Chapter

Juvenile Idiopathic Arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common form of chronic synovial joint inflammation in children. It potentially leads to disability and psychosocial outcomes for children and their families. In the absence of appropriate treatment, this can lead to joint destruction and disability. Thus, early diagnosis and aggressive treatment are essential. With the presentation of new biologic DMARDs, based on understanding the disease pathophysiology and molecular pathogenesis, the course of the disease and its outcome have been changed profoundly. In this chapter, the early diagnosis, appropriate treatment, and outcomes approaches are described. These include the latest diagnosis and management options.

Keywords: juvenile idiopathic arthritis, children, chronic arthritis, oligoarthritis, polyarthritis, spondyloarthritis, psoriatic arthritis

1. Introduction

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic childhood disease and one of childhood's most common chronic diseases with unknown etiology and complex genetics. The new nomenclature applies the term juvenile idiopathic arthritis (JIA) [1].

Arthritis means intra-articular swelling or the presence of two signs or symptoms: limited range of motion, pain on motion, warmth, and redness. Intra-articular swelling may be due to intra-articular effusion or an increase in synovial thickness. In terms of the duration of arthritis, it can be divided into two categories: 1. Acute: for less than six weeks, 2. Chronic: more than six weeks [2]. In terms of the location of joint involvement, it can be divided into three categories: 1. Peripheral arthritis: means joints involvement of upper and lower limbs, 2. Axial: includes spinal joints involvement, and 3. Referral: includes the involvement of the hip joint [3]. In terms of the number of joints involved in a disease, arthritis can be divided into three categories: 1. Monoarthritis: means single joint involvement, 2. Oligoarthritis: means simultaneous involvement of four joints or less, and 3. Polyarthritis: it means the simultaneous involvement of more than four joints. In terms of the pattern and timing of arthritis spread, it can be divided into three categories: 1. Migratory: it means the rotation of the involved joints in a short period of several hours to a few days, which means that the affected joint improves and the other joint becomes involved. 2. Additive: this means that another joint or joints are added to the joint involved. 3. Intermittent: involvement occurs occasionally, and at intervals, the patient has no joint symptoms (such as Lyme disease or FMF [4]. In terms of the distribution of involved joints, arthritis can be symmetric or asymmetric. Symmetric arthritis refers to the involvement of the same joint on the opposite side, such as Rheumatoid arthritis, Systemic lupus erythematosus, and RF

positive polyarticular JIA. Asymmetric arthritis is characterized by the involvement of different joints in two sides of the body. This occurs in many childhood arthritis cases such as reactive arthritis, psoriatic arthritis, and Lyme disease. Arthritis can be inflammatory or non-inflammatory. In the case of inflammatory, inflammation of articular structures such as synovium, synovial cavity, and entheses occur. Non-inflammatory arthritis is an articular disease caused by mechanical or structural changes in the joint. These joint diseases can be due to cartilage or meniscus injuries with or without accompanying changes in the subchondral bone or maybe changing in joint anatomy due to congenital, developmental, metabolic, or previous inflammatory diseases [3, 4].

Regarding juvenile idiopathic arthritis, according to the previous definitions, we are faced with chronic arthritis with a period of at least six weeks in the age group under 16 years without an unknown etiology.

2. Epidemiology and immunopathogenesis

Since different criteria and classifications (including previous definitions of JRA, JCA, and JIA) have been presented for this disease over the decades, conducting various epidemiological studies to determine the exact incidence and prevalence of the disease has faced severe challenges. The disease appears to be less common in African-American and Asian populations in the United States [5]. The disease has an average prevalence of about one per thousand children under the age of 16, similar to acute lymphoblastic leukemia and type 1 diabetes in children [6]. In most countries, the ratio of females to males is about two to one or three to one. However, these ratios vary depending on the age of onset and the type of disease. The peak of the disease is between two and four years old, although it varies depending on the sex and type of disease [7].

The pathogenesis and etiology of the disease are unknown. Like many autoimmune diseases, interactions between genetic factors, immune mechanisms, and environmental factors are involved in developing the disease. Patterns consistent with Mendelian or Monogenic inheritance have not been observed in this disease. In many cases, the level of risk to other family members has only slightly increased. HLA types are probably associated with the disease and its subtypes. Patients with early-onset oligoarticular JIA who have a relatively high concordance among siblings are most likely to have isolated associations with these subgroups. Some genes involved in JIA may be a risk factor for the disease but are sometimes neutral or even protective [8].

The primary clinical manifestation of JIA is chronic joint swelling that may lead to deformity of the affected joints due to stretching of the tendons and ligaments around the joint. Enzymes released from inflammatory cells inside the synovium or joint fluid may damage the collagen and proteoglycan matrix in the joint. Osteoclasts activation results from cytokine production by cells in inflammatory tissue, and the final pathway is probably bone demineralization and bone destruction [9].

One of the pathological hallmarks of JIA is a tumor-like spread of inflamed synovial tissue, which is called pannus, leading to further joint destruction. Pannus consists of the synoviocyte proliferation and the invasion of synovial tissue by inflammatory cells (including lymphocytes, macrophages, and dendritic cells). The infiltration of these cells into the synovium is due to vascular factors, cytokines, adhesive molecules, and chemokines. Various inflammatory cells have been found in synovial fluid. As the disease progresses, the pannus expands into the synovial space and attaches to the intra-articular cartilage, where joint destruction eventually occurs [9].

3. Classification

Due to the heterogeneity of JIA disease, its classification remains a challenge. Classification criteria have been developed for research purposes and should not be used as diagnostic criteria at a patient's bedside. However, treatment and prognosis options may still help establish a common language and understanding of disease forms. International League of Associations of Rheumatology (ILAR) recognizes that this disease is an exclusive diagnosis. The characteristics of the disease and its etiology are the uncertainty of the disease onset before the age of 16 and its duration for at least six weeks.

According to ILAR classification, JIA is divided into seven subgroups (**Table 1**).

ILAR criteria are considered as standard, and still, the proposed new systems need further approval. With a greater understanding of the genetics and pathobiology of arthritis, it is hoped that future classifications will suggest more homogeneous JIA groups with biologically distinct diseases [2].

3.1 Systemic JIA

Systemic arthritis is considered a young adult still's disease. Arthritis is present in one or more joints with fever for at least two weeks. The disease most commonly presents with daily fevers, at least three days (quotidian spiking fevers). In addition, the child should have at least one of the following symptoms: evanescent erythematous rash, hepatomegaly or splenomegaly, generalized lymphadenopathy, or serositis.

Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease different from other forms of childhood arthritis and requires different treatments. In this disease, the child has symptoms of systemic involvement, which is less common in other forms of JIA. No autoantibodies are found in the serum of patients, and the primary disorder is in the inherited immune deficiencies system [2].

3.2 Polyarthritis: rheumatoid factor (RF) positive or negative

In addition to the involvement of at least five joints, patients with positive rheumatoid factor (RF) type should have at least two RF-IgM-positive results at least

Systemic arthritis
Polyarthritis: rheumatoid factor negative
Polyarthritis: rheumatoid factor positive
Oligoarthritis: a. Persistent b. extended
Enthesitis-related arthritis (ERA)
Psoriatic arthritis
Undifferentiated arthritis a. Fits no other category b. Fits more than one category

Table 1.
Classification criteria for juvenile idiopathic arthritis: 2001.

three months apart, although this test is often performed only once at the beginning of the diagnosis. Children with first-degree relatives with psoriasis, systemic arthritis, or manifestations of enthesitis-related arthritis are excluded from this category [10].

3.3 Oligoarthritis, persistent or extended

The disease involves a subset of patients previously classified as pauciarticular JRA. The disease is divided into two subgroups:

Persistent arthritis - refers to cases in which a child has one to four joints involved during the first six months of illness, but the number of joints involved never reaches five or more during the disease.

Extended arthritis- refers to children whose number of affected joints extends to five or more after the first six months of disease.

RF positive, first-degree relatives with psoriasis and concomitant or systemic manifestations are excluded from this classification [10].

3.4 Enthesitis-related arthritis (ERA)

This group of diseases refers to cases where enthesitis-related arthritis co-exist or enthesitis alone accompanies two or more of the following:

- Sacroiliac joint tenderness, or inflammatory lumbosacral pain
- Human Leukocyte Antigen B27 (HLA-B27) positive
- First-degree relatives with acute anterior uveitis, ankylosing spondylitis, inflammatory bowel disease, or reactive arthritis
- Acute anterior uveitis
- Arthritis onset in a boy over six years old

Children with first-degree relatives with psoriasis, RF positive, or systemic arthritis are excluded from this group.

This group includes some children formerly known as spondyloarthropathies. Also, some children may develop psoriatic arthritis in the future but do not currently fulfill its diagnostic criteria [10].

3.5 Psoriatic arthritis

Psoriatic arthritis is defined as children who have psoriasis and arthritis together or children with arthritis who have two of the following three:

1. Psoriasis in first-degree relatives
2. Dactylitis
3. Nail disorders, including pitting or onycholysis

Children with manifestations of arthritis associated with enthesitis or systemic, or RF+ are excluded from this group.

3.6 Undifferentiated arthritis

If patients do not meet the criteria mentioned in one of the above subgroups or have rejection manifestations, they fall into this subgroup. Also, if children meet the criteria of more than one group, they will be included in this group [10].

4. Diagnosis

The diagnosis of JIA is based on the history and findings of the physical examination and the exclusion of all other possible causes. Further evaluation, such as plain x-ray, ultrasound, nuclear bone scan, or MRI, is recommended when a physical examination does not prove definite arthritis.

5. Laboratory examination

Laboratory tests that may be performed to rule out other causes of arthritis or to determine the type or activity of the disease include the following [11]:

- Inflammatory markers: level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level
- Complete blood cell count (CBC) and metabolic panel, including serum uric acid and serum lactate dehydrogenase (LDH)
- Liver function tests and evaluation of renal function with serum creatinine levels
- Anti-nuclear antibody test (ANA)
- Rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (Anti-CCP)
- Additional tests: Serum total protein, Serum albumin, Fibrinogen, Ferritin, D-dimer, Angiotensin-converting enzyme (ACE), Anti-streptolysin O (ASO), Anti-DNase B, and urinalysis
- Tests to check for infectious causes, as the case may be.

6. Imaging studies

Radiographic changes in JIA include [11]:

- Swelling of soft tissue
- Osteopenia or Osteoporosis
- Narrowing of joint space
- Bony erosion
- Intra-articular ankylosis

- Periostitis
- Growth disorders
- Epiphyseal compression fracture
- Joint subluxation
- Synovial cysts

These changes are usually seen in children about one to two years after the onset of the disease and if not treated properly.

7. General principles of treatment

The medical treatment includes pharmacological and non-pharmacological treatments performed by a multi-group team. The following are considered in the group of non-drug therapies [11];

- Psychosocial interventions
- Programs to improve school performance (such as academic counseling)
- Nutrition improvement
- Physical therapy
- Occupational therapy

8. Disease course, outcome, and prognosis

JIA is a nomenclature that includes different diseases with different pathophysiology, manifestations, course, and outcome. With early diagnosis and aggressive appropriate step-wise treatment, the long-term outcome of JIA has improved in the last forth decades. There are different criteria for determining disease outcomes. Wallace et al. defined a set of criteria for the evaluation of clinical outcomes in JIA. Inactive disease (according to Wallace) criteria was defined as a state of no active joints, no systemic symptoms, no uveitis, normal erythrocyte sedimentation rate (ESR), and/or C-reactive protein (CRP), and a physician's global assessment of disease activity indicating no disease activity. Furthermore, there are some different definitions for disease remission. The American College of Rheumatology criteria for complete remission of the disease are as follows [12]:

- Lack of inflammatory joint pain
- Lack of morning stiffness
- Lack of fatigue
- Lack of synovitis

- Lack of damage progression, which is determined by consecutive radiographic examinations

- Lack of high ESR and CRP levels

Also, different risk factors and prognostic factors exist for each of the subtypes. It potentially can cause serious complications, such as musculoskeletal deformities (including joint deformity and contracture), short stature, leg-length discrepancy, osteopenia and osteoporosis, increased risk of infections, cataract, decreased visual acuity, synechia, blindness, and macrophage activation syndrome. Each subtype's expected course, poor prognostic factors, and outcomes will be discussed later in detail.

9. Systemic-onset JIA

9.1 Clinical manifestations and diagnosis

Systemic JIA was formerly known as pediatric still's disease, systemic JRA, or systemic-onset juvenile idiopathic arthritis. This type of JIA is characterized by intermittent spiky fevers, evanescent erythematous rash, and arthritis. This disease is more similar to autoinflammatory diseases and may be different from other types of JIA. Diagnosis can be challenging because there are no specific diagnostic tests, and arthritis, which is essential for a definitive diagnosis, is often absent early in the disease. In addition, infections, malignancies, and other diagnoses should be ruled out before being labeled as these diseases can similarly cause fever, skin rashes, and joint pain. The diagnosis is clinical and is based on quotidian pattern (daily fevers spikes), typical evanescent erythematous rashes, and arthritis is characterized by typical laboratory findings, including leukocytosis with neutrophil predominance, elevated acute phase reactants including thrombocytosis, and high ferritin. In general, unfortunately, the disease does not have a specific diagnostic test. Differential diagnoses include infectious arthritis, other autoimmune and inflammatory disorders, malignancy, and malaria [13].

9.2 Treatment

In children with mild to moderate symptoms and without debilitating symptoms, a non-steroidal anti-inflammatory drug other than aspirin is recommended as initial treatment. In general, a drug test with non-steroidal anti-inflammatory drugs (NSAIDs) alone should not take more than a few weeks. The addition of adjuvant medication is common in children who find or continue to have significant symptoms despite treatment.

Traditionally, many pediatric rheumatologists add a glucocorticoid to the patient who has not responded to initial NSAIDs treatment or who has had a severe disease from the beginning. However, long-term use of glucocorticoids is associated with significant side effects. Biological agents, especially interleukin 1 and 6 blockers, are used as a primary and single treatment with increasing frequency. These factors are effective in reducing clinical symptoms in patients resistant to NSAIDs and glucocorticoids. There are growing findings that suggest that biological agents may also be helpful in the care of children with severe illness instead of glucocorticoids at the time of diagnosis. The decision to start treatment with a biological agent alone or combined with glucocorticoids is initially made considering the type of biological agent used, and after discussing the potential benefits and harms of treatment for the patient and family.

In patients who do not respond to the initial test of treatment with an NSAID alone, or in those whose early symptoms include high fever, other severe systemic symptoms, or debilitating polyarthritis, it is recommended that a biological agent such as Anakinra, Canakinumab, or Tocilizumab is added until a glucocorticoid is taken. Anakinra is used in some at a dose of 2 mg per kilogram of body weight daily up to a maximum of 100 mg. Canakinumab is usually given at a monthly dose of 4 mg per kilogram of child body weight with a maximum dose of 300 mg. Typically, 12 mg per kg intravenous injection or 162 mg subcutaneous injection is used every two weeks for children weighing less than 30 kg. Also, 8 mg per kg intravenous injection with a maximum dose of 800 mg every two weeks or 162 mg subcutaneous injection every week for higher body weights.

It is recommended that glucocorticoids be used when they do not respond immediately to a biological agent. When the current definition of an immediate response varies from center to center, some pediatric rheumatologists wait more than a week to add a glucocorticoid if polyarthritis, fever, and rash persist. They all add a glucocorticoid if there is evidence of severe macrophage activation syndrome or serositis. Both glucocorticoids and biological agents usually persist until disease control. Clinicians may then discontinue glucocorticoids first because the drug is associated with unavoidable intoxication in long-term use. Discontinuation of the biological agent may be possible if the disease is controlled. Prednisolone should be limited to o.5–1 mg/kg, although doses higher than 2 mg/kg or pulsed treatment with methylprednisolone may be necessary in severe cases. The treatment in cases with the polycyclic course and recurrent attacks is similar to the initial treatment. Treatment of the chronic and persistent disease depends on whether the patient has early systemic signs and symptoms (including fever, rash, and serositis), early arthritis, which can be progressive and destructive, or both. Interleukin 1 and 6 blockers are the most effective biological agents for early systemic disease and may also be effective for chronic arthritis. Tumor necrosis factor (TNF) alpha-blockers, concomitant T-cell stimulation blockers (Abatacept), and methotrexate can be used as adjunctive therapies to treat chronic arthritis. Other non-biological disease-modifying anti-rheumatic drugs (DMARDs) such as cyclosporine and tacrolimus, and cytotoxic agents such as cyclophosphamide are complementary choices in cases that do not respond to standard treatment containing biological agents.

The potential toxicity of drugs used in systemic arthritis should be carefully evaluated compared to the progressive, debilitating side effects and often the persistence of uncontrolled disease. Therefore, patients presenting with severe manifestations of the disease or those who resist treatment with NSAIDs should be referred to an experienced pediatric rheumatologist for disease management. Screening and monitoring of the disease are essential in the patients being treated [14, 15].

9.3 Course, prognosis, and complications

The course of systemic JIA is highly variable, although there are three typical pre-biological patterns in the disease: monophasic, polycyclic, and persistent (chronic). In the monophasic pattern, complete remission usually occurs within 4 to 6 months (occasionally in two to four years) and does not recur. In polycyclic or relapsing form, flares of systemic manifestations are with mild arthritis, and among them, remission and inactivity of the disease occur. This period can vary from a few months to several years. Finally, persistent destructive arthritis is often present in the persistent type despite reducing systemic manifestations, usually the most common form of the disease (50%) [16].

Three patterns of chronic disease activity in patients with persistent systemic JIA:

1. Systemic manifestations without or with mild arthritis, including fever, skin rashes, and sometimes recurrent macrophage activation syndrome.

2. Persistent (chronic) systemic manifestations and progressive arthritis.

3. Progressive destructive arthritis despite improvement of systemic manifestations. Despite treatment, some patients develop progressive destructive arthritis.

Systemic JIA-induced morbidity and mortality have decreased with treatment progress, but mortality is still high in patients with severe disease, especially those with recurrent or unknown macrophage activation syndrome and severe pulmonary or vascular complications [17]. Patients with active disease (those with fever, arthritis, high platelet count, persistent need for glucocorticoids) six months after disease onset have a worse prognosis for disease persistence and destructive arthritis [18].

Macrophage activation syndrome is the most common complication of systemic JIA. With the early detection and application of biologic DMARDs such as IL1 and IL6 inhibitors, complications such as severe growth retardation and osteoporosis are currently less common. There may be an increased incidence of rare but severe pulmonary complications that require further investigation.

9.4 Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of systemic JIA that should be treated as a life-threatening emergency. Clinical and histopathological features of macrophage activation syndrome are similar to hereditary lymphohistiocytic hemophagocytosis or HLH. However, diagnostic criteria for it are often not used to diagnose MAS in systemic JIA. Evidence suggests that there is a common genetic component in patients with systemic arthritis and MAS, as well as protein-altering variants in genes associated with HLH [19].

9.4.1 Clinical manifestations

Typically, MAS occurs during the first few days or weeks after the systemic-onset JIA, although it can occur at any time during the disease course. MAS occurs in 10% of children with systemic JIA but can develop subclinically in about 30–40% of other patients. Some patients have recurrent attacks of MAS. Triggers for this syndrome may be viral or bacterial infections or the administration of new drugs, but the initial irritating incident is often not apparent [20].

Children may present with spontaneous bleeding, bruising, liver dysfunction, drowsiness, seizures, coma, or shock. Persistent fever and skin rash (as opposed to intermittent daily fever and the typical evanescent skin rash of mild acute systemic JIA), lymphadenopathy, and hepatosplenomegaly are other common findings. White blood cell count, hemoglobin, platelet count, and serum fibrinogen typically decline abruptly. Liver function tests, triglycerides, and LDH increase rapidly. Ferritin can also reach as high as 10,000 ng/ml or even higher. In addition, a paradoxical decrease in erythrocyte sedimentation rate (ESR) due to fibrinogen consumption occurs, which is a vital diagnostic key. Typically, a bone marrow aspiration reveals multiple benign macrophages that indicate hemophagocytosis. However, not all bone marrow samples from patients with MAS show such a finding and may appear normal [20].

9.4.2 Diagnosis

Early diagnosis of MAS in a patient with systemic JIA may be difficult because systemic JIA flare-ups have similar clinical manifestations. In addition, a review of published literature suggests that patients treated with biologics may have fewer clinical manifestations of MAS, which may make it even more difficult to diagnose; for example, tocilizumab-treated patients have no fever or lower level of fever, and their CRP and ferritin levels are significantly lower. Diagnostic criteria for HLH are often not applicable to MAS in patients with systemic arthritis. Although these syndromes are clinically similar, HLH criteria are so strict that they cannot detect early MAS in patients with systemic JIA when they respond more to treatment. Part of the problem lies in the fact that patients with systemic JIA naturally have significantly increased levels of white blood cells and platelets along with acute-phase reactants such as ESR and fibrinogen so that normal premature levels of these blood tests can be misleading because they are caused by declining levels and is a signal of imminent MAS. For this reason, many efforts are underway to develop applicable clinical diagnostic criteria and scoring tools to diagnose MAS in patients with systemic JIA [21].

The 2016 classification criteria for MAS in systemic arthritis were expanded to identify more valuable criteria by combining consensus methods by experienced individuals and analyzing actual patients' data.

These criteria require increased ferritin and one of the other two criteria. These criteria include [22]:

- Thrombocytopenia (platelets 181,000 or less)
- Elevated liver enzymes (including AST > 48 U / L)
- Hypertriglyceridemia (above 156 mg /dl)
- Hypofibrinogenemia (360 mg/dl or less)

A diagnostic scoring tool to differentiate MAS in systemic arthritis from active systemic JIA without MAS, called systemic MAS scoring MAS / sJIA (MS), was developed and validated in 2019. In this criterion, multinational patient data collected were used to classify the MAS in 2016. Fever is a mandatory criterion for diagnosis and does not fit into scoring, although, as noted above, it may not be present in patients with systemic JIA treated with tocilizumab even in the presence of MAS. This scoring still needs validation in the clinical field and may need to be revised to include biological use in its calculations. This tool can also differentiate between these two diseases with high sensitivity and specificity. The MAS / HLH (MH) score strongly confirms the age of onset, neutrophil count, fibrinogen, splenomegaly, platelet count, and hemoglobin. Having an age of 16 years or less at the onset of the disease and neutrophil of less than or equal to 1400 per liter are the most critical factors in differentiating HLH from macrophage activation syndrome involving systemic JIA [23].

9.4.3 Treatment

When MAS is diagnosed or suspected, treatment should be started urgently with high-dose glucocorticoids, often using a 30 mg/ml methylprednisolone pulse at a maximum dose of 1 gr daily intravenously. There have been case reports of successful treatment with cyclosporine, cyclophosphamide, etoposide, or anakinra. Treatment of resistant MAS cases in patients with systemic JIA is the same as treatment regimens for HLH [24].

10. Oligoarticular JIA

10.1 Clinical manifestations and diagnosis

Children with JIA of the oligoarticular type, formerly known as juvenile rheumatoid arthritis (JRA) of pauciarticular JRA type, have involvement of four joints or less during the first six months after the disease onset. These patients are divided into two main subgroups: 1. Patients who do not have more joint involvement after the first six months of the disease have persistent oligoarticular JIA. 2. Those with four or fewer joints are involved during the first six months of disease onset, but more joints are added over time, resulting in five or more joints eventually becoming involved, known as extended oligoarticular JIA [2].

Oligoarticular JIA is the most common group of JIA, accounting for almost half of all cases. In the USA and Europe, the disease is more common in girls than boys and peaks at two to three years of age. The typical manifestation of the disease is painless limping. Large joints, especially the knees and ankles, are the most commonly involved joints, but the pelvic joints are never the primary joints involved. Except for uveitis, there are no obvious systemic manifestations [25].

Diagnosis of oligoarticular JIA in children is made with arthritis of four joints or less during the first six months of the disease by excluding the other causes of oligoarthritis. There are no diagnostic laboratory tests for the disease. Antinuclear antibodies (ANA) are frequently present in these patients and are associated with an increased risk of iridocyclitis. Patients with an elevated ESR or unexplained anemia are more likely to have a recurrent disease and become an extended oligoarticular JIA. Differential diagnoses of oligoarticular JIA include the other types of JIA such as psoriatic arthritis, polyarticular JIA and ERA, Lyme disease, IBD, pigmented villonodular synovitis, other infectious, autoinflammatory, and autoimmune diseases, and malignancy, all of which may involve four or fewer joints at the onset [26, 27].

Recurrence occurs in approximately a quarter of initially healthy patients. Some patients with the oligoarticular disease eventually develop chronic degenerative arthritis. Manifestations in the first six months of the disease poor prognostic factors include symmetric involvement, ankle or wrist involvement, laboratory evidence of inflammation (elevation of ERS or CRP), radiographic evidence of joint destruction, and hip or cervical joints arthritis [28].

10.2 Treatment

Patients with mild to moderate disease activity, lack of risk factors for poor prognosis, and lack of joint stiffness usually respond to non-steroidal anti-inflammatory drugs and intra-articular injections of glucocorticoids. However, patients with more significant illnesses who do not respond to initial treatment for intra-articular injection or who initially have severe disease activity and poor prognostic risk factors require treatment with methotrexate or other DMARDs. Biological agents such as TNF blockers are used in patients with a moderate or severe disease with poor prognostic manifestations who do not respond to treatment with non-biological DMARDs. TNF blockers are also used in patients with progressive oligoarticular JIA and patients with uveitis [28–31].

10.3 Course, prognosis, and complications

Uveitis is the worst complication of the disease, occurring in approximately a quarter of patients with oligoarticular JIA. Patients with detectable ANA and those

under the age of six at the time of diagnosis are at the highest risk. Mainly, there are no symptoms of uveitis, so routine screening is essential. An ophthalmologist should perform screening and a thorough examination with a slit lamp, and an alternative optometric or fundoscopic examination is insufficient. Complications include cataracts, synechia, glaucoma, band keratopathy, and macular edema (**Table 2**) [32].

The leg-length discrepancy is the second most common complication of oligoarticular JIA. This complication frequently occurs in both bone length and width. Injection of glucocorticoids into the knee and ankle joint early in the course of the disease may prevent this complication [33].

Referral	
• Patients should be referred at the time of diagnosis, or suspicion, of JIA	
Initial screening examination	
• Should occur as soon as possible and no later than six weeks from referral	
• Symptomatic patients should be seen within a week of referral	
Ongoing screening	
• Screening at two-monthly intervals from the onset of arthritis for six months	
• Followed by 3–4 monthly screening for time outlined below:	
○ Oligoarticular JIA, psoriatic arthritis, and enthesitis-related arthritis irrespective of ANA status onset under 11 years	
Age at onset	**Length of screening**
< 3 years	8 years
3–4 years	6 years
5–8 years	3 years
9–10 years	1 years
○ Polyarticular, ANA positive JIA, onset <10 years	
Age at onset	**Length of screening**
<6 years	5 years
6–9 years	2 years
○ Polyarticular, ANA negative JIA, onset<7 years Five-year screening for all children	
○ Systemic JIA and rheumatoid factor positive polyarticular JIA Uveitis risk is very low; however, diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated	
○ All categories, onset >11 years One year screening for all children	
○ After stopping immunosuppression, e.g., methotrexate Two-monthly screening for six months, then revert to previous screening frequency as above	
○ After discharge from screening Patients should receive advice about regular self-monitoring by checking vision uniocularly once weekly and when to seek medical advice Screening may need to continue indefinitely in situations where a young person may be unable to detect a change in vision or be unwilling to seek re-referral Annual check by an optometrist as a useful adjunct	

Table 2.
British society for pediatric and adolescent rheumatology/Royal College of ophthalmology guidelines for uveitis screening in JIA.

11. Polyarticular JIA

11.1 Clinical manifestations

The age of onset of polyarticular JIA onset has a bi-modal distribution. The first peak is between the ages of two and five, and the second peak is between ten and 14 years old. It is more common in girls than in boys of all ages [2].

The clinical presentation of polyarticular JIA varies and tends to show different patterns depending on the age of the disease onset. In children under ten years of age, polyarticular JIA often begins similar to oligoarticular disease with the involvement of one or two joints. The progression of the disease is often subtle until an intercurrent infection dramatically exacerbates the symptoms of the disease. The disease inevitably progresses and spreads to five or more joints during the first six months of disease onset. Joint involvement is typically symmetrical. Older children and adolescents usually have a rapid onset of multi-joint involvement, including a large number of small joints of hands and feet within two to three months of the disease onset [34].

There are no diagnostic laboratory findings for JIA. However, patients may have an ANA-positive test and an increased ESR of 40 mm in the first hour or so, anemia, and hypergammaglobulinemia. In most patients, the Rheumatoid factor is negative. In some patients in this group, rheumatoid factor (RF) or anti-cyclic citrullinated peptide (Anti-CCP) is positive, which is associated with the severity of the disease, symmetrical involvement of small or medium-sized joints, degenerative course of arthritis, and prolongation of the disease with a rheumatoid arthritis-like course. Other autoantibodies are not commonly seen in patients with polyarticular JIA [35].

11.2 Diagnosis

Diagnosis is made in children with arthritis in more than four joints during the first six months of the disease and by rejecting other causes of polyarthritis.

11.3 Differential diagnoses

include several diseases that may be self-limiting or chronic, including other forms of JIA such as psoriatic, systemic, enthesitis-related, reactive arthritis, early-onset rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, sarcoidosis, inflammatory bowel disease, epiphyseal dysplasia, and minocycline-induced autoimmunity [27].

11.4 Treatment and prognosis

Polyarticular JIA treatment aims to treat underlying synovitis and inflammation. Immediate treatment that relieves the patient's arthritic symptoms and protects the patient's function is essential for a better outcome. The treatment regimens chosen depend on prognostic factors, disease activity, as well as physician and family preferences, which are adjusted based on the clinical response. Risk factors include positive RF, positive anti-CCP, and joint degeneration. Disease activity is measured by the clinical Juvenile Disease Activity Score based on ten joints (cJADAS-10). It is recommended that initial treatment with a DMARD be performed in all patients with polyarticular JIA. Methotrexate is preferable to sulfasalazine, leflunomide, or a three-drug combination of methotrexate, sulfasalazine, and hydroxychloroquine. Methotrexate at a dose of 10 mg per square meter of the body per week in patients with low disease activity or an anti-TNF

biological agent with methotrexate in cases with moderate to severe disease activity is primarily used. Indications for using a TNF blocker with or in comparison with methotrexate include the presence of severe polyarthritis, inferior prognostic manifestations, or factors associated with a poor response to methotrexate, such as predominant involvement of the axial joints. The NSAIDs are not suitable as a single drug but as adjunctive therapy to relieve symptoms. Folic acid or folinic acid supplements are used in all children with JIA receiving methotrexate, which has been shown to have beneficial effects, and there is no convincing conflicting data against them. In patients who do not respond to treatment with methotrexate and a TNF blocker, treatment decisions are made on a case-by-case basis. The use of abatacept or tocilizumab is preferable to switching the TNF blocker. Choices include using a combination of DMARDs, other biological agents, or a small molecule inhibitor under the supervision of an experienced pediatric rheumatologist. Adolescents with positive RF and positive Anti-CCP are likely to show early onset of rheumatoid arthritis. For this reason, these children should be treated like adults with moderate to severe rheumatoid arthritis [36].

12. Psoriatic JIA

12.1 Pathogenesis, clinical manifestations, and diagnosis

Psoriatic JIA or psoriatic arthritis is clinically non-homogenous. In children, the age of onset of the disease is bimodal. The first peak occurs mainly in preschool girls and has a clinical picture similar to oligoarticular JIA with a high probability of positive ANA. The second peak is in mid-to-late childhood and resembles adult-onset psoriatic arthritis. The presentation and severity of the disease can be quite different, and the skin manifestations of psoriasis can occur long after the onset of arthritis. Articular involvement may vary from mild enthesitis to polyarticular involvement of the peripheral and axial joints. Inflammation may occur in only one joint or a large number of joints, with or without the involvement of the sacroiliac joints, spine, or peripheral entheses. Dactylitis or sausage-shaped swelling of the fingers is a common manifestation in younger children, while axial enthesitis-related arthritis is more common in older children. Enthesitis refers to inflammation of the joints where ligaments, tendons, capsules, fascia, and other fibrous structures attach to bone. Overt psoriasis Vulgaris may not be present. Nail pitting is more common in psoriatic JIA than skin-limited psoriasis. RF is typically negative and is considered an exclusion criterion. Inflammatory markers include ESR and CRP, and platelet counts may be mild to moderate but are often normal, even in the presence of polyarticular disease. Bone changes and joint space narrowing indicate significant cartilage loss, typically seen only after the advanced disease onset [37].

Psoriatic arthritis is currently diagnosed in children where arthritis occurs in the presence of established psoriasis. However, classic skin rash during presentation does not occur in about half of children with psoriatic arthritis and sometimes occurs even ten years or more after the onset of the joint symptoms. Besides, psoriasis in young children may be mild, atypical, and transient, often mistaken for eczema initially; therefore, diagnostic uncertainty is expected. Laboratory tests and radiologic studies have limited value in diagnosing psoriatic arthritis [37].

Differential diagnoses of psoriatic arthritis mainly include other subtypes of JIA, particularly oligoarticular and RF negative polyarticular and enthesitis-related arthritis. Apart from other types of JIA, differential diagnoses depend on the type of clinical presentation.

12.2 Treatment, prognosis, and outcome

Psoriatic arthritis is a relatively common subtype in JIA, but its clinical presentation can be very varied. Except for confirmation of suspected sacroiliitis by contrast-enhanced MRI, laboratory tests and radiological studies have limited value in managing psoriatic arthritis. Like other types of JIA, initial treatment for psoriatic arthritis depends on summing up all the clinical, laboratory, and radiographic manifestations of the disease to prevent cartilage or bone damage. The standard treatment algorithm for psoriatic arthritis is similar to other JIA cases, with a few exceptions. Some rheumatologists use NSAIDs as the primary treatment for monotherapy. However, NSAIDs do not typically induce remission; therefore, it is generally best used with a DMARD in patients with extensive or moderate to severe disease. Arthritis in the large joints, as well as dactylitis of the fingers, may be treated with glucocorticoid injections. DMARDs are indicated at diagnosis in patients with multiple joint involvements or those who have not remission with intra-articular injection of glucocorticoids. Failure to achieve disease remission is followed by the addition of a secondary DMARD, or more commonly by anti-TNF treatment. Systemic glucocorticoids are generally less commonly used, and antimalarial agents are avoided because of the risk of worsening psoriatic rash. The effectiveness of other biologic agents such as anti-IL-12/23, anti-IL-17, abatacept, apremilast, and Jak inhibitors has been shown in various studies [38].

Axial involvement in psoriatic arthritis is phenotypically similar to ankylosing spondylitis. Treatment should be started in patients with psoriatic arthritis who have symptoms of axial involvement or limited spinal mobility, even if these changes have not yet been shown on plain graphs. Anti-TNF agents are generally most effective, while NSAIDs can relieve symptoms in a group of patients. Other DMARDs have minimal impact. Interleukin-17 blocking agents, such as Janus kinase (JAK) inhibitor, appear to be allowed in adult studies. Monitoring and treatment of uveitis in psoriatic arthritis is similar to other subgroups [38].

Traditional treatment of psoriasis is indicated for skin disease associated with psoriatic arthritis. Usually, skin involvements are not very troublesome because joint manifestations occur early. After all, early use of systemic agents such as methotrexate and TNF inhibitors also has high effects on skin disease [39].

Poor outcomes and long-term disability are generally seen in patients who have a long delay in diagnosis or those who have not started effective treatment, although physicians or families often try to take necessary steps to induce disease remission [40].

13. Spondyloarthritis

13.1 Clinical manifestations and diagnosis

The terms spondyloarthropathy and spondyloarthritis refer to seronegative and related inflammatory diseases characterized by involvement of the spine (sacroiliitis and spondylitis), large joints (asymmetric oligoarthritis, especially of the lower extremities), and the entheses (enthesitis and enthesopathy). Diseases that fall into this category in children include enthesitis-related arthritis (undifferentiated spondyloarthritis), juvenile ankylosing spondylitis (differentiated spondyloarthritis), reactive arthritis, psoriatic arthritis, and arthritis with inflammatory bowel disease [41].

The onset of the disease is gradual but may initially be followed by a febrile illness or a musculoskeletal trauma. Arthritis is usually oligoarticular, asymmetric, and initially involves the large joints of the lower extremity. The knee, ankle, and mid-foot are the most common joints involved during the presentation. Common

manifestations accompanied include painful ligaments or tendons at the junction with the bone (enthesitis), inflammatory back pain or sacroiliac pain, morning stiffness, and limited spine movement [41].

Extra-articular manifestations include anterior uveitis, related skin manifestations, and recurrent gastrointestinal complaints. These manifestations may be associated with undifferentiated spondyloarthritis or suggest an alternative diagnosis, including a systemic disease such as inflammatory bowel disease and mechanical, developmental, and orthopedic disorders other than spondyloarthritis [41].

HLA-B27 is associated with enthesitis-related arthritis and has an increased incidence in all types of spondyloarthropathies. In juvenile ankylosing spondylitis, up to 90%, and in enthesitis-related arthritis, up to 50% can be positive [42].

13.2 Treatment

Treatment for spondyloarthritis aims to reduce symptoms, control inflammation, and prevent disability. The appropriate treatment depends on which manifestations are present, especially whether spinal involvement and whether spondyloarthritis is a manifestation of a systemic disease such as psoriatic arthritis, reactive arthritis, or inflammatory bowel disease. Traditional treatment with NSAIDs is recommended in all cases. In case of no response and active enthesitis, TNF inhibitor is preferable to methotrexate or sulfasalazine. In cases of TNF blocker contraindication, patients with mild enthesitis and patients with active peripheral polyarthritis, methotrexate or sulfasalazine can be used concomitantly. In cases of chronic active enthesitis, low-dose oral glucocorticoids can be used as bridge therapy in the short term (less than three months). In addition, this treatment can be used in cases of high disease activity, limited mobility, or significant symptoms [36, 42].

14. Conclusions

JIA is the most common cause of chronic arthritis in children. In approach to a child with chronic arthritis, the physician should be alert about the wide differential diagnoses and consider and rule in or rule out the probable causes according to the history and examination. A full history and physical examination will provide a good background for an appropriate approach. Unfortunately, there is not a specific diagnostic laboratory test for confirming the diagnosis. Some important causes such as infections, malignancies, metabolic disorders, endocrine diseases, connective tissue disorders, and immune deficiencies should be in the mind of the physician. Early diagnosis and aggressive treatment are the principles of the management to prevent significant disease complications. Long-term clinical, laboratory, and ophthalmologic follow-up are necessary.

Acknowledgements

We would like to extend our sincere gratitude to all members of the Pediatric Rheumatology Ward in Mofid Children's Hospital, Tehran, Iran, and special thanks to Dr. Vahideh Zeinali, the head of the hospital library.

Conflict of interest

The authors declare no conflict of interest.

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