



A Child with Musculoskeletal Pain - Is It Arthritis?



Dr. TL Lee

Dr. TL Lee MRCPCH, FHKAM (Paed)
Department of Paediatrics and Adolescent Medicine,
The University of Hong Kong,
Queen Mary Hospital

Prevalence Of Musculoskeletal Pain In Children And Adolescents

Musculoskeletal (MSK) pains in children are common, affecting 10%-20% of schoolchildren. MSK pain was responsible for 6.1% of the office visits of children between 3 and 14 years of age, and more than 10% of those are adolescents. Similar rates have been described by other series.^{1,2} In a telephone survey conducted by the Hong Kong Arthritis and Rheumatism Foundation in 2002, 52% of parents (total 520 families) said that their children have complaints of musculoskeletal pain in the past 6 months. Although most of these pains are not the result of a serious underlying disease, they could cause significant morbidity. Some children with musculoskeletal pains will have conditions that are either life-threatening or potentially crippling. We will discuss how to approach the problem and sort out the serious causes among them in the primary care setting. The diagnosis and recent advances of therapy of juvenile idiopathic arthritis will be updated.

Differential Diagnoses

The differential diagnoses of MSK pain in children are listed in **Table 1**. In trying to determine the diagnosis in a child with MSK pain, it is helpful to categorize the pain as localized or diffuse, and then to decide whether the child

is systemically unwell (febrile, anorexic, lethargic, and so on). If the pain is localized and the child is systemically well, most likely diagnoses are "growing pains", "mechanical" knee pains, strains and sprains, bone tumours, pauciarticular-onset juvenile idiopathic arthritis (JIA). For the definition of growing pains, there is no single, definitive test to diagnose. Hence it continues to be diagnosed more by exclusion than inclusion. The best definition was proposed by Peterson.^{3,4} The inclusion criteria for diagnosis of growing pains are intermittent (nonarticular) pains in both legs that generally occur late in the day or at night. The exclusions are the reverse of the inclusions with the addition of physical (swelling, redness, trauma, reduced joint range, limping) and objective signs. **Table 2** summarizes the distinguishing features of 'growing pains'. If the pain is localized but the child is systemically unwell, the most important causes to be ruled out are septic arthritis or osteomyelitis. If the pain is diffuse but the child is systemically well, the differential diagnoses are hypermobility syndrome or diffuse idiopathic pain syndrome (fibromyalgia). If the pain is diffuse and the child is unwell, important causes such as leukemia, neuroblastoma, systemic-onset JIA, polyarticular JIA and systemic lupus erythematosus (SLE) should be considered. However, although these groupings are helpful, there will be exceptions. It cannot be overemphasized that when approaching a child with musculoskeletal pain, it is

Categories	Infectious Diseases	Rheumatic Diseases	Childhood Malignancies	Miscellaneous orthopaedic conditions:	Noninflammatory Conditions of Bones and Joints	Genetic and congenital diseases	Others
Examples	Septic arthritis Osteomyelitis Lyme disease Viral-related arthritis "Reactive" arthritis	Juvenile idiopathic arthritis (JIA) Rheumatic fever Systemic lupus erythematosus Juvenile Dermatomyositis Scleroderma Vasculitis syndromes Overlap syndromes	Leukemia Neuroblastoma Others (e.g. bone tumours)	Legg-Calve-Perthe disease Slipped capital femoral epiphysis Osgood-Schlatter disease Patellofemoral syndrome Discitis Osteonecrosis / Avascular necrosis syndromes Musculoskeletal trauma	Idiopathic limb pains ("growing pains") Pain amplification syndromes (Fibromyalgia / Chronic fatigue syndrome) Reflex Sympathetic dystrophy (RSD) Hypermobility Syndrome	Congenital hip dysplasia Clubfoot	Haemarthrosis Pigmented Villonodular Synovitis

Table 1 Differential Diagnosis of Joint Pain





imperative to determine whether the problem could be caused by trauma, infection or a neoplastic condition before considering other possibilities, as a delay in diagnosing such conditions may have catastrophic consequences. After gathering a complete history and performing thorough physical examination, the physician can focus on limited differential diagnoses.

	Inclusions	Exclusions
Nature of pain	Intermittent; some pain-free days and nights	Persistent; increasing intensity
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee-in muscles	Joint pain
Onset of pain	Late afternoon or evening	Pain still present next morning
Physical examination	Normal	Swelling, erythema, tenderness; reduced joint range of motion; limping
Laboratory tests	Normal	Abnormal objective findings, eg, ESR, radiograph, bone scan

Table 2 Definition of "growing pains"

History and Physical Examination

To determine whether the child is likely to be suffering from arthritis, ask the following five questions:⁵ (i) Is the pain articular or nonarticular? To determine this, active and passive ranges of motion of the affected joints should be evaluated. A patient with a true joint problem will describe pain or restriction for all ranges of motion tested in the specific joint and will describe reaching the limit of joint motion as the most painful (often called stress pain). A patient with a nonarticular problem will describe pain or restriction for only some of the ranges of motion of that particular joint, and reaching the limit of the range may not necessarily be associated with the most pain. (ii) Is the problem inflammatory or non-inflammatory? This will form the basis of treatment. A patient with inflammatory articular problems will have a history of one or all of the following: joint swelling, warmth and limitation of joint motion. These signs are not associated with noninflammatory articular problems. An inflamed joint will be stiff in the morning for at least 30 minutes and after periods of rest during the day; non-inflammatory forms of arthritis such as osteoarthritis will not be associated with morning stiffness. (iii) Is the problem acute or chronic? (iv) What is the pattern of the joints involved (e.g. symmetry, small or large joints and number of joint involvement)? and (v) Are there any extra-articular features (e.g. dry eyes, dry mouth, digital ischaemic ulcers, rheumatoid nodules, alopecia, oral or nasal ulcerations, uveitis, malar erythema, photosensitivity, pleuritis, pericarditis, Raynaud's phenomenon, sclerodactyly, esophageal dysmotility.....) will help the physician to arrive at a specific rheumatologic diagnosis.

Laboratory and Imaging Investigations

Laboratory testing to provide supportive evidence of rheumatic diseases include urinalysis, complete blood

count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and selected biochemistries (e.g. muscle-related enzymes, anti-streptolysin O (ASO) titre or anti-DNAse B, Lyme serology and immunoglobulin levels.....). These tests are only an adjunct to signs and symptoms noted from the history and physical examination. These tests are rarely diagnostic of a specific disease; rather, they provide evidence of chronic disease, end organ dysfunction, or inflammation. As many as 5-9% of healthy children have a low-positive titre ANA and have no associated diseases. A negative ANA test does not exclude SLE or JIA, and a positive ANA test is not diagnostic or disease-specific. Thus, ANA and rheumatoid factor (RF) must be analyzed in the context of objective abnormalities and signs/symptoms of entire clinical condition.

Radiographs are often helpful and should always be ordered before arranging for bone scans, computerized tomography (CT) or magnetic resonance imaging (MRI) scans. Normal radiographic findings do not exclude the diagnosis of JIA or of osteomyelitis at an early stage, but radiographs are usually sensitive for bone tumours or fracture. CT scans is excellent at imaging bone detail such as osteoid osteoma and spondylolysis. Musculoskeletal ultrasound is helpful to detect joint effusion, tenosynovitis and bursitis. MRI is helpful in imaging soft-tissue injury and marrow infiltration. Bone scans are sometimes indicated when infection, tumour or ischemia are suspected whilst plain film are not revealing in the early disease stage.

With careful and systemic history enquiry, physical examination and relevant investigations, diagnoses could be arrived at in most cases. Most are benign conditions and could be treated in the primary care setting. But those children with inflammatory arthritis should be referred to tertiary centres for further evaluation as the management is multi-disciplinary and current use of disease modifying anti-rheumatic drugs (DMARDs) is complex and close monitoring by a specialist is warranted. The following section will discuss the definition, classification and current management of juvenile idiopathic arthritis (JIA).^{6,7}

Juvenile Idiopathic Arthritis - Diagnosis and Current Management

Definition and Classification

JIA is defined as presence of arthritis (swelling or effusion, or presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat) in one or more joints. The age at onset is less than 16 years old. The duration of arthritis lasts for 6 weeks or longer and other causes of arthritis (e.g. septic arthritis, malignancy) are excluded. Chronic arthritis in children represents a heterogeneous group of diseases with unknown aetiology. To classify these patients in more well-defined diagnostic categories, the International League Against Rheumatism (ILAR) classification is the definition used by most paediatric rheumatologist worldwide. The ILAR classification is shown in Table 3.



Disease(Onset type)	Disease (Course subtype)
Systemic arthritis	
Polyarthritis RF-	
Polyarthritis RF+	
Oligoarthritis	Persistent Oligoarthritis
	Extended Oligoarthritis
Enthesitis-related arthritis	
Psoriatic arthritis	
Others (unclassified)	

Table 3 ILAR classification criteria for Juvenile Idiopathic Arthritis

Current Management of JIA

Multi-disciplinary Approach

A coordinated multi-disciplinary team care consisting of paediatric rheumatologist, nurse specialist, social worker, physiotherapist, occupational therapist, orthopaedic surgeon, clinical psychologist and ophthalmologist is the key to success of management of JIA. The aims of treatment are to preserve cartilage, control pain and preserve range of motion, muscle strength, and function; to manage systemic complications; to facilitate normal nutrition, growth, and physical and psychological development.

Medical Therapy

1. Non-steroidal Anti-inflammatory Medications (NSAIDs)

Traditional NSAIDs such as naprosyn or ibuprofen still constitute the first line therapy for most children with JIA. The COX-2 inhibitors (rofecoxib and celecoxib) do not inhibit production of gastroprotective prostaglandins and gastrointestinal side effects are less. Since COX-2 inhibitors reduce prostacyclin synthesis without platelet activation, it is postulated that in susceptible patients with a pre-existing prothrombotic state the COX-2 inhibitors may predispose to thrombosis. In September 2004, one of the COX-2 inhibitors (rofecoxib [Vioxx]) has been withdrawn from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events and stroke, according to an alert from MedWatch, the U.S. Food and Drug Administration (FDA) safety information and adverse event reporting programme. Therefore, naprosyn or ibuprofen is the first choice in children until further long term safety data are available.

2. Disease Modifying Anti-Rheumatic Medications (DMARDs)

Methotrexate (MTX)

Methotrexate remains the remission-inducing agent of first choice for persistent and active arthritis. Most paediatric rheumatologists will initiate methotrexate therapy early in the disease course, sometimes within 8 to 12 weeks of initiation of NSAID therapy in order to preserve the cartilage if the patient fails to respond to NSAIDs. Daily folic acid supplementation may alleviate the side effects of nausea, vomiting, gastrointestinal upset and mucosal stomatitis without compromising the

therapeutic effect. If the response is inadequate, subcutaneous route is advised because of variation of bioavailability of oral MTX.⁸ Most studies have demonstrated no severe liver damage in children taking methotrexate for extended periods. Methotrexate is teratogenic and adolescent patients are advised about prevention of pregnancy and total abstinence from alcohol drinking. The patients should be informed of the nature, toxicities, precautions, expected duration of therapy and subcutaneous injection technique.

Corticosteroid

Intra-articular corticosteroid is safe and effective treatment in managing synovial inflammation in a child with monoarticular or oligoarticular arthritis. It is sometimes indicated in treatment of particular symptomatic joints in a child with polyarticular arthritis. It provides sustained anti-inflammatory effect on synovium lasting for 4- 6 months in most cases. It has been shown by magnetic resonance imaging studies that intra-articular steroid therapy resulted in significant suppression of inflammation and pannus formation while cartilage integrity is well preserved.

Moderate or high dose systemic corticosteroid therapy should be reserved for patients with systemic onset arthritis with severe systemic symptoms that cannot be controlled with NSAID, such as macrophage activation syndrome, symptomatic serositis and myocarditis. For all other subtypes of JIA, even low dose corticosteroid should be used selectively because the potential toxicity may outweigh any long-term benefits for articular disease.

Combination DMARDs Therapy

If conventional treatment with a single DMARD fails to adequately control clinical symptoms or to prevent disease progression, rheumatologists are increasingly prescribing combination DMARD therapy. Options include hydroxychloroquine, sulphasalazine or cyclosporine. Leflunomide has been shown in preliminary studies to be safe and more effective than placebo in children. Headache, diarrhoea, abdominal pain, elevated liver enzymes, reversible hair loss and skin rash are the reported side effects. Cyclophosphamide is not used commonly except in refractory severe JIA.

Biologic Agents

The tumour necrosis factor (TNF) inhibitors, etanercept (enbrel) and infliximab (remicade), have shown promising results in the treatment of refractory JIA. Etanercept has been shown to be effective in randomized double blinded controlled study in children with JIA⁹ and its long term safety (>2 years of continuous treatment) has also been demonstrated.¹⁰ However, children taking TNF inhibitors should be monitored closely for infections. Other potential useful new biologics include anti-IL-6 receptor antibody (MRA), Adalimumab (recombinant human IgG1 monoclonal antibody) and anakinra (interleukin-1 receptor [IL-1Ra]).





Autologous Haemopoietic Stem Cell Transplantation (AutoHSCT)

Despite the emergence of new therapeutic agents which appear to be more effective in treating JIA, there surely will still be some patients who remain resistant to medical therapies. AutoHSCT may be the final alternative therapy for this group of patients. Reports of good response of children with JIA to AutoHSCT have been published.^{11,12} We have also performed AutoHSCT for two patients with refractory JIA in 2001 and 2003. Complete remission for more than 3 years is achieved in one patient and the other one has arthritis flare-up 9 months after AutoHSCT but the disease was readily controlled with moderate dose MTX.

Conclusion

Musculoskeletal pains are common complaints among schoolchildren. Although most are not caused by a serious underlying disease, some may be life-threatening or potentially crippling. When attempting to reach a diagnosis, the physician should first exclude whether the symptoms might be due to trauma, infection or a tumour. Children with chronic arthritis have a high risk of continuing active arthritis over many years, often persist into adult life. There are many promising developments in the understanding and improved treatment options in JIA. In order to minimize permanent joint damage and prevent long term disability, earlier and more aggressive therapy is advised for those with persistent arthritis. A multidisciplinary team

approach is very important in management of JIA. It is hoped that with the availability of new treatment options and earlier and more aggressive treatment approach in JIA, the outcome of patients with JIA could be further improved.

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