Suez Canal University Medical Journal Vol. 24 (2), 2021
Pages 93-103

Review Article

Juvenile Idiopathic Arthritis: An Overview for the Clinician

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Abstract

Juvenile idiopathic arthritis (JIA) is a diagnosis that applies to all forms of arthritis of unknown aetiology, they all have in common a chronic inflammatory process targeting the synovial membranes of the joints. The classification of JIA into categories that are homogeneous is essential to facilitate genetic and immunological studies and to improve the understanding of the pathologic processes underlying the disease. JIA has a substantial impact on the physical and psychological functions of the patients. Therefore, the goals of treatment are disease remission, pain relief, preservation of psychological and physical well-being, and prevention of long-term damage related to either the disease itself or its therapies. The optimal approach for the management of JIA patients is based on a multidisciplinary team. Although we still do not have drugs that are able to completely cure the disease, prognosis has significantly improved due to major progress in therapy. The introduction of biological drugs has dramatically improved the prognosis for children with JIA.

Keywords: JIA, Classification, Polyarticular, Oligoarticular, Biologics

Introduction

JIA is not a single disease however, it is a diverse group of diseases that encompasses all forms of arthritis of unknown aetiology occurring before the age of 16 years, persisting for longer than 6 weeks, and where other causes of arthritis have been excluded. Joint inflammation manifests with pain in the joints, effusion, decreased range of motion, or skin warmth over the joints[1]. The clinical skills needed for paediatric musculoskeletal examination require the proper knowledge of the development of the musculoskeletal system and the various ranges of normality and abnormality. An experienced paediatric rheumatology team provides the best care for JIA patients. Awareness and recognition of suspected JIA need to be raised among doctors in primary and secondary health care who are likely to deal with children for better referral to paediatric rheumatology services[2].

Epidemiology

JIA is the most common chronic rheumatic disease in children and adolescents. Studies on the incidence and prevalence of JIA

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yielded varying results. This may be due to the difference in the diagnostic criteria used, methodological issues, the sample size, genetic background, or potential environmental precipitating factors. There are few studies verifying JIA prevalence in populations other than those of European ancestry. JIA Prevalence has been reported as 0.07 to 4.01 per 1000 children and the annual incidence as 0.008 to 0.226 per 1000 children[3]. Although robust epidemiological studies are limited in Egypt, the few data we have pointed towards a similar range[4]. European descent seems to be an important predisposing factor for psoriatic JIA and oligoarticular JIA. Black and native North American patients were more predisposed to have rheumatoid factor (RF)-positive polyarthritis and less likely to have oligoarticular JIA[5].

Diagnosis and Classification

The diagnosis of JIA requires the persistence of arthritis of at least one joint in a child less than 16 years of age for more than 6 weeks for whom other causes of arthritis were excluded. The differential diagnosis for JIA is wide and should be considered in all children presenting with arthritis[1]. Several efforts have been made in the past to classify the heterogeneous group of arthritis gathered under the umbrella term of JIA and to find a consensus on a common nomenclature. Based on the predominant clinical and laboratory features presented during the first 6 months of disease, the International League Against Rheumatism (ILAR), defined the current classification of JIA categories [6]. The purpose of this classification is to generate homogeneous JIA categories. It divides JIA into 7 subtypes: systemic-onset JIA (sJIA), oligoarticular JIA, RF-positive polyarticular JIA, RF-negative polyarticular JIA, psoriatic JIA (PsJIA), enthesitis-related arthritis (ERA), and undifferentiated JIA. It has become evident that ILAR nomenclature has some limitations. From a practical point of view, the ILAR criteria are not easy to apply owing to their complicated network of inclusion and exclusion criteria [7]. Furthermore, emerging molecular data challenge the present ILAR subtypes. For example, it was assumed that childhood-onset arthritis is different from adult-onset arthritis; nevertheless, genetic studies have revealed more similarities than differences [8]. The legal distinction between childhood and adulthood is the age of 18 years which does not correspond to the cut- off age of diagnosis of JIA which is 16 years[9]. Positive anti- citrullinated protein antibodies (ACPAs) patients are not encompassed in the definition of RF- positive JIA patients. Patients with characteristics consistent with sJIA but lacking overt arthritis are excluded from this category[10]. In 2015, the Paediatric Rheumatology International Trials Organization (PRINTO) defined disease entities within childhood- onset arthritis (defined as onset less than 18 years) that have homogeneous clinical and laboratory features. They identified Four main categories, entitled systemic JIA, RF- positive JIA, early- onset antinuclear antibodies (ANA)- positive JIA, and enthesitis/ spondylitis related JIA. Although this categorization has not been formally validated yet, it is considered a first step toward defining JIA categories more accurately[9]. Recently, Nigrovic and his colleagues proposed a four-cluster model for arthritis in both adults and children. They combined genetic patterns with demographic and clinical data and divided inflammatory arthritis into 4 main categories irrespective of paediatric or adult-onset: seropositive, seronegative (early-onset JIA remains within the seronegative arthritis cluster), systemic, and spondylarthritis. This model allows each category to remain internally

heterogeneous and serves as a guide for research and concept generation rather than clinical practice[8].

Etiopathogenesis

JIA has a complex multifactorial origin in which genetic susceptibility combined with environmental triggers leads to uncontrolled innate and adaptive immune responses toward self-antigens, causing inflammation and disease. Infections, trauma, and stress are the most responsible environmental aetiological factors[1]. The importance of genetic factors has become evident by the observation of familial aggregation of JIA, with a sibling recurrence risk ranging from 15 to 30 which is similar to that of type 1 diabetes[11]. Susceptibility genes of JIA can be generally divided into HLA genes and non-HLA-related genes. HLA region explains only 8–13% of the total variation of JIA susceptibility. Non-HLA-related genes include cytokine and other immune genes. HLA alleles associations observed for oligoarthritis include HLA-A2, HLA-DRB1*11, and HLA-DRB1*08. As in adults with rheumatoid arthritis, RF-positive polyarthritis has been associated with HLA-DR4. About 76% of patients with ERA were HLA-B27 positive, compared with a population frequency of around 10%[12]. Improvements in the technology of genotyping have led to the shift towards genome-wide association (GWA) studies. Association with JIA at genome-wide significance was confirmed for three susceptibility genomic loci (human leukocyte antigen [HLA], protein tyrosine phosphatase, non-receptor type 22 [PTPN22], and PTPN2)[13]. A recent study used joint analysis considering all JIA subtypes identified five novel susceptibility loci bringing the total of genome-wide significant regions for JIA to 22 risk loci. Enrichment analysis identified EBF1 and RELA as crucial transcription factors contributing to the risk of the disease[14].

Juvenile Idiopathic Arthritis subtypes

Systemic JIA

Systemic arthritis (sJIA) is considered a unique category in JIA as it is characterized by the presence of prominent systemic features. The ILAR definition of sJIA requires the presence of arthritis in one or more joints with or preceded by a high spiking fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by one or more of the following: Evanescent (non-fixed) erythematous rash, Generalized lymph node enlargement, Hepatomegaly and/or splenomegaly, or Serositis[6]. The disease does not show a preferential age at onset and occurs as often in boys as in girls. It accounts only for 5-15% of children with JIA and is considered the equivalent of "adult-onset Still's disease" but, it carries the greatest mortality and morbidity of all JIA subtypes[15]. Laboratory findings in sJIA indicate systemic inflammation and include thrombocytosis, leucocytosis, anaemia, increased liver enzymes levels, and increased erythrocyte sedimentation rate (ESR), increased c-reactive protein (CRP), and increased serum ferritin level. ANA positivity occurs in only 5% to 10% of patients, and RF is rarely positive. The differential diagnosis of sJIA includes infection, inflammatory bowel disease, acute rheumatic fever, vasculitis, systemic lupus erythematosus, Leukaemia, and malignancy. Macrophage activation syndrome (MAS) is a life-threatening complication of sJIA characterized by activation of macrophages and T cells leading to a tremendous inflammatory response. MAS is characterized by sustained fever not the quotidian fever pattern of sJIA, anaemia, liver

function abnormalities, hepatosplenomegaly, rash, central nervous system dysfunction, and coagulopathy. laboratory features of MAS include decreased platelets, and white cell count, decreased ESR, increased ferritin level, hypofibrinogenemia, hypertriglyceridemia, and hemophagocytosis on bone marrow aspirate[16]. Treatment of MAS should be started immediately, which necessitates early diagnosis. Treatment includes pulse therapy with methylprednisolone, cyclosporine , and IL-1 inhibitors[17].

Oligoarticular JIA

According to ILAR classification, oligoarticular JIA is diagnosed if the child has 4 or fewer joints involved in the first 6 months of disease. This category is further divided into persistent and extended oligoarticular JIA based on the number of additional joints involved after the first 6 months[7]. It affects more than 50% of children with a peak of incidence between 1 year and 3 years of. It affects girls more than boys, the female to male ratio is 3-5:1. Children with persistent oligoarthritis often have a better prognosis and may enter remission, although they remain at high risk for flares of the disease[18]. Nearly 50% of patients with oligoarthritis progress to develop polyarthritis within 2 years of the disease onset. Involvement of joints of upper limbs and higher ESR at onset have been identified as predictors for progression to the extended type. The extended oligoarticular type has a more cautious prognosis as fewer children enter remission. Oligoarticular JIA is asymmetric arthritis mainly affecting the large joints, most commonly the ankles, knees, elbows, and wrists. The shoulders and hips are less commonly involved and usually, there is no involvement of the neck or spine. Oligoarthritis children usually have normal acute phase reactants and normal complete blood cell count (CBC). The RF is always negative.

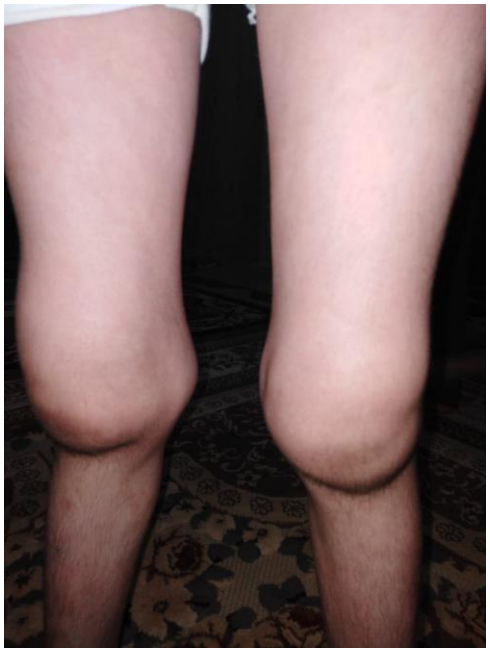

Figure1: Bilateral knees effusion in a child with oligoarticular JIA

Oligoarticular JIA patients have positive ANA in 30% to 65% of cases and it is associated with anterior uveitis in 15% to 30% of patients. Most children develop uveitis within 5 to 7 years after the onset of arthritis. Uveitis is usually asymptomatic which

mandates routine ophthalmology visits to prevent irreversible damage. high-risk patients should be checked routinely by a pediatric ophthalmologist every 3 months for 4 years [19]. Treatment typically starts with steroid eye drops to control inflammation of the eye. About half of the patients need methotrexate (MTX) and or biological drugs to control the disease. The biologics used in uveitis are the monoclonal tumor necrosis factor (TNF)-α inhibitors (adalimumab and infliximab)[19].

Polyarticular juvenile idiopathic arthritis

The ILAR defined Polyarticular JIA as having arthritis in 5 or more joints during the first 6 months. Based on the presence or absence of RF, polyarticular JIA is further subdivided into RF-positive and RF-negative polyarthritis. It accounts for about 20% to 40% of patients with JIA[6]. RF-positive polyarticular JIA is similar in features and prognosis to adult RA patients. It accounts for less than 5% of patients with JIA. It predominantly affects girls and usually starts in late childhood or adolescence. The usual presentation is that of progressive erosive symmetric arthritis, involving the small joints of the hands and feet and the wrists. The large joints, usually knees and ankles, can also be involved early but usually in association with small joint involvement. Systemic features such as constitutional upset and fever may be present at onset, and patients may have rheumatoid nodules. antibodies to cyclic citrullinated peptides can be found in this category. ANA may be positive, but it is not associated with an increased risk of developing chronic uveitis. Radiological changes tend to occur earlier than in the other JIA subtypes and are observed mainly in the hands and feet[20]. RF-negative polyarticular JIA is an entity consisting of three different phenotypes. The first disease subgroup is an oligoarticular JIA-like condition with the involvement of five or more joints in the first 6 months; the main features of the disease are female predominance, early disease onset, asymmetric arthritis, increased risk of uveitis, ANA positivity, and the association with HLA-DRB1*0801. The second phenotype simulates the RF-positive polyarticular JIA. It has a variable disease prognosis with symmetric involvement of both small and large joints, early disease onset, and negative ANA. The third subset is known as "dry synovitis" often follows a destructive course. It carries the worst prognosis and is poorly responsive to treatment with frequent disease sequelae[1].

Figure 2: Left wrist and hand swelling in a child with polyarticular JIA

Enthesitis Related Arthritis

The ILAR definition of enthesitis-related arthritis (ERA) includes arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, the presence of HLA-B27 antigen, the onset of arthritis in a male over 6 years of age, acute (symptomatic) anterior uveitis or, history of (enthesitis-related arthritis, ankylosing spondylitis, sacroiliitis with inflammatory bowel disease, acute anterior uveitis, or Reiter's syndrome) in a first-degree relative[6]. It affects boys more often than girls. Arthritis begins initially in the lower limbs. It is usually asymmetrical and oligoarticular but in 25% of patients, it may have a polyarticular onset. Hip involvement at disease onset is quite frequent (while it is exceptional in the other JIA categories). Arthritis is often accompanied by enthesitis (inflammation of the point where a tendon, ligament, or fascia inserts into the bone) which is the most characteristic feature of this JIA category. Symptoms of spinal arthritis and sacroiliitis are uncommon at presentation, it should be confirmed with MRI. Uveitis occurs in these patients, but it is symptomatic, presenting with red eyes, pain, and photophobia. Uveitis is usually unilateral, may be recurrent, and generally does not cause long-term damage. The course of the disease is usually variable and remission has been reported in about 44% of patients[21].

Psoriatic arthritis

The ILAR diagnostic criteria of juvenile psoriatic arthritis (PsA) require the presence of simultaneous arthritis and typical psoriatic rash or, if the rash is absent, the presence of arthritis and any two of the following: positive family history of psoriasis in a first-degree relative; dactylitis (swelling of one or more digits that extends beyond the joint margins); and pitting of the nails[6].

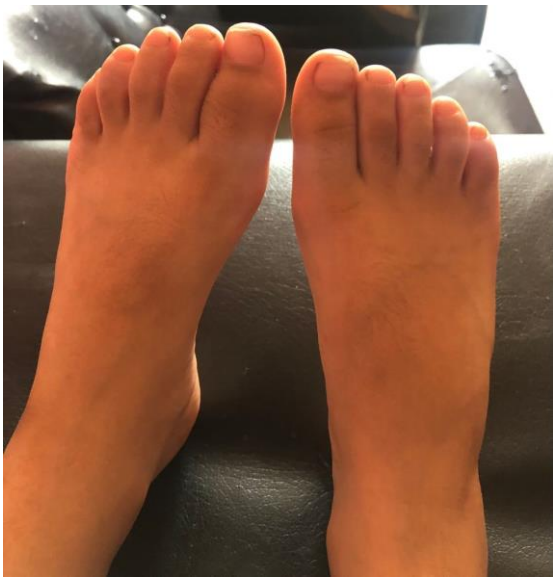

Figure 3: Dactylitis of the left first metatarsophalangeal joint in a child with psoriatic arthritis.

The diagnosis of juvenile psoriatic arthritis could be challenging as arthritis generally occurs a few years before the development of typical psoriatic rash. Arthritis varies from symmetrical small-joint arthritis to asymmetric large-joint arthritis in the lower limbs. Arthritis may progress to polyarthritis simulating seropositive RA.

Involvement of the distal interphalangeal joint typically indicates psoriatic arthritis. ANA can be found in low or moderate titres in some patients[22]. The long-term prognosis of PsA is variable, due to its heterogeneity and the paucity of available information. ANA positive patients need to be checked every three months with slit-lamp examination[22].

Undifferentiated arthritis

This category does not represent a separate subgroup, but it includes patients who do not fulfil inclusion criteria for any category or fulfil the criteria for more than one category. Undifferentiated arthritis includes about 10-15% of all JIA cases[6].

Measurement of Disease Activity

The regular assessment of disease activity in JIA patients is crucial to monitor the course of the disease and assess the efficacy of treatment. The Juvenile Disease Activity Score (JADAS) is an imperative tool for the assessment of changes in disease activity. It is composed of the following four measures: physician's global assessment of disease activity, measured on a 0-10 visual analogue scale (VAS) where 0 means no activity and 10 means maximum activity; parent global assessment of well-being, measured on a 0-10 VAS where 0 means very well and 10 means very poor; ESR, normalized to a 0 to 10 scale; and the number of joints with active disease[23]. Depending on the count of incorporated joints, three versions of the JADAS were developed: JADAS-10, JADAS-27, and JADAS-71. The total score of JADAS is calculated by simply summing the scores of its four components. Values for remission, minimal disease activity, and acceptable symptoms have been defined for each JADAS version[24]. JADAS has some limitations, uveitis has not been evaluated, and the systemic features for sJIA are not fully addressed in the score. Therefore, the systemic Juvenile Arthritis Disease Activity Score (sJADAS) was developed. It was constructed by adding a fifth new item that quantifies the activity of systemic features to the four items of the original JADAS[25].

Treatment

Treatment should be started as soon as a diagnosis of JIA has been made as irreversible damage to the joints and surrounding tissue is known to occur very early in the course of the disease and occurs in about 60% of Polyarticular JIA patients. Early intensive therapy in JIA during the window of opportunity where the disease is most responsive to treatment can alter the course of the disease and improve long-term disease outcomes, including prevention of cumulative joint damage[26]. Several sets of treatment recommendations have been developed for patients with JIA that can help physicians to choose the appropriate management plan[27]. Recent advances in the management of JIA have made remission an achievable goal for most children. Therefore, the incorporation of a treat-to-target approach in the management of JIA patients aiming for remission will improve the outcomes of the disease. Treating JIA requires a team approach with the involvement of the family as well as of other specialists[28].

Non- pharmacologic treatment

Non- pharmacologic approaches should be personalized and used as indicated by individual needs, previously proven benefits, and expert opinion. Physiotherapy and occupational therapy are integral parts of the therapeutic approaches in JIA patients. Consequently, treatment by properly trained therapists together with instructions for self-sufficient disease-adopted daily exercise sessions are recommended to improve joint mobility. The custom-

made orthosis is recommended for prevention or correction of deformities, stabilization of joints, prevention of false weight-bearing. The use of orthosis should follow individual physician-directed advice[29].

Pharmacologic treatment

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are considered the first line drugs for controlling inflammation, pain, and fever. They should be offered to patients with all JIA categories. Combination between different NSAIDs at the same time is not indicated. NSAIDs should be given with meals to reduce gastric complaints. Prophylaxis of NSAID-induced gastric complications in JIA patients should be considered in patients receiving long-term NSAIDs treatment[30].

Intra-articular corticosteroids

Intra-articular corticosteroids are used as first-line therapy for oligoarticular JIA and as an adjuvant therapy to control local inflammation in all JIA categories. Triamcinolone hexacetonide is the drug of choice especially in large joints because of its longer effect. More soluble forms, such as methylprednisolone acetate are preferable for smaller or difficult to access joints to avoid local side effects due to extravasation of triamcinolone hexacetonide from joint spaces[31].

Systemic corticosteroids

Systemic corticosteroids are mainly indicated for the management of the extra-articular manifestations of sJIA. High-dose 'pulse' intravenous methylprednisolone (10–30 mg/kg/day to a maximum of 1 g/day on 1–3 consecutive days) can be used effectively to control these systemic features. In other JIA subtypes, corticosteroids should be used selectively to alleviate pain and stiffness in patients with severe active polyarthritis not responsive to other therapies or as a bridging therapy until the full therapeutic effect of a recently initiated DMARDs or biologic agent is attained. They are also used in the management of uveitis. The lowest possible dose of steroids should be used and for the shortest possible period to avoid adverse events particularly arrest of growth and osteoporosis[30].

Conventional disease-modifying anti-rheumatic drugs (DMARDs)

Methotrexate

Methotrexate (MTX) is an antimetabolite with immunosuppressant properties that has a disease-modifying effect. methotrexate is the first drug choice of DMARDs used in the treatment of all JIA categories. The usual dose of MTX is 10-15 mg/m2/week (max 20 mg/week) orally or parenterally. Using the subcutaneous route is recommended over the oral route. To prevent adverse events, folic or folinic acid is administered 24 hours after MTX administration at a dose in mg that is half of MTX dose[32].

Leflunomide

Leflunomide (LEF) is considered as another second-line DMARD that can be used in polyarticular JIA patients. It could be an alternative option for Polyarticular JIA patients unresponsive or intolerant to MTX. The usual dose in children < 40 kg is 10 mg/day and in those > 40 kg the dose is 20 mg/day[33].

Sulfasalazine

Current treatment guidelines support the use of sulfasalazine (SZS) in enthesitis-related arthritis but not in other JIA categories. Although some studies showed beneficial effects of sulfasalazine in Polyarticular JIA, side effects were frequently reported, particularly gastrointestinal symptoms, skin rashes, and leukopenia[27].

Biologic agents

TNFα-inhibitors

Biologic agents that target various pathogenic pathways are now available. TNFα-inhibitors (Etanercept and Adalimumab) are very effective in polyarticular JIA patients. Recently in 2020, the FDA approved another TNFα-inhibitor; Golimumab for use in polyarticular JIA patients older than 2 years of age. Initiation of treatment with TNFα-inhibitors is indicated in polyarticular JIA patients who failed NSAIDs, local GC, and Conventional synthetic DMARDs, one of which must be MTX in recommended doses for a minimum of 3 months, unless contraindicated, or toxicity/intolerance occurs. Combination therapy of biologics with methotrexate is recommended over biologic monotherapy. Adalimumab is approved in patients with anterior uveitis. Etanercept is approved in patients with ERA and psoriatic arthritis. Infliximab is not approved in JIA patients[34].

interleukin 6 inhibitors

interleukin 6 (IL-6) is a pro-inflammatory cytokine that stimulates the production of other pro-inflammatory cytokines, such as TNF and IL-1. Tocilizumab is an interleukin 6 blocker. It is proved to be effective, safe, and useful in both systemic JIA and polyarticular JIA[27].

Interleukin 1 inhibitors

Anakinra and canakinumab are interleukin-1(IL-1) inhibitors that blocks the activity of interleukin-1. They are indicated in systemic JIA and macrophage activation syndrome. They are administered subcutaneously and are rapidly effective for the systemic features[34].

T-cell co-stimulatory blockade

Abatacept is a selective T-cell co-stimulation modulator that proved to be very effective in polyarticular JIA patients. It is administered intravenously in polyarticular JIA children refractory to anti-TNF agents[35].

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