

Affected joints are usually warm and swollen with reduced range of motion, but not erythematous. Large joints are more commonly affected, with smaller joints affected in polyarticular disease. Examination of a child with arthritis should always include the temporomandibular joints and cervical spine, as arthritis in these joints is often underappreciated. Complications of cervical spine involvement include bony ankylosis and atlanto-axial subluxation. Temporomandibular joint involvement may cause significant malocclusion.

Investigations

The diagnosis of JIA is essentially a clinical one. Therefore, laboratory investigations are used to confirm the diagnosis and to aid in disease classification. Useful preliminary investigations include full blood count (FBC) and inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) as these are often elevated. The RACGP guidelines recommend that these be performed if symptoms are present for more than 4 weeks. The levels of ESR and CRP in active JIA are variable. A FBC may show anaemia of chronic disease if there has been longstanding inflammation.



Table 2. Differential diagnosis of JIA

- Septic arthritis
- Postinfective/reactive arthritis
- Systemic lupus erythematosus
- Acute lymphoblastic leukaemia
- Trauma
- Joint hypermobility
- Fibromyalgia
- Complex regional pain syndrome
- Osteomyelitis
- Bone tumour
- Inflammatory bowel disease
- Henoch-Schönlein purpura or other vasculitis
- Rheumatic fever

Adapted from The RACGP. Clinical guideline for the diagnosis and management of juvenile idiopathic arthritis, 2009. Available at www.racgp.org.au/guidelines/musculoskeletal diseases

The white cell count is often moderately elevated at diagnosis, except in systemic onset disease where counts may be in the tens of thousands. Rheumatoid factor (RF) should be performed in patients with polyarthritis as its presence has prognostic significance. The presence of a positive antinuclear antibody (ANA) confers risk for the development of asymptomatic uveitis, particularly in those with oligoarticular onset disease, but should be performed in all JIA patients.⁴ Anticyclic citrullinated peptide (anti-CCP) antibodies are not routinely tested in JIA, but may indicate severe disease.⁵ Human leukocyte antigen (HLA) B27 should be tested in children who present with signs and symptoms consistent with enthesitis related arthritis (*Table 1*) and can indicate susceptibility to the development of axial arthritis. If there is concern that arthritis is part of an underlying connective tissue disease or vasculitis then dsDNA, extractable nuclear antigens (ENA), C3, C4 and immunoglobulin testing is useful.

Plain X-rays at presentation can be useful in demonstrating larger effusions, however erosions are unusual in early disease. Ultrasound is useful in confirming joint effusions. The RACGP guidelines suggest that imaging be performed if symptoms are present for more than 4 weeks. Further imaging, such as whole body bone scan and magnetic resonance imaging (MRI), are usually performed by paediatric rheumatologists.

Extra-articular manifestations

Uveitis

Uveitis is the most common extra-articular manifestation in JIA. It is often asymptomatic at onset, typically nongranulomatous and affects the anterior chamber. However, it is potentially devastating, as approximately one-third of patients will develop posterior synechiae,

cataract, band keratopathy, glaucoma, or macular edema.⁶ While the prevalence is 9% across all categories of JIA,⁷ 15–20% of children with oligoarthritis will develop uveitis compared with 5–10% of those with polyarthritis. It is rarely seen in systemic arthritis⁸ (*Table 3*). Ninety percent of cases occur within 4 years of diagnosis of JIA. Regular screening by an ophthalmologist is required.^{4,9} Newly diagnosed patients are ideally screened within 6 weeks of diagnosis.¹⁰ Other complications of uveitis and its treatment include macular oedema, band keratopathy, posterior synechiae, glaucoma and cataracts.¹¹ The frequency of ophthalmologic screening according to the American Academy of Paediatrics guidelines is determined by the degree of risk (*Table 4*).⁴ However, in children with HLA-B27 positive disease, of which uveitis occurs in 10–15%, uveitis is usually symptomatic and therefore does not require routine screening.⁸

Uveitis is generally treated with topical steroids, although in resistant cases treatment with methotrexate or biologics may be required, requiring close collaboration between the affected child’s rheumatologist and ophthalmologist.

Recent evidence suggests that the risk of development of uveitis is age dependent in girls but not in boys, and that the interval from diagnosis of JIA to the development of uveitis is longer the younger the onset of JIA, especially in ANA positive patients. These findings may have implications for future recommendations regarding uveitis screening in JIA.¹²

Growth disturbance

Generalised growth failure in JIA is secondary to prolonged disease activity.¹³ This is most marked with systemic arthritis due to the highly inflammatory nature of this subtype and the frequent need for prolonged oral corticosteroid therapy. However, long term disease control is paramount in preventing growth restriction in all JIA subtypes. Growth hormone (GH) has been used in the treatment of short stature associated with JIA with some promising results,^{14,15} however this requires the involvement of a paediatric endocrinologist.

Bony overgrowth may result from prolonged inflammation, causing limb length discrepancy¹³ (*Figure 1*). The exception to this is the mandibular ramus, in which hypoplasia occurs due to

Table 3. Stratification of uveitis risk in JIA⁹

Factor	Low risk	High risk
Gender	Male	Female
Age of onset of JIA	>6 years	<6 years
Type of JIA	Systemic arthritis	Oligoarthritis
Duration of JIA	>4 years	<4 years
ANA	Negative	Positive
Rheumatoid factor	Present	Absent



the positioning of the growth plate of the mandibular condyle immediately below the articular cartilage.¹⁶

Treatment

The goals of JIA treatment are to prevent pain and joint damage and to maintain normal growth, joint function and muscle strength. The past 10–20 years have seen an expansion in therapeutic options for children with JIA thus improving outcomes significantly. Monitoring for drug toxicity is an important part of the long term management of patients with JIA.

It is beyond the scope of this article to discuss medical treatment in detail, but readers are referred to an excellent treatment algorithm for different JIA subtypes for more information.¹⁷

Common medications and patient monitoring

NSAIDs

The RACGP guidelines recommend commencement of nonsteroidal anti-inflammatory drugs (NSAIDs) as first line therapy for JIA, along with paracetamol, weak opioids (eg. codeine) and simple nonpharmacological interventions. Nonsteroidal anti-inflammatory

drug are generally well tolerated in children.¹⁸ The most common side effects are gastrointestinal symptoms such as nausea and appetite loss. Other side effects include behaviour disturbance, headache and pseudoporphyria rash, which is more common in fair skinned children¹⁹ (Figure 2). There is concern about the long term cardiovascular risk with NSAID use in adults,²⁰ however, there are no data available regarding this in children. Regular laboratory monitoring of JIA patients taking NSAIDs alone is probably unnecessary.²¹

Methotrexate and biologic agents

Methotrexate is also generally well tolerated in children. The most common side effects are gastrointestinal, with up to 12% experiencing nausea and abdominal discomfort.²² Elevation of liver enzymes more than twice the upper limit of normal occurs in approximately 3% of patients²³ and usually resolves with temporary cessation and/or a decrease in dose. Cytopenias caused by bone marrow depression are rarely severe in children. Regular testing of liver enzymes, FBC and renal function is recommended for all patients taking methotrexate every 1–3 months at routine rheumatology clinic visits, irrespective of dose or duration of treatment,¹⁷ although more recent evidence suggests that frequent laboratory monitoring may not be necessary, especially in children with JIA who are otherwise healthy.^{23,24}

Biologic agents, such as tumour necrosis factor alpha (TNF- α) antagonists, are well established in the treatment of JIA when first and second line therapies have failed to control the disease. Etanercept, a tumour necrosis factor antagonist, was approved for use in children with severe polyarticular disease in 2003 and abatacept, a selective T-cell activation inhibitor, has recently been approved by the Therapeutic Goods Administration for use in children also with polyarticular JIA.

Patients taking these medications require regular monitoring of FBC and liver function. Screening for latent mycobacterium tuberculosis infection with a Mantoux or Quantiferon Gold test and chest X-ray should be performed before starting anti-TNF- α therapy.

Methotrexate and TNF- α antagonists both have immunosuppressive effects and should be withheld during a febrile illness. Bacterial and viral illnesses can be more common in these patients and there should be a low threshold for initiating antibiotic therapy during a febrile illness. However, these medications can be recommenced at full dose once the fever subsides. Live attenuated viral vaccines (eg. measles/mumps/rubella, varicella) are contraindicated in patients taking methotrexate and/or TNF- α inhibitors because of the risk of severe disease, even from the attenuated viral strain.²⁵

Corticosteroids

The use of corticosteroids is generally reserved for systemic onset disease, but even in this subset of patients, steroid therapy already has a diminishing role due to the advances in the development of biologic therapies for JIA.

Table 4. American Academy of Paediatrics recommendations for uveitis screening⁴

Risk level	Definition	Screening frequency
High	Oligo or polyarticular onset <6 years at onset ANA positive	3–4 monthly
Medium	Oligo or polyarticular onset ≥6 years at onset ANA negative	6 monthly
Low	Systemic onset disease	12 monthly



Figure 1. Pseudoporphyria rash in a child taking NSAIDs



Figure 2. Bony overgrowth at the right knee in a child with JIA

Multidisciplinary care

The importance of multidisciplinary care to develop an individualised plan for affected children cannot be underestimated as it gives the best chance of meeting the child's medical, psychological and educational needs. Most paediatric tertiary referral centres in Australia have such teams available for JIA patients. In particular, physiotherapists and occupational therapists play a crucial role in JIA management by helping to maintain joint range of motion and function. This may be done by the development of a muscle strengthening and joint range of motion exercise program to be practised at home, use of splints or access to hydrotherapy. Occupational therapists can also assist in helping schools provide aids such as sloping desks and pen grips as well as facilitating access to computers for patients with significant hand or wrist involvement. Outcomes for children with JIA are improved if occupational therapists and physiotherapists have paediatric training and experience, so most referrals for these services are made within paediatric centres. Patients in more remote areas can benefit from Team Care Arrangements, particularly if there is liaison between the rheumatology team and local therapists.

In addition, support groups such as Arthritis Australia can play a useful role in supporting families with an affected child.

Long term outcomes

In general, outcomes for children with JIA have improved significantly in the past 10–20 years. In particular, mortality rates have declined.^{26,27} In a retrospective review over the previous 20

years, Thomas et al (2003)²⁶ reported a standardised mortality ratio for females of 5.1 and males of 3.4. In 2010, this is reported to have reduced to 0.57 (males and females combined).²⁷ However, up to half of young adults with JIA will have ongoing disease activity and up to one-third will have chronic disability.²⁸

In retrospective studies, a 10 year remission rate of 50% was seen in oligoarthritis compared with 40% for systemic arthritis and 15% for polyarthritis.^{13,29} The social impact of JIA is significant with higher unemployment in adults with JIA despite equivalent educational attainment.³⁰ Young adults with JIA are more likely to have body image issues and difficulty forming relationships. Disease related sexual dysfunction is common.³¹

However, many of the studies of prognosis are from retrospective cohorts from the 1980s. Since that time outcomes have improved significantly with the use of disease modifying antirheumatic drugs (DMARDs) and biologic therapies for children with JIA. Results from a recent inception cohort study demonstrated that at 6 months after enrolment, median values of active joint counts were highest in patients with RF positive and RF negative polyarthritis. Fifty percent or more of patients with oligoarthritis, systemic arthritis, enthesitis related arthritis, and undifferentiated arthritis had no active joints. However, low levels of disease activity persisted in many.³²

Conclusion

Juvenile idiopathic arthritis is the most common rheumatic disease in childhood. Approximately 50% of children will have active disease as adults. General practice plays an important role in the early detection, initial management and ongoing monitoring of children with JIA. Disease management using a multidisciplinary approach can prevent long term sequelae. The recently published RACGP guidelines provide practical support for GPs to ensure best practice and to help prevent lifelong disability in this group of patients.

Summary of important points

- Juvenile idiopathic arthritis occurs in approximately 1:500 Australian children.
- Early detection is critical to ensure prompt treatment and to prevent long term complications.
- Uveitis and growth disturbance are the most common extra-articular manifestations of JIA.
- Outcomes for JIA are improved with multidisciplinary team management.

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Conflict of interest: none declared.



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