Juvenile Idiopathic Arthritis
Essential Elements of Care

MR Alam

Summary:

The chronic arthritides in childhood remain a poorly understood group of conditions. Their classification has been a source of much confusion over the years with differences in terminology used by different research groups. Childhood arthritis is an important cause of short term morbidity in children and can lead to long term joint destruction and disability. Proper diagnosis and early aggressive intervention can minimize both the short and long term morbidity of the disease, thereby improving outcome during childhood as well as in adulthood. The various sub-types of JIA with their clinical features, diagnosis and differential diagnosis have been described. An outline of current management strategies and outcome of treatment are given and potential future developments are highlighted.

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Introduction & Nomenclature:

Juvenile idiopathic arthritis (JlA) is a relatively rare disease affecting 1 in 1000 children in UK[1]. Important changes have occurred in the last decade regarding the course of juvenile idiopathic arthritis and resultant long-term disabilities. Published studies demonstrate that at least 50 percent of all children with JIA continue with active disease as they enter adulthood. Persistent synovitis leads to joint destruction in children much sooner than previously thought, often within 2 years of the onset of disease. The long-term impacts on the ability to function and the effects of chronic disability can be profound. Additionally, juvenile idiopathic arthritis can have detrimental effects on the physical and psychological growth of a child. There may be disruption of the family unit, divorce and other psychological stresses that affect all members of the family. The above considerations have prompted pediatric rheumatologists to treat children with juvenile idiopathic arthritis early and aggressively. The current treatment goal is resolution of disease with return to normal growth, development and activities[7]. In order to do this, patients must be accurately diagnosed as early as possible and then treated persistently until their disease resolves. It is widely thought that a comprehensive team approach is associated with a superior outcome. There has been too little awareness of the major role played by modem treatment regimen in JIA where methotrexate has transformed the outlook for most children with severe disease[4, 5].

Juvenile idiopathic arthritis is the umbrella term for a group of chronic childhood arthritis of unknown causes in children below sixteen years of age & persisting for at least six weeks[2, 19, 24]. The earliest formal description of this disease was given by Sir George Frederick Still in 1897. this work was done when he was a registrar at the hospital for sick children, Great Ormond Street, London. In this initial description of 19 patients, he identified three patterns of arthritis, one of which came to be known later as Still's Disease (now known as systemic onset JIA)[67, 68]. Subsequently different classifications were given by researchers.

According to American College Of Rheumatology it is called Juvenile rheumatoid arthritis (JRA) lasting at least six weeks with several subtypes e.g.

1. Puciarticular (1 to 4 joints involved)
2. Polyarticular (5 or more joints involved)
3. Systemic JRA
4. Spondyloarthropathies

According to European League against Rheumatic Association it is called JCA (juvenile chronic arthritis) lasting at least 3 months with following subtypes

- Puciarticutar (1 to 4 joints involved)
- Polyarticular (5 or more joints,RF negative)
- Systemic JCA
- Spondyloarthropathies

Finally the term JIA (Juvenile Idiopathic Arthritis) was first proposed in 1994 & later revised in 1997 by the International league against rheumatism as compromise for the American term JRA & the European term JCA[50,51,52]. Because the American & European classification of the disease were

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confusing, it was difficult to use the term interchangeably, in an effort to improve research and treatment, ILAR has given the name J1A.However regardless of the classification, children who develop symptoms that persist for at least six weeks before the age of sixteen years are considered to have Juvenile idiopathic arthritis. The term idiopalhic means unknown cause. This classification is gaining favour among researchers and health professionals but is not yet universally used.

JlA (Juvenile Idiopathic Arthritis) is an inflammatory disorder of connective tissue, characterized by joint swelling & pain or tenderness. It may also involve skin, heart, lungs, liver, spleen, eyes. Depending on the type the disease can occur as earty as six weeks of age, but rarely does so before the age of 6 months, peak onsets are usual between the age of one & three years and between eight & twelve years. Cause remaining unclear, but genetic factor, viral, bacterial infection, trauma and emotional stress are said to be responsible.

Difficulty arises in diagnosing cases in some of the subvarieties e.g. psoriatic arthritis, enthesitis related arthritis & systemic onset varieties.

Special problems in children:

It is important to realize that the symptoms of arthritis can vary greatly. Many children particularly young ones do not complain when they have pain in joints or may not admit it when asked. Clues that a child may be having joints problem include

- Reluctance to join in physical activities
- Unusual changes in mood
- Unwillingness to use one limb particularly
- Unusually bad behavior
- The morning journey is often difficult because of early morning stiffness
- He or she may be able to move less quickly than others between classes and sometimes teachers can play important role in recognition of the condition and improvement of quality of life

Presentation & Differential Diagnosis :

With the exception of systemic variety, children with chronic arthritis usually present with pain or swelling of joints. In determining symptoms it must be remembered that age of the child will affect how symptoms are expressed and age appropriate assessment – must be used.

Arthralgia clearly distinguishes from arthritis, where there is objective evidence of abnormality on examination of joints.

JIA is diagnosed by presence of chronic persistent arthritis of at least 6 weeks duration on children or adolescences – who are under the age of 16 years. The diagnosis of JIA also requires exclusion of other diseases, which may present in a similar manner. As JIA is an exclusionary diagnosis, it is important to be familiar with the alternative diagnosis. The required six-week duration of arthritis is an important 1st step in excluding common conditions such as viral arthritis, trauma, Henoch-Schonlion purpura and rheumatic fever.

Orthopedic conditions such as “Legg-Calve Perthes” disease must be excluded which may have similar presentations.

Septic arthritis needs to be considered when there is monoarticular arthritis accompanied by fever, severe pain and exquisite tenderness.

Perhaps one of the most concerning aspects of diagnosis of JIA is the recognition that some childhood malignancies such as leukemia and haematoblastoma may present with musculo-skeletal pain or arthritis. Elevated ‘lactate dehydrogenase’ is the only test that can differentiate malignancy from JIA.

Chronic childhood rheumatic diseases like Systemic Lupus Erythomatosus; Mixed Connective Tissue Diseases; Juvenile Dermatomyosities are important differential diagnoses.

Children with growing pains have nocturnal lower extremity pain that can be relieved by comfort such as massage.

The most common subtype of JIA is oligoarthritis (1-4 joints), which may lead to polyarticular variety in course of time. One of the recognized associations of JIA is chronic frequently asymptomatic iritis. Children with involvement of 5 or more joints in the 1st 6 months are classified as polyarticular type. Generally polyarticular type tends to be symmetrical.

Systemic variety is the least common subtype. This type of arthritis is considered while fever has been present for at least 2 weeks with rash. Serositis, anemia of chronic disease, lymphadenopathy, hepatosplenomegaly all may be seen. Leucocytosis and thrombocytosis are commonly seen.

A careful history should distinguish between mechanical, inflammatory and non-organic joint pain. Examination will confirm objective evidence of join inflammation. Once a diagnosis of arthritis has been reached, the length of history and the exclusion of other causes of arthritis (e.g. infection, connective tissue disorder) will lead to a diagnosis of JIA.

Radiological and laboratory investigations are not necessary in making a diagnosis of JIA. Investigation may be useful in ruling out other pathology, determining the disease subtype and assessing disease activity in some children.

Diagnosis:
Diagnosis of JIA remains a clinical one & essentially one of exclusions in addition to pattern recognition. There are no clinical, laboratory or radiologic tests that are pathognomonic for this disease.

Laboratory investigations –
ESR: May be normal in oligoarthritis and polyarticular arthritis, but is usually very high (>60 mm/hr) in systemic onset disease. If high in patients with oligoarthritis, consider infection, underlying spondyloarthropathy (e.g., IBD, Reiter's syndrome), or malignancy.

WBC: Should be normal in oligoarthritis and polyarticular juvenile arthritis. Elevated WBC with a left shift is sometimes seen in systemic onset juvenile arthritis, including leukemoid reaction (>30,000). Remember that a normal peripheral WBC and smear cannot exclude the diagnosis of leukemia.

Platelet Count: Usually normal, except in active systemic onset juvenile arthritis, where it may be elevated (>500,000). If platelet count is low, consider malignancy).

Other investigations should be done only to exclude other diagnosis.

Ensuring the correct diagnosis is essential for further management. The misdiagnosis of non-organic joint pain as arthritis will cause immense difficulties to the child and family and may be very difficult to undo. A delay in correctly diagnosing a child with JIA will lead to a delay in the child receiving appropriate therapy that may result in long-term sequele.

Management:
Management of JIA includes multidisciplinary approach like rheumatologist, physician, pediatrician, physical medicine specialists, teachers, social workers, psychologists etc. drug treatment includes NSAIDs, DMARD, steroid. The aim of modern treatment for JIA is rapid induction of disease control to prevent joint damage, to maximize joint function & to achieve a normal joint function for patients.

Methotrexate in JIA:
Weekly methotrexate is an established treatment in pediatric rheumatology & its efficacy shown by different randomized control trials[4, 5, 7, 33]. Among DMARDs, methotrexate has transformed the outlook for children with JIA. Most of the evidences from uncontrolled clinical trails suggested that methotrexate is an effective agent for treating active JIA. A more recent randomized controlled double blind crossover multi center study by woo, et. al looked at the effectiveness and safety of orally administered methotrexate in extended oligoarticular & systemic arthritis. This study used methotrexate at dose of 15 to 20 mg/m^2/week. A significant improvement occurred in three of five variables (ESR, physicians and patient's global assessment). (The study by Giannini et al forms the basis of current use of methotrexate in pediatric rheumatological practice). This was a six month randomized, double blind controlled multi center study of 127[43, 44. 45, 46] children with resistant JIA (Mean age 10.1 years, mean disease duration 0.5-1 years). 63% of the group treated with 10mg/m^2/week improved compared with 32% of those treated with 5 mg/m^2/week & 36% of placebo group.

Mechanisms of action of methotrexate:
Methotrexate is a folate analogue with an amino (NH_2) & methyl (CH_3) group. It binds dehydrofolate (DHFR) with high affinity and inhibits synthesis of thymidylate and purine, which are essential compound of DNA.

Although the primary mechanism of action of methotrexate in JIA or adult RA is not clearly known, recent reviews suggest that the anti-inflammatory effects of methotrexate seems to be related to the extra cellular adenosine release and its interaction with specific cell surface receptor[44].

Dose & route of administration:
In general, children with JIA, methotrexate therapy started at a dose of 10 to 15 mg/m^2/week or 0.3-0.6 mg/kg/week. However children seem to tolerate much higher dose than adult and some series describe using up to 20-25 mg/m^2/week in children with refractory cases, with relative safety in the short term. At doses more than 15 mg/m^2/week the parental route may be preferred.

A recent multinational, randomized controlled study by Pediatric Rheumatology International Trials Organization (PRINTO) compared 30mg/m^2/week in children with polyarticular JIA who failed to improve with 8-12.5 mg/m^2/week. Maximum response was found with 15 mg/m^2/week and there was no added benefit of the 30mg/m^2/week dose over 15mg/m^2/week[47].

Folic acid supplementation:
A recent multi center randomized double blinded placebo controlled trail showed that 2.5-5mg folic acid supplementation 2 days after methotrexate reduced the incidence of increased liver enzyme but had no effect on the incidence of other gastrointestinal and mucosal side effects[26].

Side effects:
Nausea is infrequent and can be lessened by use of antiemetics like Ondansetron, consideration needs to be given to be psychological support of children in methotrexate, in whom habitual nausea may sometimes occur[48, 49].

Sulphasalazine:
Three recent studies have confirmed earlier reports that Sulphasalazine is effective in oligoarticular & polyarticular varieties of JIA. Usual doses are 40-50 mg/kg of body wt/day (maximum 2gm/day). In a placebo controlled study 10 of 69 patients withdrew due to side effects, which were reversible[31, 32, 33].

Leflunomide:
Leflunomide, an orally administrated inhibitor of pyrimidine synthesis has been shown to be safe and effective long term therapy for adult with rheumatoid arthritis. In a pilot open-label study of children with polyarticular course JIA, 52% of those receiving leflunomide had a response even though all patients either had no response to or were intolerant to methotrexate. To confirm this a total 48 weeks randomized control multicentre (32 centres in 12 countries from march 2002-jan 2003) study was conducted to compare leflunomide with methotrexate in children (3-17 yrs), with active polyarticular JIA. Of 94 patients, randomized response rate was 89% and 68% in methotrexate and leflunomide respectively at 16 weeks and improvement was maintained at 48 weeks. Methotrexate was used in a dose of 0.5 mg/kg/week (25 mg/week) and leflunomide 10-20 mg/day according to body wt. following a bolus dose of 100 mg/day (for l-3 days according to body wt). Methotrexate & leflunomide both resulted in high rate of improvment in JIA patient (polyarticular type) but at doses used in that study methotrexate was more effective than leflunomide[62-66].

Monitoring Methotrexate and other DMRD therapy:
Before commencing DMARD therapy baseline information regarding CBC, Liver function, renal function should be obtained. Full blood count and liver and renal function monitoring is required fortnightly until a stable dose is achieved. Thereafter monthly monitoring for 6 months, increasing to 6 weekly is the usual practice[28-30].

TNF α blocker (Etanercept):

Tumor necrosis factor was identified in synovial fluid in 45% patient of JIA & found to play a proinflammatory role in pathogenesis.

In a randomize double blind multi-centre study, TNF α blocker was found safe, effective in children with poly articular JIA who did not tolerate or had an inadequate response to methotrexate. At the end of open study 74% of patient had a 30% improvement, 64% had a 50% improvement & 36% had a 70% improvement[43].

Refractory JIA:
Refractory juvenile idiopathic arthritis should be considered when the disease does not respond to

high dose of Methotrexate (1 mg/Kg/week, subcutaneously)[23, 56]. Combination of methotrexate with other DMRDS e.g. sulphasalazine, leflunomide are required in such cases and in some JIA subtypes such as ehthesitis related and systemic onset JIA[69-73]. Eternercept as monotherapy or in combination with methotrexate resulted in signifixcant improvement in sign and symptom of JIA. More aggressive therapies like IV methylprednisolone & cyclophosphamide can be considered in some cases of refractory JIA, since the biological agents is not possible for most patients[23, 37, 39, 42].

General aspects of management:

Nutrition:

All children with chronic rheumatic disease are susceptible to both growth retardation and malnutrition[7, 8]. Fatigue, non-specific abdominal pain, or worry about poor body image may all cause anorexia, limiting dietary intake. Ensuring an adequate protein, calorie and calcium intake is important but supplements including iron, folic acid, and vitamin D may also be indicated[58-60].

Physiotherapy and splints:

Physiotherapists ensure that both passive and active exercise schedules are implemented to maintain joint movement and improve muscle function.

Compliance:

Education of children with chronic disease and their parents about the need to take medication according to prescribed regimens is essential. Parents may be wary about giving children about the multiple medications, which are often necessary. In a useful review of factors affecting compliance it was noted that between 55-95% of medication (including self-administered or by parents for younger children) is taken correctly, but adhere with physiotherapy regimens is lower at 46-86%. Where there is suspected lack of compliance with oral therapy, perhaps with adverse social factors, in association with poor disease control, the administration of methotrexate sub-cutaneously by home care team may be useful.

Written information about arthritis, treatment and support groups should be offered to children, adolescents and parents.

Remission rate or when to discontinue the therapy:

The question of when, how and by what criteria, attempt should be made to withdraw methotrexate therapy in JIA is still more a clinical art than a science. “Remission” is a controversial concept in JIA. The criteria for “remission” or “relapse” have never been operationally defined and prospectively tested in JIA. In literature on JIA, the cited criteria for remission are often subjective and have not included long-term physical and functional outcomes.

However, methotrexate withdrawal may result in disease flare in more than 50% of patients as shown by Ravelli et al, a feature also noted by others[26]. The ease with which remission is achieved when methotrexate is re-established is still unclear. Reported rates of “remission” in JIA treated with methotrexate vary from 6.9% to 45%; the average duration of methotrexate treatment until “remission” is around one year at a weekly dose 10-15 mg/m^2.

The first phase of remission is the achievement of inactive disease which is defined as: no joints with active arthritis; no fever, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; and a physician’s global assessment of disease activity indicating no disease activity. Clinical remission on medication is defined as inactive disease on medication for a full six months, and clinical remission off medication is achieved when there is inactive disease off of medications for a full 12 months. Although many children can achieve clinical remission on medications, most will have a flare of their arthritis within three years of discontinuing medications.

Once there is complete remission, effective medications are continued for 6 to 12 months before tapering[45].

Complications of JIA:

Complication may be local or systemic, disease related or as a consequence of treatment.

Localized joint problems can be minimized by good, early control of inflammatory process. Children with inflamed joints will rapidly develop flexion deformities which may become fixed if inadequately managed. Drug treatment is combined with

physiotherapy and the judicious use of splinting to maintain correct joint position and function. Persistent inflammation in a joint may lead to bony overgrowth at that joint. This is seen particularly in children with oligoarthritis and involvement of one knee. If not controlled this may lead to overgrowth of that knee and a leg length discrepancy. Undergrowth of the mandible as a consequence of temporomandibular joint involvement may lead to significant functional and cosmetic problems.

Disturbance of overall growth is well recognized in children with JIA. Many children with JIA develop marked osteopenia. Poor diet, inactivity and steroids may contribute but other factors more directly related to disease process are clearly involved.

Anemia in severe JIA may be a significant problem and detract from the well being of child[60].

Oligoarticular arthritis is associated with chronic uveitis which is asymptomatic and may therefore go undetected for considerable time unless screened for.

Amyloidosis is well described in this condition and was previously reported to occur in around 10% of European cases[36].

Prognosis:

JIA is a chronic disease with perhaps 50% of patients will have active arthritis in adult years. JIA impacts the life style of not only the child but also the whole family. There is still very little published data to predict which patients will have a prolonged disease course & which medications are likely to be effective in which type of patients. In general those with involvement of few joints do better than those with systemic disease or RA factor positive JIA. Fifteen year follow up studies from USA & Italy of 227 patients from all subgroups of JIA show that frequently the long-term outcome is good, the worst prognostic factors were identified as the severe type of arthritis score at onset; early hand involvement & symmetrical arthritis with suggestion that ESR may have some predictive value related to quality of life[15, 16, 61].

Future developments in JIA

The aetiology of JIA remains elusive. It is hoped that an improved classification system will facilitate further research by identifying more homogeneous patient groups for study. As our understanding of these conditions improves, so the search for a 'cure' should prove more fruitful.

New developments in the field of antirheumatic therapy include biologic agents (such as anti-cytokine drugs) and new immunosuppressive agents with improved toxicity profiles. Stem cell transplantation is being increasingly used in the field of autoimmune disease and several children with severe JIA have been successfully transplanted.

Conclusion:

JIA is the most common group of rheumatic disease in childhood. Diagnosis is made on the basis of clinical criteria. The effective treatment needs multidisciplinary approach. Awareness amongst general pediatricians/ rheumatologist/ physicians, early recognition, prompt introduction of specific DMARD (e.g. methotrexate, Sulphasalazine) therapy either singly or as a combination at appropriate doses, in addition to other supportive therapies (NSAIDs, Intra articular Steroid etc.) are measures that will improve outcome and quality of life for these children. Nowadays, parents are more likely to request for newer therapies & adequate time is needed to address their concerns about the disease and the drugs.

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