Juvenile rheumatoid arthritis: A clinical approach and pharmacological management

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ABSTRACT

Juvenile Rheumatoid Arthritis is a chronic arthritis of unknown etiology. It remains a diagnosis of exclusion because no specific laboratory test or physical finding is diagnostic. There are 3 main subtypes: Pauciarticular, Polyarticular and Systemic in onset. The management of Juvenile Rheumatoid Arthritis requires the expertise of a multidisciplinary team, including Pediatrician, Pediatric Rheumatologist, Ophthalmologist, Orthopedic Surgeon and Rehabilitation personnel. This review will focus on the diagnostic approach and pharmacological management of Juvenile Rheumatoid Arthritis in. The aim of this review is to standardize the treatment of Juvenile Rheumatoid Arthritis in Saudi Arabia.

Keywords: Juvenile Rheumatoid Arthritis, Antinuclear antibodies, glucocorticoids, disease modifying anti-rheumatic drugs.


A comprehensive history and physical examination are essential in assessing a child with arthritis. It is appropriate to consider the following questions in addition to the basic evaluation of whether or not an arthritis is present: Is there evidence that the disease is limited to the joints or could this be an articular presentation of a systemic disorder? If symptoms are predominantly joint related a detailed history about the pain often points to its cause.

The following questions should be asked of every child suspecting to have Juvenile Rheumatoid Arthritis (JRA): How long has the pain been present? Is there evidence of morning stiffness? Is there history of joint swelling? Is there history of limitation in the range of motion? How many joints are involved? What is the distribution? Is there diurnal variation in the severity of the pain? Does the pain interfere with daily activities?

Investigations. There is no specific diagnostic test or combination of studies that can make the diagnosis, but several laboratory studies can be used to provide evidence of inflammation, to support the clinical diagnosis of JRA and to monitor disease activity and toxicity of therapy.1

To investigate a child with JRA, it is better to subdivide the investigations into: (a) Investigations that assess the inflammatory process and (b) Investigations that assess the affected joints.

Investigations that assess the inflammatory process. General blood tests: White blood cells. Usually children with JRA have normal to mild leukocytosis. However, marked leukocytosis (greater than 15,000 cells/mm³) with neutrophilia is typically seen in SO-JRA.3

Hemoglobin. Children with moderately extensive joint involvement usually develop normocytic hypochromic anemia (attributable to chronic disease). Although some patients of SO-JRA have iron deficiency anemia, bone marrow iron stores are normally suggesting defective marrow mobilization and red cell utilization of iron. The degree of anemia parallels the severity of the inflammatory process. Usually such patients show improvement in their anemia as disease activity is controlled.2

Platelets. Platelets serve as an acute phase reactant in SO-JRA. It is a useful crude test to monitor the disease activity. Again low platelets in a child with findings suggesting SO-JRA should raise the possibility of other diseases such as malignancy.
Tests to assess liver function and coagulation. Usually these tests are normal in children with JRA. However, coagulation abnormality, hypofibrinogenemia and elevated serum liver enzyme values, have been described as part of macrophage activation syndrome in SO-JRA. Bone Marrow Aspiration (BMA). If the patient has symptoms and signs suggestive of SO-JRA, but not classical, or the patient has suggestive clinical findings, but with leukopenia or thrombocytopenia, the recommendation is to do BMA before starting steroid therapy, since malignancy, particularly acute leukemia may present with similar findings like SO-JRA.

Acute phase reactants. These tests are not specific for JRA, however, they are useful to evaluate the inflammatory process and therapeutic efficacy. They include erythrocyte sedimentation rate (ESR), C-reactive protein, serum amyloid-A, complement components and others. It is important to notice that normal ESR results do occur in patients with some disease activity.

Autoantibodies. Antinuclear Antibodies (ANAs). The frequency of ANA positivity in JRA patients have been reported in widely varying percentages (4-88%). The highest frequency is in girls of younger age at onset of pauci-JRA subtype.

The presence of ANA helps to identify those with pauci-JRA who are at greatest risk for eye involvement. It is important to appreciate that titers of ANA are not consistently related to either arthritis or uveitis. ANAs should not be used as diagnostic tests, because it is associated with a number of infections, neoplastic disease, other rheumatic diseases and even healthy children.

Rheumatoid Factor (RF). IgM-RF is a serological hallmark of adult RA, but RF occurs much less frequently in children.

RF is found in a number of systemic diseases including infections and other rheumatic conditions, thus, RF is not helpful for diagnostic purposes except to evaluate and identify older girls with polyarthritis who are at high risk for symptoms and signs identical to those found in classic adult RA.

Investigations that assess the affected joints. Synovial fluid/membrane studies. Synovial fluid analysis is an infrequent investigation in children with JRA. It is not diagnostic of JRA, but it is vital in excluding septic arthritis in a child presenting with monoarthritis of unknown etiology.

Inflammatory synovial fluid in general contains increased numbers of WBC (200-100,000/cm³), with >50% PMN.

Usually bloody synovial fluid indicates trauma or hemophilia. A brownish coloration of old blood suggests a diagnosis of villonodular synovitis.

Synovial membrane biopsy. It is rarely carried out in children with JRA, because it is an invasive procedure and does not help in differentiating among subtypes of idiopathic chronic arthritis. However, it may help in chronic infections such as tuberculosis, and other causes of chronic arthritis such as sarcoidosis.

Imaging studies. Conventional radiography. Radiographic changes are variable depending on the stage of the disease. Such changes include: Early changes: joint effusion, soft tissue swelling, osteoporosis. Later changes: epiphysial overgrowth, joint space narrowing. Latest changes: bone erosions, destruction.

Early radiographic changes are not specific, but with disease progression, late typical changes develop.

The primary purpose of radiography in early disease is to exclude other conditions that might be associated with bony changes such as metaphyseal rarefaction in acute leukemia.

Bone scan. It is a sensitive, but not specific test. It is useful in confirming the presence of articular disease and its distribution. Bone scan is indicated to detect occult inflammatory process or bone infection or when neoplastic (benign or malignant) lesion is considered to be a possible cause for a child's musculoskeletal symptoms.

Management. Early diagnosis and treatment by an experienced team improves prognosis. Treatment includes education about the disease, physical therapy, medical therapy and occasionally surgical intervention.

Parents should understand the natural history of JRA and its manifestations and potential complications. Here we will focus on the pharmacological management of JRA, describing the current recommendations.

When planning therapy for JRA, the following should be the goals: Reduce inflammation, prevent deformities using the least toxic medications and maximize growth and development all by using the least toxic medications.

Currently available agents used to treat JRA. Nonsteroidal antiinflammatory drugs (NSAIDs), such as Naproxen and Indomethacin. Disease modifying antirheumatic drugs (DMARD), such as Hydroxychloroquine and Sulfasalazine. Glucocorticoids. Immunosuppressive drugs, such as Methotrexate, Azathioprine and Cyclosporine. Biologic response modifiers, such as Intravenous Immunoglobulin.

These agents provide symptomatic antiinflammatory relief, however, none is curative.

It is better to approach to the pharmacological treatment of children with JRA according to the subtype of JRA. (Figures 1, 2 and 3).

NSAIDs remain the mainstay of treatment for arthritis. Naproxen is a widely used NSAID in JRA patients. Naproxen provides symptomatic relief,
Figure 1 - How children with pauci-JRA can be treated.\textsuperscript{12,13}

Figure 2 - How children with polyarticular JRA can be approached.

*Should be seen by Pediatric Rheumatologist.*
while its role in asymptomatic joint swelling is the improvement in range of motion and joint swelling.

The most common side-effects of NSAIDs are abdominal pain and anorexia. Naproxen should be taken with food to minimize gastric irritation.\textsuperscript{12,14}

Carefully planned intra-articular steroid injection can be used in children with pauci-JRA unresponsive to NSAIDs or even as an alternative to NSAIDs. It is a safe and effective tool in pauci-JRA and it may have long lasting beneficial effects on the joint.\textsuperscript{12,15}

Second line agents (ie other than NSAIDs) and systemic steroids are not usually required in pauci-JRA patients, however, those who evolve into polyarticular subtype should be treated accordingly.

It is essential that all pauci-JRA patients should be followed regularly (every 3 months) by ophthalmologist regardless of the symptoms.

It is difficult to predict which patients will have more severe disease. However, children with RF positive polyarticular and those with a rapidly evolving conversion from pauci to poly subtype may have the poorest prognosis.\textsuperscript{11,14}

Because one third of children with JRA are adequately responsive to NSAIDs alone, earlier intervention with 2nd line agents (typically Methotrexate) might be the most efficacious approach.\textsuperscript{16} Methotrexate has become the most commonly used 2nd line agent in JRA at present,
common starting doses of Methotrexate in JRA and other chronic arthritis are in the range of 10 to 15mg/m²/wk. However, higher doses (25mg/m²/wk) have been used especially in the treatment of refractory cases.17,18

Steroids may be considered in pulses, orally or intra-articularly while awaiting the response of Methotrexate, which may take 6 to 8 weeks.12,14

It is recommended to maintain a therapeutic dose for at least one year after complete cessation of the disease activity, then reducing the dose by 2.5mg every 3 to 4 months.15,17

Before starting Methotrexate, the patient should have normal hepatic and renal functions, as well as normal hematologic status as baseline. During Methotrexate therapy, it is recommended to check hepatic function and complete blood count every 4 weeks.

**Systemic onset - JRA.** Systemic manifestations are an important component of the disease. However, the eventual outcome is more dependent on the number of joints involved.

**Follow up and assessment.** It is crucial that parents understand the nature of the disease, the aims of therapy and the importance of regular clinic visits. The following are some of the clinical and laboratory guidelines for monitoring the disease activity and the effects of medications.

At each visit, the physician must assess whether the disease is active or not. Symptoms of inflammation, prolonged morning stiffness indicate active disease.

Other clinical assessments of disease activity include fatigue, limitation in daily activities and systemic features in case of SO-JRA.

The physician must assess the side-effects of current medications.

The musculoskeletal examination may not adequately reflect the disease activity. Therefore, periodic laboratory measurements (e.g. CBC, ESR) should be performed.

Patients whose disease is inactive may be seen every 4 to 6 months, while newly diagnosed patients, patients with active disease should be seen more frequently (2-3 months).

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**References**