Current Practice

Juvenile idiopathic arthritis: An overview

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Juvenile idiopathic arthritis (JIA) is defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown aetiology beginning before the sixteenth birthday and persisting for at least six weeks with other known conditions excluded[1]. JIA is one of the common chronic diseases of childhood with a prevalence of approximately 1 in 1000 in the West[2]. JIA often persists into adulthood and can result in significant long-term morbidity, including physical disability[3]. Recent major advances in treatment have greatly improved short and medium term outcome for children with JIA[4]. In this article I will discuss classification, clinical presentation, differential diagnosis and recommended treatment of JIA.

Classification of JIA

The widely accepted classification is that by ILAR[1]. This classification is important primarily for research but it is also used as a clinical tool. According to the ILAR classification there are seven groups of JIA. Depending on the number of joints involved within the first six months of presentation JIA is divided into oligoarthritis or polyarthritis[1]. In oligoarthritis there are four or less joints involved. When five or more joints are involved and the rheumatoid factor (RF) is positive, the entity is called RF positive-polyarthritis and when RF is negative, RF negative-polyarthritis[1]. Juvenile psoriatic arthritis is JIA in association with psoriasis[1]. Other types are systemic arthritis, enthesitis related JIA and undifferentiated arthritis[1]. There are inclusion and exclusion criteria for each type[1]. Undifferentiated arthritis is arthritis that does not fulfil inclusion criteria for any category[1].

Clinical presentation of JIA

Oligoarthritis

Typically, oligoarthritis is seen in children of three to four years of age[5]. It is commoner among females and usually involves large joints such as knees, ankles and elbows initially[5]. A limp which is seen in the morning due to involvement of a knee or knees is a common presentation[5]. Morning stiffness of half an hour or more is characteristic. On examination, joint effusion and limitation of the range of motion is present. There can be elevated inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or thrombocytosis but normal ESR, CRP or full blood counts (FBC) do not exclude arthritis. Oligoarthritis is called 'extended oligoarthritis' when more than 4 joints are involved after the first 6 months[1]. The main concern with oligoarthritis is association of asymptomatic uveitis which needs ophthalmology referral and follow-up.

Polyarthritis-RF positive

The age of onset is around 9-12 years and the female: male ratio is 6-12:1[6]. Typically there is a symmetrical polyarthritis of the small and large joints often affecting wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints[6]. Low-grade fever and other systemic features may be seen. Differential diagnosis includes systemic lupus erythematosus (SLE). Uveitis is uncommon. Prognosis and treatment are similar to adult rheumatoid arthritis[6].

Polyarthritis-RF negative

The mean age of onset is 6.5 years, with two peaks at toddler to pre-school and pre-adolescent[7]. Girls are more frequently affected than boys. Two distinct subsets are recognized[7]. The first resembles early onset oligoarthritis with more joints affected earlier. It is asymmetrical, the onset is less than 6 years, females are affected more than males, ANA is positive and there is a high risk of uveitis[8]. The second comprises symmetrical synovitis of large and small joints, the onset is 7-9 years and PIP joints are affected more than MCP joints. The outcome is variable. This type is known as "dry synovitis"[9]. There is negligible joint swelling, but stiffness, flexion contractures and normal or slightly raised ESR are found. It often responds poorly to treatment and can follow a destructive course[9].

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Systemic arthritis

Daily high spiking fevers is the most important criterion to diagnose systemic arthritis[10]. The typical quotidian pattern may only become obvious once treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is started. The characteristic rash is present in more than 90% of patients at the outset. The liver is mildly enlarged and 30% of children have mild splenomegaly. There is generalized lymphadenopathy in 50% with small freely mobile, painless nodes. Serositis, typically pericarditis with or without effusion is usually mild and asymptomatic[10]. Differential diagnosis includes infections, haematological malignancies, periodic fever syndromes and Kawasaki disease in young children. Investigations show leucocytosis with neutrophilia, thrombocytosis, anaemia with very high ESR and CRP and high serum ferritin[10]. Macrophage activation syndrome (MAS) is the dreaded complication of systemic onset JIA and early identification and institution of treatment is essential. There are no validated criteria to diagnose MAS[11].

Psoriatic arthritis

Psoriatic arthritis is arthritis and psoriasis or arthritis with two of the following viz. dactylitis, nail changes of psoriasis or psoriasis in a first degree relative[1]. In early onset psoriatic arthritis risk of asymptomatic uveitis is present[12].

Enthesitis related arthritis

This comprises arthritis and enthesitis, or arthritis or enthesitis with at least two of the following features viz. sacroiliac tenderness and/or inflammatory lumbar pain, HLA B27 positivity, onset of arthritis in a male over six years of age, acute symptomatic anterior uveitis and history of ankylosing spondylitis, enthesitis related arthritis, sacro-iliitis with inflammatory bowel disease, Reiter syndrome or acute anterior uveitis in a first degree relative[1]. Enthesitis is inflammation of the entheses, the sites where tendons or ligaments insert into the bone[13].

Differential diagnosis

When children present with fever and joint symptoms, the possibility of septic arthritis or osteomyelitis has to be considered in the differential diagnosis. Reactive arthritis following viral infections is usually short lived[14]. Rheumatic fever and post streptococcal reactive arthritis[15] are also seen among our children. Mechanical types of joint pains can be due to joint hypermobility[16]. When children present with limp, hip pain or referred pain in the knee, possibility of Perthes disease and in obese young boys, possibility of slipped upper femoral epiphysis has to be looked for. Back pain in children can be due to spondylosis or spondylolisthesis[17]. In systemic diseases like sickle cell disease, haemophilia and glycogen storage disorders, involvement of joints can occur. Whenever symptoms are atypical or associated with night pain in joints or when the child is systemically unwell, possibility of a malignancy has to be considered[18]. If blood counts are low, bone marrow biopsy is indicated to exclude haematological malignancies. SLE, dermatomyositis and vasculitis also can have joint symptoms.

Periodic fever syndromes that can present with joint symptoms and fever, include Chronic Infantile Neurological, Cutaneous and Articular (CINCA) syndrome[19] which closely resembles systemic onset JIA. Systemic onset JIA onset is after 6 months of age and in CINCA symptoms begin very early in life. Other periodic fever syndromes that can have joint symptoms are Hyper-immunoglobulinaemia D syndrome (HIDS)[20] and Tumour Necrosis Factor receptor associated periodic fever syndrome (TRAPS)[21].

Treatment recommendations in JIA

Guidelines and recommendations developed by the American College of Rheumatology (ACR) are intended to provide guidance of the particular pattern of practice and not to dictate care of a particular patient[22]. Each recommendation is characterized by the patient's clinical factors, treatment group, current medication, disease activity and features of poor prognosis[21]. There are 5 treatment groups according to 2011 ACR recommendations, and with updating in 2013, there are 6 groups[23].

1. *History of arthritis of 4 or fewer joints*
   This group includes patients with ILAR categories of persistent oligoarthritis, enthesitis-related arthritis and undifferentiated arthritis who have developed active arthritis in only 4 or fewer joints in total throughout the history of their disease course. Patients with systemic arthritis and active sacro-iliac arthritis are considered in separate treatment groups.
2. *History of arthritis in 5 or more joints*
   This group includes ILAR categories of extended oligoarthritis, RF positive polyarthritis or RF negative polyarthritis as well as enthesitis related arthritis and undifferentiated arthritis who have developed active arthritis in 5 or more joints in total throughout their disease.

3. *Active sacroiliac arthritis*
   This includes all patients with clinical and imaging evidence of active sacroiliac arthritis.
4. *Systemic arthritis with active systemic features and variable synovitis*
   Active systemic features are defined as presence of any combination of the following features: fever, evanescent rash, lymphadenopathy, hepatomegaly, splenomegaly or serositis.
5. *Systemic arthritis without significant active systemic features, with variable synovitis*.
6. *Systemic arthritis with features of Macrophage Activation Syndrome*.
   Features of MAS are defined as any combination of the following: persistent (rather than quotidian) fever, cytopenias or falling cell counts (particularly platelets), falling ESR, hypertriglyceridaemia, hypofibrinogenaemia, haemophagocytosis, transamnitis, coagulopathy, organomegaly, hyperferritinaemia or central nervous system dysfunction.

JIA disease activity
Active joints and active arthritis are defined as joints with swelling not due to deformity or joints with limitation of motion and with pain and tenderness. ACR recommendations are based on 3 disease activity levels: low, moderate and high.

Features of poor prognosis
The presence of one listed feature is sufficient to classify as having poor prognosis for the purpose of these recommendations.

Treatment options
These recommendations cover the use of NSAIDs, intra-articular glucocorticoid injections, non-biologic disease modifying anti-rheumatic drugs (DMARDS), biologic DMARDS and systemic glucocorticoids for the treatment of active systemic features and Macrophage Activation Syndrome. Indications for systemic glucocorticoids for the treatment of synovitis is not considered in ACR recommendations owing to lack of published evidence. DMARDS indicated in the treatment of JIA are methotrexate, sulfasalazine and leflunomide. Sulfasalazine is preferred to methotrexate in enthesitis related arthritis. Calcineurin inhibitor cyclosporine is recommended in treatment of systemic arthritis with features concerning for MAS. Biologic DMARDS are TNF alpha blockers, IL-1 inhibitors, IL-6 inhibitor- Tocilizumab and abatacept.

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