Overview of Juvenile Idiopathic Arthritis

17

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Learning Objectives

1. To provide a general introduction to JIA with a particular emphasis on classification
2. To discuss the etiopathogenesis of JIA
3. To discuss the clinical presentation of various subtypes of JIA
4. To discuss the fallacies of the current ILAR classification

Introduction

Juvenile idiopathic arthritis (JIA) is not a single disease but a diagnosis that applies to all forms of arthritis of unknown origin, with onset prior to the 16th birthday, lasting more than 6 weeks and where other causes have been excluded [1]. The diverse groups of the diseases we call JIA all have in common a chronic inflammatory process primarily targeting the synovial membrane. In more severe cases, persistence of inflammation may lead to an increased risk of osteocartilaginous damage and physical functional disability. The etiology of JIA is still unknown. The heterogeneity of these disorders implies that different factors probably contribute to the pathogenesis and cause the various forms of childhood chronic arthritis. The identification of categories that, at least from a clinical point of view, seem homogeneous is essential to enable immunological and genetic studies aiming to improve our understanding of the basic biologic processes underlying these diseases. Although the past two decades have witnessed significant advances in classifying children with chronic arthritis [2], issue of classification remains far from complete. The picture that now emerges is that while some JIA subsets identify clearly distinct disease entities, others still seem to include heterogeneous conditions.

Due to their peculiarities in terms of genetic background and clinical phenotype, systemic-onset JIA and spondyloarthropathy will be addressed in separate chapters.

Epidemiology

JIA is one of the most common chronic rheumatic diseases in children, potentially responsible for both short-term and long-term physical disability. Although present across the world, its incidence and prevalence vary considerably throughout. Reported annual incidence rates of

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chronic childhood arthritis have ranged from less than 1 per 100,000 in Japan to more than 20 per 100,000 in Norway. Studies in high-income countries have reported a prevalence that varies between 16 and 150 per 100,000 [1], with higher occurrence in Northern Europe [3–5]. Outside Europe, a prevalence of 400 per 100,000 has been signaled by an Australian community-based survey [6]. Differences due to the genetic background or the potential environmental factors, as well as methodological issues (i.e., clinic or practitioner-based studies compared to community-based study populations, etc.), could explain the variable results of the epidemiological studies [7].

Relative frequency of the various JIA categories varies substantially according to geographic and ethnic differences [8]: oligoarthritis, by far the most common category in Western countries, is in fact quite rare in countries such as Costa Rica [9], New Zealand, and South Africa, where polyarthritis seems to be predominant; also in India polyarthritis outnumbers oligoarthritis and systemic-onset disease [10]. Although JIA affects females more frequently, the female to male ratio differs strongly according to JIA-onset categories and geographic or racial groups (i.e., male predominance has been reported from parts of Asia).

Etiopathogenesis

JIA is a complex autoimmune disease whose etiology is still unknown. It has a complex multifactorial origin in which a combination of genetic susceptibility and largely unidentified environmental triggers lead to immune imbalance. Unrestricted pro-inflammatory immune response leads to synovial inflammation and in turn to potentially irreversible joint damage. Although to a considerable extent different factors probably contribute to the pathogenesis of diverse JIA categories, nonetheless, certain generalizations can be made.

Various environmental factors, especially infections, have been implicated in the etiopathogenesis of JIA [11, 12], but no specific microorganism has been singled out as a trigger due to the lack of proper prospective studies. The link between vaccinations and JIA pathogenesis has been debated for several years. Although some vaccinations (i.e., rubella vaccination) may cause transient arthralgia and even arthritis, studies have failed to relate vaccination to the onset of JIA or disease exacerbation. Notably, it is now accepted that vaccination in children with JIA is overall safe and effective [13–15].

Genetic susceptibility to JIA has been supported by the concordance rate and similarity in disease phenotype between monozygotic twins (20–40 %) [16]. Studies on sibling pairs affected by JIA have estimated the overall relative sibling risk (λs) for this disease to range from 15 to 30 [17, 18]. The sibling recurrence risk (λ_s) is calculated as the prevalence of the disease in siblings of affected individuals divided by the prevalence of disease in the general population and reflects the importance of genetic factors in a certain disease. The most common onset type in 164 affected siblings was oligoarticular (65 % overall), further underscoring its genetic background. Recent technological advances in the field of genetics have shed light on the interplay between genetic susceptibility and immune function in JIA. Genome-wide association studies (GWAS) have contributed to identify some of the most prominent genetic regions involved in JIA. The reported association of JIA with both HLA class I (HLA A-2 and HLA-B27) and HLA class II (HLA-DRB1 and HLA DP) alleles, which are primarily involved with antigen presentation to CD4 and CD8 T cells, highlights the importance of the adaptive immune response in JIA [19, 20]. In addition, a large number of non-HLA candidate genes (PTPN22, MIF, SLC11A6, WISP3, and TNFα) including a number of cytokine genes and genes linked to immune pathways have been identified to have an association with JIA [18, 21–25]. In this respect, some of the most noteworthy gene regions are IL-2 pathway-related genes which are crucial for T-cell differentiation and function [23].

The observation that gene expression profile of peripheral blood mononuclear cells (PBMC) varies among different JIA subtypes [26] has reinforced the concept that JIA is not a single dis-

ease but instead a group of different diseases having chronic arthritis as a common feature.

The primary pathological process in JIA is a chronic synovial inflammation, in which the immune system plays a critical role. Notably, evidence has proved that the inflamed synovial fluid regulation depends on a balance between regulatory (suppressive) T cells and pro-inflammatory effector T cells [27–31]. Regulatory T cells (Tregs), which express the transcription factor FoxP3, are crucial for the maintenance of immune tolerance [32] due to their capacity to suppress other immune cells. A better understanding of the basic mechanisms of immune regulation in JIA may impact future perspectives for the development of specific therapies to restore the immune balance.

The autoreactive immune response in JIA is thought to be triggered by an adaptive (T cell or B cell) response toward a self-antigen [31, 33].

Recently, a growing interest has developed toward molecules that can regulate the inflammatory response. DAMP (damage-associated molecular patterns) molecules or alarmins are upregulated during local damage and stress and are targets for both innate and adaptive immune responses [34]. Their increased levels can act as surrogate biomarkers for the inflammatory process, as extensively shown for S100 proteins. These proteins were found to be sensitive biomarkers of low-grade inflammation in patients with clinically inactive disease on MTX therapy, differentiating clinical and true immunological remission and helping the safe withdrawal of MTX therapy [35, 36]. Another group of DAMP molecules are the heat shock proteins (hsp), highly conserved immune-dominant proteins that are upregulated during cellular stress. Data from experimental models have shown a potential protective role of an autoimmune T-cell response against self-hsp60. This observation has been confirmed in ex vivo studies in JIA, in which the presence of anti-hsp60 T cells correlated with a favorable immune phenotype and a good clinical prognosis [37–40].

The constant interplay between adaptive and innate immune activation is pivotal in determining the chronicity of inflammation in JIA. In parallel to activation of the adaptive immune response, innate immune activation contributes to the synovial inflammation in JIA. This includes a role for neutrophils, which are abundantly present in inflamed synovial fluid and have an aberrant gene expression profile. Various studies have shown that in the plasma of JIA patients, the levels of many cytokines and chemokines are increased compared to that of healthy control, revealing a predominantly pro-inflammatory profile, especially in synovial fluid and during active disease [33]. Future studies should examine how these cytokines, alone or in concert, can provide profiles that may help in the clinic for diagnosis, for prognosis, and for response to therapy.

Clinical Features

Juvenile idiopathic arthritis is defined as any arthritis (defined as joint swelling or joint pain and limitation of motion) that persists for at least 6 weeks, that is of unknown origin, and that has its onset before 16 years of age. JIA is therefore a diagnosis of exclusion based on a careful history taking, a thorough physical examination, and laboratory tests meant to rule out other known causes of arthritis in childhood as reported in Table 17.1. Pattern recognition is the key to a diagnosis of JIA. The onset of arthritis in JIA is more often insidious than acute and is fixed, and usually swelling is more than the pain. Joint stiffness in the morning or gelling after prolonged rest occurs frequently in the active phase of the disease. Joint involvement may be monoarticular, oligoarticular, polyarticular, symmetric or asymmetric depending on the specific JIA category. Though any joint can be affected, large joints such as the knee and the ankle are commonly involved in oligoarthritis and are responsible for the common complaint of limping; small joints of the hands and feet are usually involved in polyarticular-onset and systemic disease. The temporomandibular joint (TMJ) should also be carefully examined, given the high prevalence of TMJ disease at the time of diagnosis [41] and that early detection of TMJ inflammation is crucial to

Table 17.1 Differential diagnosis of arthritis in children

Inflammatory
Infection: septic arthritis, osteomyelitis, tuberculosis, Lyme arthritis
Reactive arthritis secondary to extra-articular bacterial (e.g., streptococcal, enteric bacteria) or viral infections (e.g., hepatitis B, parvovirus, Epstein-Barr virus, varicella, rubella)
Malignancies: leukemia, lymphoma, neuroblastoma
Inflammatory bowel disease-associated arthritis
Sarcoidosis
Connective tissue diseases: systemic lupus erythematosus, vasculitis, juvenile dermatomyositis, Sjogren syndrome, mixed connective tissue disease
Immunodeficiency-associated arthritis
Other: chronic recurrent multifocal osteomyelitis, cryopyrin-associated periodic syndromes (CAPS) including chronic infantile neurological cutaneous and arthritis syndrome, familial Mediterranean fever, etc.
Hematological disorders: hemophilia, hemoglobinopathies (e.g., sickle cell disease)
Mechanical
Trauma: accidental and nonaccidental injury
Osteochondroses
Avascular necrosis and other degenerative disorders: Perthes, slipped upper femoral epiphysis, idiopathic chondrolysis
Inherited: skeletal dysplasias, congenital dislocation of the hip
Benign hypermobility syndrome
Inherited storage disorders, e.g., mucopolysaccharidoses, lipidoses, etc.
Collagen disorders, e.g., Ehlers-Danlos, Marfan's, Stickler's syndrome
Solid tumors:
Benign: osteoid osteoma, pigmented villonodular synovitis, hemangioma, lipoma arborescens
Malignant: synovial sarcoma, osteosarcoma, rhabdomyosarcoma
Idiopathic pain syndromes
Local: reflex sympathetic dystrophy
Generalized: fibromyalgia

prevent severe mandibular growth abnormalities and condyle deformities. Although not frequent at disease onset, cervical spine involvement should be promptly recognized to avoid severe neurologic complications [42]. Hip involvement at disease onset is very rare except in patients with enthesitis-related arthritis.

Laboratory investigations are useful for the exclusion of other disorders, to aid categorization of the JIA subsets associated with specific serologic or immunologic markers and to monitor the extent of inflammation. Immunological markers such as antinuclear antibodies (ANAs), rheumatoid factor (RF), and HLA-B27 are helpful but not specific; ANA and IgM RF, in fact, may be transiently positive after a viral illness and are also present in other connective tissue disorders and even in healthy children [43]. Acute phase reactants help in monitoring disease activity in some patients, but it is important to note that children with JIA, especially those with oligoarthritis, may have normal values at the disease onset. In the systemic and polyarticular categories, ESR and CRP are usually significantly raised often along with thrombocytosis. Anemia, usually secondary to chronic inflammation, can occur in all forms of JIA but is more pronounced in systemic JIA.

Classification

Defining the diverse groups of arthritis under the term of JIA has proven to be a challenge. In the 1970s two classifications had been proposed (Table 17.2), one by the American Rheumatism Association, in which the condition was called juvenile rheumatoid arthritis (JRA) [44], and the other by the European League Against Rheumatism (EULAR), in which the term juvenile chronic arthritis (JCA) was adopted [45].

EULAR criteria differed from the ACR criteria in several respects including disease duration (arthritis must have been present for at least 3 months), disease subtypes (juvenile ankylosing spondylitis, psoriatic arthropathy, and arthropathies associated with inflammatory bowel disease were included), and nomenclature (the term juvenile rheumatoid arthritis was applied only to children with arthritis and RF seropositivity). In 1993 the International League of Associations for Rheumatology (ILAR) [2, 46] classification for JIA was proposed with the aim to reach a consensus on a common classification and nomenclature and to delineate relatively homogeneous categories of JIA which are suitable for etiopathoge-

Table 17.2 ACR criteria versus EULAR criteria for classification of juvenile arthritis

ACR criteria for classification of juvenile rheumatoid arthritis	EULAR criteria for classification of juvenile chronic arthritis
Age at onset of arthritis <16 years	Age at onset of arthritis <16 years
Arthritis (*swelling or effusion or presence of two or more of the following signs: limitation of range of motion, tenderness or pain on motion, and increased heat*) in one or more joints	Arthritis in one or more joints
Duration of arthritis: 6 weeks or longer	Duration of arthritis: 3 months or longer
Three onset types: (defined by disease type in the first 6 months) (a) Polyarthritis: ≥5 inflamed joints (b) Oligoarthritis: <5 inflamed joints (c) Systemic onset: arthritis with characteristic fever[a]	Six types: (defined by characteristics at onset) (a) Pauciarticular: <5 joints (b) Polyarticular: >4 joints, rheumatoid factor negative (c) Systemic: arthritis with characteristic fever (d) Juvenile rheumatoid arthritis: four joints, rheumatoid factor positive (e) Juvenile ankylosing spondylitis (f) Juvenile psoriatic arthritis
Exclusion of other forms of juvenile arthritis	

[a]*Daily (quotidian or intermittent) fever spiking to greater than 39 °C for at least 2 weeks*

netic studies. In the ILAR classification, JIA subtypes are categorized based on predominant clinical and laboratory features presenting during the first 6 months of disease. The principle underlying ILAR classification is that all categories are mutually exclusive. The categories and exclusion criteria are summarized in Table 17.3. Due to their peculiarities in terms of clinical findings, genetic background, and immune pathogenesis, systemic-onset JIA and enthesitis-related arthritis will be discussed in separate chapters.

Table 17.3 ILAR classification of JIA: categories, frequency, and age distribution

ILAR category	Frequency (%)	Preferential onset age
Systemic arthritis *Exclusions: a, b, c, d*	5–15	Any pediatric age
Oligoarthritis *Exclusions: a, b, c, d, e*	30–60	Early childhood
Rheumatoid factor-positive polyarthritis *Exclusions: a, b, c, e*	3–7	Late childhood or adolescence
Rheumatoid factor-negative polyarthritis *Exclusions: a, b, c, d, e*	10–25	Biphasic distribution: early peak <6 years and late peak >6 years
Enthesitis-related arthritis	5–10	Late childhood or adolescence
Psoriatic arthritis *Exclusions: b, c, d, e*	3–10	Biphasic distribution: early peak <6 years and late peak >6 years
Undifferentiated arthritis	10–20	

Exclusion criteria. (a) Psoriasis or a history of psoriasis in the patient or first-degree relative. (b) Arthritis in an HLA-B27-positive male beginning after the sixth birthday. (c) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis or a history of one of these disorders in a first-degree relative. (d) The presence of IgM rheumatoid factor on at least two occasions at least 3 months apart. (e) The presence of systemic JIA in the patient

Oligoarthritis

Oligoarthritis is defined as arthritis that affects four or less joints during the first 6 months of disease [2]. In the ILAR classification, children who otherwise satisfy these criteria are excluded from this category if they have psoriasis or a history of psoriasis in a first-degree relative, a human leukocyte antigen (HLA)-B27-associated disease, and a positive rheumatoid factor (RF) test or if the disease occurs in a male patient older than 6 years [2]. Oligoarticular JIA is the most common JIA subtype in Western countries: a lower percentage was reported from India (25%), North American Indian population (26%), and other racial groups (31%) compared to North

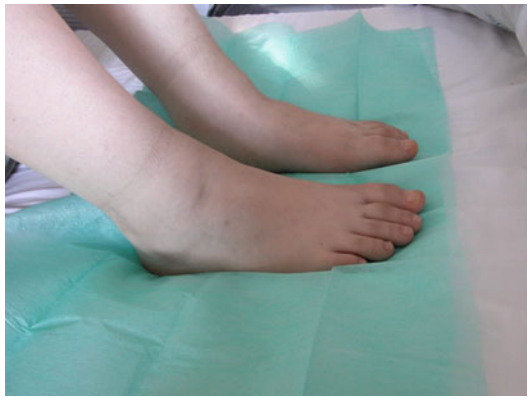


Fig. 17.1 Ankle involvement in a patient with oligoarticular juvenile idiopatic arthritis

American and European patients (58 %) [47]. Typically disease onset is in early childhood with a peak incidence between 1 and 2 years of age. The large majority of patients show an asymmetric arthritis involving mainly large joints, early onset (before 6 years of age), female gender predilection, a high frequency of positive antinuclear antibodies (ANAs), and a high risk of developing chronic iridocyclitis. The homogeneity of this subtype is mirrored by a strong association with some HLA alleles (HLA-DRB1*08 in particular). Oligoarthritis affects primarily the lower limbs, with the knee joint being most commonly involved, followed by the ankle (Fig. 17.1). In oligoarthritis, acute phase reactants are usually normal or moderately increased. Tests for ANAs are positive in 65–85 % of children, especially in females and in those with uveitis [1]. The specific antinuclear antigens responsible for the ANA positivity in JIA have not yet been identified.

ILAR classification recognizes two subcategories of oligoarthritis based on the number of joints involved after the first 6 months of the disease: persistent oligoarthritis, where the disease is confined to four or fewer joints, and extended oligoarthritis, in which arthritis spread to more than four joints [2]. Involvement of the wrist, symmetric arthritis, and a high ESR have been identified as warning signals of progression to the extended phenotype, which may occur in up to 50 % of patients [48]. An increased CD4 to CD8 ratio was found in peripheral blood or synovial fluid mononuclear cells of patients who later developed persistent oligoarthritis and remitting disease, compared to patients who developed a polyarticular disease course, underscoring the pivotal role of T cells in oligoarticular form of JIA [49].

Of note ANA-positive patients, regardless of whether they have persistent or extended oligoarthritis, have similar clinical characteristics (e.g., age at onset, sex ratio, asymmetry of articular involvement, etc.), denoting that these two subcategories of oligoarthritis represent the same disease, varying only in the spread of arthritis [50–52].

About one third of patients with oligoarticular JIA develop a chronic, nongranulomatous anterior uveitis that involves the iris and the ciliary body (iridocyclitis) and can cause severe visual impairment. Recognized risk factors for uveitis are age at disease onset, gender, the presence of ANA, and the JIA subtype [53, 54]. The onset of chronic uveitis is usually insidious and often asymptomatic. Later in the disease course, ocular pain, redness, headache, photophobia, and change in vision are reported by nearly one half of the patients with chronic uveitis. Two thirds of cases of uveitis are bilateral [55, 56], and generally it occurs at the time of diagnosis or shortly thereafter, although in less than 10 % of patients, it precedes the onset of arthritis. The development of uveitis after 7 years from onset of arthritis has rarely been reported [57, 58]. Its course may be chronic or relapsing and independent of arthritis [59]. Though inflammatory cytokines (IL-1β, IL-2, IL-6, interferon-γ, and TNFα) have been reported in ocular fluids and tissues [60], uveitis pathogenesis and the link between inflammatory joint and ocular diseases are not yet clear. Serious ocular complications associated with iridocyclitis include posterior synechiae, band keratopathy, cataract, and glaucoma [12, 59, 61, 62]. The outcome of iridocyclitis relies on early diagnosis and treatment. Since uveitis is asymptomatic at onset, slit-lamp examination every 3 months should be carried out in ANA-positive patients: the evidence of increased protein concentration and inflammatory cells in the anterior chamber of the eye suggests anterior uveitis. Although uveitis is more frequent in ANA-positive oligoarticular JIA, it is also manifested in 14 % of RF-negative polyarthritis and in 10 % of psoriatic

arthritis, while it is uncommon in systemic JIA or RF-positive polyarthritis [54, 56]. Sudharshan and colleagues described uveitis in 40 Indian children with JIA who were referred for ophthalmological evaluation in a 6-year period due to eye symptoms. Patients' features differed considerably from Caucasian study cohorts in that most were boys, the mean age at evaluation was 9 years, and only two patients were ANA positive, and complications were very common (cataract in 63 % of the eyes and band keratopathy in 62 % of the eyes) [63]. Whether these findings reflect differences in the disease (i.e., HLA-B27-associated arthritis) or the pattern of referral (they were all symptomatic) is not entirely certain. Over the last decade, the prognosis of oligoarticular JIA has greatly improved. Health status reports of 376 children with oligoarticular JIA showed that half no longer required medications a year after disease onset and that 98 % were in Steinbrocker functional class I or II after 5 years follow-up [64]. In a study aiming to identify early predictors of long-term outcome, ANA positivity and younger age at the disease onset correlated with longer active disease duration [65].

Rheumatoid Factor-Positive Polyarthritis

RF-positive polyarthritis is defined as the involvement of five or more joints during the first 6 months of disease and by the presence of positive rheumatoid factor (RF) on two occasions at least 3 months apart during the first 6 months of disease [2]. RFs are antibodies (IgM) that bind to the CH2 and CH3 domains of the Fc portion of immunoglobulin G (IgG) and are detectable by agglutination, nephelometry, or enzyme immunoassay [66]. It is considered the pediatric counterpart of adult RF-positive rheumatoid arthritis (RA) and shares a similar clinical phenotype, serology, and immunogenetic profile. The shared epitope (SE) present in some HLA-DR4, HLA-DR1, and HLA-DR14 alleles is associated with an increased risk for both adult RA- and RF-positive JIA [67]. In Europe, children with RF-positive polyarthritis represent approximately 5 % of the JIA population. There is a female predominance, and the onset occurs usually in late childhood or adolescence with a symmetric polyarthritis affecting principally wrists and the small joints of the hands and feet (Fig. 17.2). The large joints, usually knees and ankles, may also be affected generally along with small joint involvement. ESR and C-reactive protein are elevated, and a moderate normochromic and normocytic anemia is often associated. RF-positive polyarthritis is the only JIA category with positive antibodies to cyclic citrullinated peptides [68]. In adults these antibodies are present years before the onset of RA [69, 70] suggesting their potential pathogenic role.

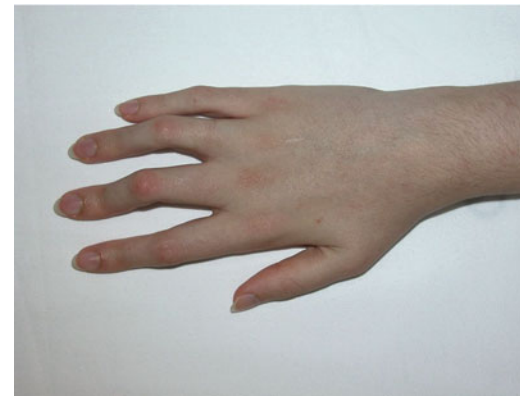


Fig. 17.2 Involvement of the small joints of the hand in a patient with Rheumatoid Factor positive polyarthritis

Rheumatoid nodules, typical of adult RA, have been reported in about a third of patients in the first year of disease [71]. Nodules which are firm, mobile, and nontender often occur on bony prominences and pressure points such as distal to the olecranon, on flexor tendon sheaths, and on the soles of the feet. Low-grade fever, lymphadenopathy, and weight loss may occur with active disease, while severe extra-articular disease manifestations including aortic valve regurgitation [72] and pulmonary involvement [73] are very rare in children. Two types of pulmonary involvement have been reported: lymphoid interstitial pneumonitis and bronchiolitis obliterans. The time interval between the clinical presentation of pulmonary disease and onset of JIA has ranged from 10 to 20 years after JIA onset. Symptoms include tachypnea, dyspnea, a nonproductive cough, and fever. Pulmonary function tests usually show reduced lung volumes

and decreased diffusion capacity. A restrictive pattern is typical of interstitial pneumonitis, while an obstructive pattern is present in case of bronchiolitis obliterans. Chest radiography may be normal, while HRCT abnormalities include ground-glass changes suggesting inflammation bronchiectasis and/or honeycombing.

Aggressive medical treatment of RF-positive polyarthritis is warranted because of its almost uniformly poor prognosis. Patients with RF-positive polyarthritis, in fact, have the lowest remission rate (5 %) off medication among children with chronic arthritis monitored for 10 years [74]. Radiological changes occur earlier and more frequently in RF-positive polyarthritis than in the other JIA categories and are observed particularly in the hands and feet [75, 76]. Although the availability of new therapies such as biological agents has considerably decreased the development of deformities, ulnar drift at the wrist, boutonniere and swan neck deformities of the fingers, hallux valgus, hammertoe, and cock-up toe deformities are not uncommon in this JIA subtype.

Rheumatoid Factor-Negative Polyarthritis

It is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of IgM RF [2]. Its frequency varies according to geographical origin: polyarthritis accounts for approximately 20 % of JIA patients in British and Canadian studies, while its percentage was significantly higher in other racial groups such as East Indian (61 %) or native North American Indian (64 %) [16]. This disease is less defined than RF-positive polyarthritis; its variations in clinical characteristics, course, and outcome suggest that this JIA category is probably the most heterogeneous subtype [1, 12, 50]. At least three distinct clinical phenotypes can be identified. A subset that is comparable to adult-onset RF-negative RA is characterized by overt symmetric arthritis of large and small joints, onset at school age, elevated ESR, negative ANA, and variable outcome. The second subset resembles ANA-positive early-onset oligoarthritis in many respects (early age at onset, positive tests for ANA, asymmetric arthritis, female predominance, increased risk of chronic iridocyclitis, and association with HLA-DRB1*08) but for the number of joint involved during the first 6 months of disease. These similarities have led to the hypothesis that this subset and early-onset oligoarthritis are the same disease, the former representing a more aggressive phenotype than the latter [50, 52, 77]. The fact that ANA-positive RF-negative polyarthritis is seldom seen in countries such as Costa Rica, India, New Zealand, and South Africa in which ANA-positive oligoarthritis is also rare [47, 54] further supports this hypothesis. This idea has finally gained support from gene expression studies demonstrating B-cell signature [78] and an association with HLA-DRB1 [79] that were similar for both oligoarticular and polyarticular forms of diseases in JIA with early-onset arthritis (≤6 years).

In a small subset of RF-negative patients with polyarthritis, clinical signs of joint effusion and synovial hypertrophy are negligible, although these children have joint stiffness and progressive joint contractures associated with normal or slightly raised ESR [80, 81]. This third subset of RF-negative polyarthritis known as “dry synovitis” is often poorly responsive to treatment and could follow a destructive course.

Among children with RF-negative polyarthritis, knees, wrists, and ankles are the most commonly affected joints. Small joint involvement of the hands or feet may occur early or late in the disease course. Clinical signs of hip involvement are present in fewer than 20 % of children at disease onset, but progressive abnormalities of the hip joint become evident with long-term follow-up. Systemic manifestations in children with seronegative polyarthritis are unusual but can include fatigue, growth failure, and low-grade fever. Subcutaneous nodules occur rarely (<1 %) in RF-negative polyarthritis.

Although RF-negative polyarthritis has a variable outcome, which reflects the heterogeneity of this category, substantial morbidity and functional disability have been reported in most affected children. Oen and colleagues reported that only 25 % of 80 children with RF-negative polyarthritis had achieved remission by the age of 16 years [65].

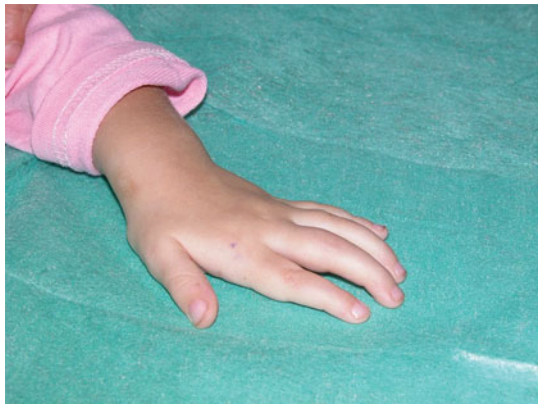
Table 17.4 Classification of psoriatic arthritis

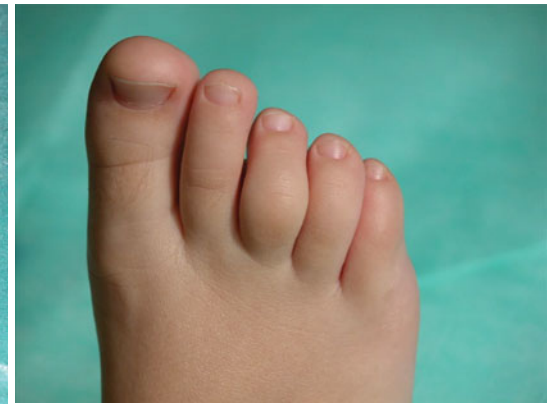
	Vancouver	ILAR (Edmonton revision)
Inclusion	Arthritis plus psoriasis or arthritis plus at least two of the following	Arthritis and psoriasis or arthritis and at least two of the following
	Dactylitis	Dactylitis
	Nail pits	Nail pits or onycholysis
	Psoriasis in a first- or second-degree relative	Psoriasis in a first-degree relative
	Psoriasis-like rash	
Exclusion criteria	None	(a) Arthritis in an HLA-B27-positive male beginning after the sixth birthday (b) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis or a history of one of these disorders in a first-degree relative (c) The presence of IgM rheumatoid factor on at least two occasions at least 3 months apart (d) The presence of systemic JIA in the patient

Juvenile Psoriatic Arthritis (JPsA)

The diagnosis of juvenile psoriatic arthritis by the ILAR criteria requires the simultaneous presence of arthritis and a typical psoriatic rash or, if the latter is absent, the presence of arthritis and two of the following: dactylitis (swelling of one or more digits/fingers that extends beyond the joint margins), nail pitting or onycholysis, and a family history of psoriasis in a first-degree relative [2]. Approximately half of the children with JPsA develop the skin disease years after the onset of arthritis. Other criteria for the diagnosis of JPsA are the so-called Vancouver criteria (Table 17.4). The main difference between these two sets of criteria is that Vancouver criteria lack exclusion criteria that are present in the ILAR criteria; this is relevant because according to ILAR criteria, a diagnosis of JPsA cannot be made if the arthritis begins in a boy over the age of 6 years who is HLA-B27 positive or in the presence of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis or a history of one of these disorders in a first-degree relative [82].

The frequency of JPsA ranges from 5–10% for all JIA cases using the ILAR criteria [12, 47, 83–85] to 8–20% of patients with JIA [83, 85, 87] when the more inclusive Vancouver criteria are employed. Age of onset data suggests a biphasic distribution, with a peak around age 2–3 years and a second peak in adolescence [88, 89]. The definition of JPsA is controversial [90]. This subtype does not represent a clearly defined entity: it encompasses, in fact, a heterogeneous set of arthritic phenotypes characterized by certain hallmark clinical features as well as considerable overlap with other subtypes of JIA. Younger children (<5 years old), most commonly female and with ANA-positive test, tend to develop asymmetric oligoarthritis and have a high risk of chronic iridocyclitis [85, 91]. This subgroup appears very similar to the early-onset oligoarticular JIA, the main difference being that patients with JPsA tend in some series to develop more frequently a polyarticular course. By contrast, older-onset JPsA patients exhibit a gender ratio closer to 1:1, with a tendency to enthesitis and to develop sacroiliitis during follow-up, similar to several adult patients with psoriatic arthritis who share features with spondyloarthropathies [85, 91–94]. The ILAR classification, in which patients with enthesitis are by definition excluded, by default defers the latter group to the category of undifferentiated arthritis. Arthritis in JPsA begins as an oligoarthritis in approximately 80% of children with the knee most frequently affected, followed by the ankle, wrists, and small joints of the hands [95]. In children with JPsA, dactylitis, which is included in the diagnostic criteria, is observed in 20–40% of patients; its swelling is typically uniform, giving the appearance of a "sausage digit" (Figs. 17.3 and 17.4). Ultrasound (US) exami-





Figs. 17.3 and 17.4 Dactylitis in a patient with psoriatic arthritis. The swelling is typically uniform giving the appearance of a "sausage digit"

nation shows tenosynovitis of the digit flexor tendons as a dominant finding, with or without synovitis in the adjacent joints. Subperiosteal new bone growth can also increase the thickness of the digit. Overt psoriasis occurs in 40–60 % of patients with JPsA usually as the classic vulgaris form [83, 86, 91]. Prevalence of nail changes in JPsA cases is seen in approximately 50–80 % [85, 91]. As in other JIA subsets, young patients with ANA positivity are at highest risk of chronic uveitis, and periodic screening with slit lamp should be performed. Acute anterior uveitis can occur in older children, usually associated with the presence of HLA-B27 [92].

Laboratory tests are of limited diagnostic value in JPsA. Inflammatory markers, including ESR and CRP, may exhibit mild to moderate elevation, but are frequently normal [85, 91].

The long-term prognosis of PsA is not well defined, due to its heterogeneity and the lack of available information.

Undifferentiated Arthritis

Approximately 15 % of children with chronic arthritis are classified as belonging to a seventh category, undifferentiated arthritis [2]. This category does not represent a separate subset, but includes patients who do not fulfill inclusion criteria for any category or who meet the criteria for more than one category.

Future Perspectives for JIA Classification

The ILAR classification, which was conceived as "work in progress," has been recently criticized since there is evidence that while some categories represent quite definite disease entities, others still include heterogeneous disorders [50, 96]. Pivotal genetic and immunological studies, by improving the link between immunopathogenesis and clinical disease phenotypes, have enhanced the need to refine the classification criteria to better identify clinically homogeneous entities [97]. Systemic JIA appears to be a syndrome which includes a group of disorders characterized by an autoinflammatory hallmark. This group should include patients with systemic features without arthritis, as in adults, and switching the nomenclature similar to that used by the adult physicians, by adopting the name "Still's disease," might therefore be considered [96]. Enthesitis-related arthritis (ERA) is a form of undifferentiated spondyloarthritis. It would be advisable to substitute the term "juvenile spondyloarthropathy" in place of ERA which suggests a childhood-specific arthritis not observed in adults [96]. Early-onset, ANA-positive oligoarthritis is a well-defined entity that is seen only in childhood. There is clear evidence that some patients with this disease are mistakenly classified into other categories (RF-negative polyarthritis, PsA). These patients should be grouped together in the new category of

ANA-positive, early-onset arthritis independent of the number of affected joints or the presence of some psoriatic features [50, 51, 77, 96]. Once this group of patients is removed from RF-negative polyarthritis, the remaining patients will presumably be represented by patients with RF-negative symmetric polyarthritis, similarly to their adult counterpart; likewise, when patients with early-onset ANA-positive arthritis are removed from the PsA category, the rest of the patients would have similar characteristics of adult PsA. Therefore, the number of joints involved or the presence of psoriasis should no longer represent by themselves a major classification criterion [50]. Overall, it is now clear that in children, as in adults, there are several different diseases which are all responsible for chronic arthritis. With the exception of early-onset ANA-positive arthritis, which is observed only in childhood, they seem to represent the childhood counterpart of adult diseases. Aligning JIA classification to adult nomenclature would alter the misleading concept that JIA is a single disease and that the various categories represent just phenotypic variants.

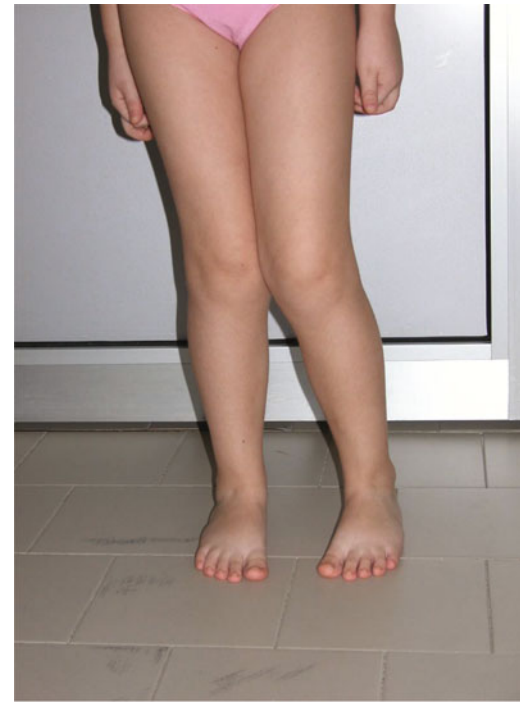


Fig. 17.5 Valgus knee secondary to joint contractures in a patient with oligoarticular juvenile idiopathic arthritis

Management

The past decade has witnessed major advances in the treatment of JIA. The main aims of these medications are to achieve complete control of the disease with normalization of physical findings and laboratory markers of inflammation, to preserve the physical and psychological integrity of the child, and to prevent any long-term consequences related to the disease or its therapy. There is evidence that a prompt control of inflammation improves the outcome and can prevent long-term sequelae [98, 99].

Since JIA is not a single disease, different therapeutic approaches should be adopted according to the diverse onset subtypes. Nonetheless, general guiding principles may be considered [100]. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are the initial treatment for the majority of JIA patients. Just a few NSAIDs are approved for use in children. The most common includes naproxen, ibuprofen, indomethacin, and meloxicam, an inhibitor of both cyclooxygenase 1 (COX1) and COX2 [101]. These are generally well tolerated, and unlike in adults fewer side effects are reported. However the majority of patients require a better control of inflammation than that achieved with NSAIDs alone. Intra-articular steroid injections are commonly needed at disease onset or during disease course since their quick effectiveness is pivotal in the prevention of deformities, e.g., valgus knee (Fig. 17.5), secondary to joint contractures, which represents an important source of damage in JIA. The long-acting steroid triamcinolone hexacetonide is used worldwide since its induced remission lasts much longer compared to other steroids [102, 103]. To inject smaller joints and those not easily reached, it is advisable however to use a more soluble corticosteroid preparation such as methylprednisolone acetate [104]. Patients who do not respond effectively to these approaches need systemic therapy with second-line agents. Due to its effectiveness and acceptable level of toxicity, methotrexate (MTX) is

considered the second-line agent of choice for persistent active arthritis [105–108]. Its efficacy begins after a lapse of 1–3 months; therefore, especially in patients with severe polyarthritis, a short course of low-dose prednisone might be considered as a bridging agent until MTX is effective. Its most common side effects are nausea, mouth sores, abdominal pain, raised liver enzymes, and, less commonly, hair loss and bone marrow suppression. Monthly blood tests should be performed to monitor liver function and bone marrow abnormalities. To reduce the side effects, supplementation with folic or folinic acid should be concomitant [109, 110]. Another second-line agent is leflunomide: although its efficacy in polyarticular JIA has been recently demonstrated in a clinical trial [111], its use in children is still limited. Overall MTX is effective in about 70 % of children with polyarthritis. For those unresponsive or intolerant to conventional antirheumatic agents, the introduction of biological medications should be considered. The soluble TNFα receptor, etanercept, was the first biologic to be registered for the treatment of children with polyarthritis/extended oligoarthritis [112]. Long-term follow-up registries for use of etanercept in JIA show tolerable side effects [113, 114]. Subsequently, other biological agents have been registered for the use in JIA. In a randomized discontinuation trial, adalimumab, a fully humanized monoclonal antibody to TNFα, showed a good efficacy in children with polyarticular JIA in combination with methotrexate or alone [115]. Furthermore, adalimumab seems to be the anti-TNF of choice in case of JIA-associated uveitis. Since cases of reactivated tuberculosis have been reported during treatment with TNF inhibitors, all children must be negative for tuberculosis tests before starting TNFα-blocking agents. Abatacept, CTLA-4 Ig, an inhibitor of costimulatory signals during antigen presentation, is an approved therapeutic option for patients with polyarthritis who are resistant to TNFα inhibitors [116, 117]. Infliximab is a chimeric monoclonal antibody against TNFα; although effective it is not registered for use in JIA [118]. Finally, the efficacy and safety of the interleukin-6 receptor inhibitor (tocilizumab) for the treatment of patients with polyarticular-course JIA have been recently demonstrated in a randomized, double-blind withdrawal trial [119]. Details on mechanism of action, safety profile, and posology of biological agents will be provided in a separate chapter. Although some expert-opinion recommendations for starting specific immunosuppressive therapies in JIA are available, reliable data for withdrawal of treatment are almost completely missing.

Treatment of Chronic Uveitis

Early diagnosis is essential for successful therapy of uveitis. The initial approach consists of topical corticosteroids (such as dexamethasone or methylprednisolone) and mydriatic eye drops to prevent the development of posterior synechiae. In patients with disease resistant to topical therapy, systemic steroid administration (prednisone 1–2 mg/kg/d orally) or methylprednisolone (30 mg/kg intravenously on 1–3 consecutive days) or subtenon injection of glucocorticoid is indicated. Limited response to systemic corticosteroid requires initiation of a second-line therapy, most commonly methotrexate [120]. The efficacy of cyclosporine in treatment of uveitis in patients with JIA is controversial [121, 122], whereas infliximab and adalimumab have been reported to be beneficial [123–127]. For patients who have failed therapy with TNF inhibitors, there is minimal data to guide subsequent management. There have been successful case reports with mycophenolate mofetil [128], abatacept [129], and rituximab [130, 131].

Prognosis and Outcome

The prognosis of patients with JIA has improved considerably in recent decades. The outcome of JIA is variable, even in the same JIA category, and it is difficult at the disease onset to predict which children will recover and which will go on to have unremitting disease with substantial risk of joint destruction and serious functional impairment. Although several indicators of a poor outcome

have been identified, including polyarticular onset of JIA, symmetrical disease, early wrist or hip involvement, the presence of RF, persistent active disease, and early radiographic changes [106, 132], the prediction of disease outcome in any individual patient remains unsatisfactory.

Although there is a large variability among studies, about 50 % of patients seem to enter adult age with active disease [133–139]. The rate of remission varies significantly with the type of disease onset, being the best for persistent oligoarthritis [140, 141]. A pronounced improvement in functional outcome has been documented in the past decade, with the proportion of patients with serious functional disability (e.g., Steinbrocker functional class III or IV at follow-up) ranging from 2.5 % to 10 % [135]. According to the results from a more sensitive measure of function, the Health Assessment Questionnaire (HAQ), approximately 40 % of young adults with JIA are somewhat limited in their functional capacity (HAQ > 0), but only 10 % are in need of assistance or aids to manage their daily routines [132].

It should be considered, however, that most of the long-term outcome studies refer to an era in which biological agents were not available. It is conceivable that the introduction of new potent therapies will further improve the long-term prognosis of children with JIA.

Through the integration of clinical medicine with genetics and immunological markers and with advanced imaging analysis, a considerable improvement in the prediction of the disease outcome is also on the horizon.

Conclusion

This chapter has outlined the current classification system of JIA as set forth by the ILAR. This classification is a work in progress and as discussed is not defining entirely homogeneous groups of patients. The subtypes of JIA are indeed different diseases and not different phenotypes of one disease. The management of these children has been briefly discussed, and it is emphasized that early diagnosis and rapid attainment of remission are important to the long-term outcome.

Take-Home Messages

1. JIA is a heterogeneous group of diseases grouped under one umbrella term.
2. The etiopathogenesis involves an interplay of the innate and adaptive immune system in a genetically susceptible host.
3. The clinical presentation, joint involvement, and uveitis risk differ in various subcategories.
4. The current ILAR classification system may not be fully identifying homogeneous groups of patients.

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