CHAPTER 7

Juvenile Idiopathic Arthritis
A. Clinical Features

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- Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis and one of the more common chronic childhood illnesses.
- JIA is an umbrella term that refers to a group of disorders that have in common chronic arthritis.
- Diagnosis requires a combination of data from history, physical examination, and laboratory testing.
- For the vast majority of patients with JIA, the immunogenetic associations, clinical course, and functional outcome are quite different from adult-onset rheumatoid arthritis.

Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis and one of the more common chronic childhood illnesses. As the term indicates, the cause is unknown. In fact, JIA is an umbrella term that refers to a group of disorders that have in common chronic arthritis. Diagnosis requires a combination of data from history, physical examination, and laboratory testing. For the vast majority of patients with JIA, the immunogenetic associations, clinical course, and functional outcome are quite different from adult-onset rheumatoid arthritis (RA). However, approximately 5% to 10% of those with JIA (those classified as polyarthritis rheumatoid factor positive) have a disease that resembles adult-onset RA much more than other types of JIA. The JIA nomenclature has in most instances replaced the older classification for chronic idiopathic arthritis in childhood—juvenile rheumatoid arthritis (JRA). The differences and similarities in the two classifications will be discussed below. In fact, this is the first edition in which the term *juvenile idiopathic arthritis* is being used in the *Primer on the Rheumatic Diseases*.

EPIDEMIOLOGY

The prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years in population-based studies (1–8). In a meta-analysis including both practitioner- and clinic-based studies, a prevalence of 132 per 100,000 [95% confidence interval (95% CI), 119,145] was reported (9). In a population-based study from Sweden, Andersson-Gäre and Fasth reported that 50% of JIA patients have active disease that persists into adulthood (5). Many of the published prevalence studies have not included adult-age JIA patients, resulting in an underestimation. The incidence ranges between 7 to 21 per 100,000 people in studies of US- and Northern European–based populations (1,9,10). All the incidence and prevalence estimates have wide confidence intervals because of the relative rarity of JIA and the small number of actual cases detected in even the largest studies. This leads to enormous differences between the lower and upper estimates of actual JIA cases. The most commonly cited figure is 70,000 to 100,000 cases (active and inactive) of JIA in the US population under age 16 (1). Using Andersson-Gäre and Fasth's report on disease persisting into adulthood, an estimated 35,000 to 50,000 people over age 16 have active JIA in the United States (5).

Juvenile idiopathic arthritis affects a much smaller portion of the US population than adult-onset RA. However, compared to other pediatric-onset chronic illnesses, JIA is relatively common, affecting approximately the same number of children as juvenile diabetes, at least four times as many children as sickle cell anemia or cystic fibrosis, and at least 10 times as many as hemophilia, acute lymphocytic leukemia, chronic renal failure, or muscular dystrophy (6).

CLINICAL FEATURES

The criteria for JIA require disease onset before the 16th birthday, persistent objective arthritis in one or more joints for at least 6 weeks, and exclusion of other

causes of childhood arthritis (7,11,12). Misdiagnosis often results when one or more of the following four key points are missed: (1) objective arthritis must be present and is defined as swelling, effusion, or the presence of two or more of the following—limitation of motion, tenderness, pain on motion, or joint warmth (i.e., arthralgia alone is not sufficient); (2) the arthritis must be consistently present for at least 6 weeks; (3) more than 100 other causes of chronic arthritis in children must be excluded; and (4) no specific laboratory or other test can establish the diagnosis of JIA, that is, it is a diagnosis of exclusion.

Juvenile idiopathic arthritis is subdivided into seven categories: systemic, polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, oligoarthritis (subcategories of persistent and extended), psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis (11,12; Table 7A-1). These subtypes demonstrate unique clinical presentations, immunogenetic associations, and clinical courses (Table 7A-2). The categories of JIA are meant to be mutually exclusive so that the inclusion criteria for one classification are also used as exclusion criteria for the other categories. For those patients who fit into more than one

TABLE 7A-1. CLASSIFICATION CRITERIA FOR JUVENILE IDIOPATHIC ARTHRITIS, SECOND REVISION, EDMONTON, 2001.

CLASSIFICATION	DESCRIPTION	PERCENTAGE OF JIA POPULATION
Systemic	Arthritis with or preceded by daily fever of at least 2 weeks duration, documented to be quotidian for at least 3 days, and accompanied by at least one of the following: rheumatoid rash, generalized lymphadenopathy, hepato- or splenomegaly and serositis Exclusions: a,b,c,d	2%–17%
Oligoarthritis, subcategory persistent	Arthritis in ≤four joints at any time during the onset or course of the disease Exclusions: a,b,c,d,e	12%–29%
Oligoarthritis, subcategory extended	Arthritis in ≤four joints in first 6 months of disease but affecting a cumulative total of ≥five joints after the first 6 months Exclusions: a,b,c,d,e	12%–29%
Polyarthritis rheumatoid factor negative	Arthritis affecting ≥five joints during first 6 months with negative tests for rheumatoid factor Exclusions: a,b,c,d,e	10%–28%
Polyarthritis rheumatoid factor positive	Arthritis affecting ≥five joints during first 6 months and positive test for rheumatoid factor at least twice at least 3 months apart Exclusions: a,b,c,e	2%–10%
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis plus any two of the following: Sacroiliac joint tenderness and/or inflammatory lumbosacral pain Positive HLA-B27 Physician-diagnosed HLA-B27–associated disease in first- or second-degree relative Symptomatic anterior uveitis Male > 6 years old at onset of arthritis or enthesitis Exclusions: a,d,e	3%–11%
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: Physician-diagnosed psoriasis in first-degree relatives Dactylitis Nail abnormalities (pitting or onycholysis) Exclusions: b,c,d,e	2%–11%
Undifferentiated	Arthritis but does not fulfill any of the above categories or fits into more than one category Exclusions: Not applicable	2%–23%

SOURCE: Data from Petty RE, Southwood TR, Manners P, et al. J Rheumatol 2004;31:390–392, *Journal of Rheumatology*.
Exclusion criteria:
(a) Psoriasis or a history of psoriasis in the patient or a first-degree relative.
(b) Arthritis in an HLA-B27–positive male beginning after the 6th 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.

TABLE 7A-2. JUVENILE IDIOPATHIC ARTHRITIS CATEGORY CHARACTERISTICS.

CHARACTERISTIC	sJIA	poJIA RF+	poJIA RF–	oJIA, PERSISTENT	oJIA, EXTENDED	pJIA	eJIA	uJIA
Number of joints with arthritis at onset	Variable	≥5	≥5	≥4	≥5	Variable	Variable	Variable
Sex ratio (F:M)	1:1	3:1	3:1	4:1	4:1	1:1	1:7	1:1
Frequency of uveitis (% of patients in that JIA category)	0%–2%	3%–10%	3%–10%	30%–50%	15%–20%	5%–20%	≤25% (acute)	••
Frequency of +RF on at least two occasions in first 6 months of disease (% of patients in the JIA category)	0%	100%	0%	0%	0%	0%	0%	3%–5%
Frequency of ≥5 joints involved during course of disease (% of patients in the JIA category)	50%	100%	100%	0%	100%	6–55%	50%	••
Percentage in clinical remission at last F/U[a]	33%–80%	0%–15%	23%–46%	43%–73%	12%–35%	–	–	–
Percentage in Steinbrocker functional class III or IV at last F/U[a]	0%–65%	5%–38%	3%–41%	0%–7%	36%–43%	–	–	–
Percentage with radiographic evidence of joint damage at last F/U[a]	14%–75%	75%–77%	40%–43%	5%–27%	25%–33%	–	–	–

ABBREVIATIONS: eJIA, enthesis-related JIA; F/U, last follow-up visit in published studies; JIA, juvenile idiopathic arthritis; oJIA, oligoarticular JIA; pJIA, psoriatic JIA; poJIA, polyarthritis JIA; RF, rheumatoid factor; sJIA, systemic JIA; uJIA, undifferentiated JIA.
[a] Data taken from meta-analysis of outcome studies in JIA and JRA populations.[17]

category or who do not satisfy all the inclusion criteria for one of the other categories, the undifferentiated arthritis category is to be used. In both the older JRA criteria, and even more so with the JIA criteria, the concept is that these systems are classifying within a single umbrella term different forms of chronic arthritis (11,12). The JIA classification was intended to have ongoing validation by both clinical and immunogenetic methods to assess the homogeneity and stability of the diagnostic categories and, if necessary, change the categories on the basis of published data (12).

In addition to the inclusion criteria, for each of the JIA categories the relevant *exclusion criteria* for that category will be indicated using the letter of the criteria in this listing:

(a) psoriasis in the patient or a first-degree relative;
(b) arthritis in a human leukocyte antigen (HLA)-B27–positive male with arthritis onset after 6 years of age;
(c) anklyosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis in a first-degree relative;
(d) presence of IgM rheumatoid factor on at least two occasions more than 3 months apart;
(e) presence of systemic JIA in the patient.

JUVENILE IDIOPATHIC ARTHRITIS, SYSTEMIC CATEGORY

Approximately 2% to 17% of children with JIA have systemic juvenile idiopathic arthritis (sJIA) (12). Classification as systemic JIA requires that the child demonstrate daily fever of at least 2 weeks duration that for at least three of those days is documented to be quotidian (defined as a daily recurrent fever that rises to ≥39°C once a day and returns to 37°C or below between fever spikes) and at least *one* of the following: (a) an evanescent, nonfixed, erythematous rash; (b) generalized lymph node enlargement; (c) hepatomegaly and/or splenomegaly; (d) serositis (pericardial, pleural or peritoneal). Systemic JIA is excluded if criteria a, b, c, or d from the list of exclusion criteria are present.

The characteristic rash is pale pink, blanching, transient (lasting minutes to a few hours), nonpuritic in 95% of cases, and characterized by small macules or maculopapules. Children with sJIA often have growth delay, osteopenia, diffuse lymphadenopathy, hepatosplenomegaly, pericarditis, pleuritis, anemia, leukocytosis, thrombocytosis, and elevated acute-phase reactants. Positive rheumatoid factor (RF) and uveitis are rare. The extra-articular features are usually mild to moderate in severity and almost always self-limited. Most systemic features will resolve when the fevers resolve; however, sJIA patients can develop pericardial tamponade, severe vasculitis with secondary consumptive coagulopathy, and macrophage activation syndrome, all of which require intense steroid therapy.

The long-term prognosis for sJIA is determined by the severity of the arthritis, which usually develops concurrently with the fever and systemic features, but in some patients does not develop for weeks or months after the onset of the fever. sJIA may develop at any age <16 years, but the peak age of onset is 1 to 6 years old. Boys and girls are equally affected.

JUVENILE IDIOPATHIC ARTHRITIS, POLYARTHRITIS RHEUMATOID FACTOR POSITIVE AND RHEUMATOID FACTOR NEGATIVE CATEGORIES

To be characterized as having polyarthritis juvenile idiopathic arthritis (poJIA), a child must have arthritis in five or more joints during the first 6 months of the disease. To be classified as poJIA, exclusion criteria a, b, c, and e must be absent. To be considered RF+, the patient must have at least two positive results for RF at least 3 months apart during the first 6 months of disease.

Approximately 2% to 10% of all children with JIA have polyarthritis juvenile idiopathic arthritis rheumatoid factor positive (poJIA RF+) and 10% to 28% have polyarthritis juvenile idiopathic arthritis rheumatoid factor negative (poJIA RF–) (12). poJIA RF+ patients are almost always girls with later disease onset (at least 8 years old) who are usually HLA-DR4 positive, have symmetric small joint arthritis, and are at greater risk for developing erosions, nodules, and poor functional outcome compared with RF– patients. poJIA RF+ resembles adult-onset RA more than any other JIA subset. Clinical manifestations and outcome of both poJIA categories are highly variable, and include fatigue, anorexia, protein–caloric malnutrition, anemia, growth retardation, delay in sexual maturation, and osteopenia. poJIA may develop at any age less than 16 years, and girls with poJIA outnumber boys with this form 3 to 1.

JUVENILE IDIOPATHIC ARTHRITIS, OLIGOARTHRITIS

To be characterized as having oligoarthritis juvenile idiopathic arthritis (oJIA), a child must have arthritis in four or more joints during the first 6 months of the disease. Relevant exclusion criteria are a, b, c, d, and e. oJIA patients are divided into two subcategories: persistent and extended. Persistent oJIA patients never have a cumulative total of more than four joints with arthritis during the course of the disease and extended oJIA patients demonstrate a cumulative total during the course of the disease of arthritis in five or more joints after the first 6 months of the disease. oJIA is the most frequent of the JIA categories (24%–58% of all JIA patients) (12). Persistent oJIA has the best overall articular outcome of all JIA categories. Up to half of the persistent oJIA patients will demonstrate monoarticular involvement in a knee joint (13). The severity of joint symptoms in these patients is usually very mild and it is not uncommon for these children to present with normal or near normal overall physical function, joint swelling, and loss of motion in the knee. Up to 50% of oJIA cases will evolve to the extended subcategory and 30% will do so in the 2 years after disease onset. Risk factors in the first 6 months of disease onset for developing oJIA, extended subcategory (i.e., more extensive and severe articular involvement), are arthritis in the wrist, hand or ankle; symmetric arthritis, arthritis in more than one joint; elevated erythrocyte sedimentation rate (ESR) and positive antinuclear antibodies (ANA) (13). Patients with oJIA are commonly younger (1–5 years old at onset), are more likely to be girls (girls outnumber boys 4 to 1), are often ANA positive, and have the greatest risk for developing chronic eye inflammation (7). Eye involvement occurs in 30% to 50% of oJIA patients (7,13). The inflammatory process primarily involves the

TABLE 7A-3. AMERICAN ACADEMY OF PEDIATRICS GUIDELINES FOR SCREENING EYE EXAMINATIONS ADAPTED FOR JUVENILE IDIOPATHIC ARTHRITIS.

DISEASE SUBGROUP	FREQUENCY OF SCREENING
Any JIA category except sJIA, ≤6 years old at JIA onset, ANA+	Every 3–4 months for 4 years, then every 6 months for 3 years, then annually
Any JIA category except sJIA, ≤6 years old at JIA onset, ANA–	Every 6 months for 4 years, then annually
Any JIA category except sJIA, ≥7 years old at JIA onset, ANA+/–	Every 6 months for 4 years, then annually
sJIA	Annually

SOURCE: Adapted from Cassidy J, Kivlin J, Lindsley C, Nocton J, Pediatrics 2006;117:1843–1845, by permission of *Pediatrics.*
ABBREVIATIONS: JIA, juvenile idiopathic arthritis; sJIA, systemic JIA.

anterior chamber of the eye and is associated with minimal, if any, symptoms in more than 80% of affected children. Because severe, irreversible eye changes, including corneal clouding, cataracts, glaucoma, and partial or total visual loss, can occur, patients should be screened at regular intervals and treated by experienced eye specialists (Table 7A-3).

The risk for persistent articular disease is very different for the oJIA subtypes. In one study, 75% of the patients with persistent oJIA achieved remission by adulthood compared to only 12% of those with extended oligoarticular JIA (13).

JUVENILE IDIOPATHIC ARTHRITIS, PSORIATIC ARTHRITIS

In contrast to the JRA criteria, patients demonstrating arthritis in association with psoriasis are included in the JIA classification. Patients manifesting chronic arthritis in association with psoriasis with an onset at or before the age of 16 are said to have psoriatic juvenile idiopathic arthritis (pJIA). However, the classic psoriatic rash may not appear for many years after the onset of the arthritis. In published studies, 33% to 62% of the patients will not, in the past or at the time the arthritis develops, demonstrate any of the dermatologic manifestations. Only about 10% of children have the onset of the rash and the arthritis at the same time. In the rest of the patients (33%–67%), the rash comes first (7). Accordingly, the JIA criteria allow for children to be classified as having psoriatic arthritis if they have arthritis and at least two of the following three criteria: dactylitis, nail pitting or onycholysis, and psoriasis in a first-degree relative. The psoriasis has to be diagnosed by a physician. The relevant exclusion criteria are b, c, d, and e. In the JIA criteria, *dactylitis* is defined as swelling of one or more digits, usually in an asymmetric distribution, that extends beyond the joint margin and *nail pitting* is defined as a minimum of two pits on one or more nails at any time. *Onycholysis* is not specifically defined in the JIA criteria but refers to the partial loosening or complete detachment of the nail from the nail bed. pJIA accounts for 2% to 11% of all JIA cases (12).

In the vast majority of cases of pJIA, the arthritis is peripheral, asymmetric, and often involves the knees, ankles, and small joints of the hands and feet. The dactylitis ("sausage digit") involves inflammation of not only the small joints of the toes or fingers but also the tendon sheath. The dactylitis is often surprisingly asymptomatic despite obvious swelling and loss of motion in the digit. At onset, about 70% of the pJIA patients have arthritis in four or more joints. In longitudinal studies, during the course of the disease, about 40% (range, 11%–100%) of pJIA patients demonstrated involvement of the sacroiliac joint (7).

Asymptomatic chronic anterior chamber uveitis clinically indistinguishable from that seen in oJIA develops in up to 20% of these patients (7,13). Accordingly, following the usual recommendations for routine slit lamp of the eyes, as described in Table 7A-3, is required in pJIA.

JUVENILE IDIOPATHIC ARTHRITIS, ENTHESITIS RELATED

This category addresses the fact that in children the axial manifestations of spondyloarthropathy may not become evident for many years. Children are classified as enthesitis juvenile idiopathic arthritis (eJIA) if they have both arthritis and enthesitis or have either arthritis or enthesitis with any two of the five following manifestations: (1) sacroiliac tenderness and/or inflammatory lumbosacral pain; (2) positive HLA-B27; (3) onset of arthritis in a male ≥6 years old; (4) acute (symptomatic) anterior uveitis; and (5) presence in a first-degree relative of ankylosing spondylitis, enthesitis-related arthritis, inflammatory bowel disease with sacroiliitis, reactive arthritis or acute anterior uveitis. The relevant exclusion criteria are a, d, and e. About 10% of all JIA patients are classified as eJIA (12).

Enthesitis refers to inflammation at the insertion of the tendon, ligament, joint capsule, or fascia into the bone. The most frequent manifestations are pain and tenderness at the enthesis but swelling is also seen at the site. Enthesitis is not specific for pJIA and is sometimes seen in other JIA categories, systemic lupus erythematosus (SLE), and healthy active children (7). The most common sites for enthesitis include the superior curve of the patella, infrapatellar at the tibial tuberosity,

attachment of the Achilles tendon, back of the foot (attachment of plantar fascia to the calcaneous), and sole of the foot at the metatarsal heads (7).

In contrast to the JRA criteria, patients with arthritis in association with inflammatory bowel disease can be classified as eJIA if the inclusion and exclusion criteria are satisfied. In patients with inflammatory bowel disease, the articular involvement may precede the gastrointestinal (GI) inflammation by months to years. Clues to the presence of GI involvement include fatigue, weight loss, growth failure, nocturnal bowel movement, mouth ulcers, erythema nodosum, pyoderma gangrenosum, and anemia (more severe than normally seen in association with the extent of the arthritis).

Patients with eJIA may also demonstrate involvement in other areas. Acute uveitis characterized by intermittent episodes of red, photophobic, painful ocular inflammation (usually unilateral) may occur in up to 25% of eJIA patients. Aortic involvement with aortic valve insufficiency has been rarely reported in children with eJIA (7).

At disease onset, the articular involvement includes peripheral arthritis in approximately 80% of eJIA patients and only 25% will have symptoms or physical findings involving the sacroiliac or lumbar spine areas. In about 85% of the patients, the arthritis will involve four or more joints. Because the eJIA criteria are relatively new and the axial manifestations can evolve very slowly, no publications provide longitudinal data specific to eJIA. Data from older related diagnostic categories can be used to give some insight as to the risk for axial involvement over time. In children diagnosed as having seronegative enthesitis and arthritis syndrome (SEA syndrome), after 11 years of follow-up, 65% had evolved to have clinically important axial involvement. In those diagnosed with juvenile ankylosing spondylitis, over 90% eventually manifest clinically important lumbar spine and/or sacroiliac (SI) joint involvement (7).

In eJIA, tests for ANA and RF are negative, and plain radiographs often do not show the characteristic changes in the SI or lumbosacral spine for many years. Bone scans are seldom helpful because radioisotope uptake is typically increased in the SI joints and the lumbar spine in all children as a consequence of skeletal growth. Computed tomography (CT) and magnetic resonance imaging (MRI) scans can be useful studies if interpreted by a radiologist familiar with axial imaging of children. There are no pathognomonic laboratory tests.

JUVENILE IDIOPATHIC ARTHRITIS, UNDIFFERENTIATED

Patients are placed in the undifferentiated juvenile idiopathic arthritis (uJIA) category if the manifestations do not fulfill the inclusion criteria for any category or the patient fulfills criteria for more than one category. In the published series, 2% to 23% of all JIA patients were classified as uJIA. In those classified as uJIA, 60% failed to demonstrate characteristics that fulfilled the eligibility criteria for one of the other JIA categories and 40% demonstrated criteria from more than one JIA category (12). In those fitting more than one category, the overlap was most commonly between the poJIA RF– category and either the eJIA or the pJIA categories. Some children overlapped the oJIA category with either the eJIA or pJIA categories (12). Longitudinal studies need to be performed to determine the eventual diagnoses in the patients placed in the uJIA category to see how many will remain as uJIA and how many will evolve to fulfill the criteria for one of the other JIA categories or diseases other than JIA.

OCULAR INVOLVEMENT IN JUVENILE IDIOPATHIC ARTHRITIS

A unique manifestation of JIA is chronic uveitis. A meta-analysis of 21 published studies on uveitis in children with JIA with a combined 4598 JIA patients (13). The data demonstrated that there are obvious differences in the incidence of uveitis in JIA patients based on geographic distribution. In Scandinavian studies, 18.5% of patients demonstrated uveitis, in studies from the United States 14.5% of patients demonstrated uveitis, and in studies from East Asia only 4.5% of patients demonstrated uveitis. The frequency of uveitis varies by JIA subtype—12% of children with oJIA, 4.3% of poJIA, and 1.8% of sJIA patients developed chronic uveitis. Other studies have documented that up to 20% of children with pJIA will develop chronic uveitis identical to the chronic uveitis associated with oJIA in terms of manifestations, chronicity, and ocular outcomes (7).

Uniform adoption of early and routine screening guidelines have been developed and recently updated (2006) by the American Academy of Pediatrics Sections of Ophthalmology and Rheumatology for children with JRA (Table 7A-3) (14). The recommendations were based on factors known to be associated with an increased frequency of developing uveitis in children with JRA: articular features, age at onset of the arthritis, duration of disease, and presence of ANA. These same factors relate to the uveitis risk for JIA categories and should be applied as shown in Table 7A-3. Despite general adoption of routine screening for uveitis and rapid institution of treatment, the outcome for chronic uveitis in children with JIA is still associated with an unacceptably high frequency of serious complications. In this meta-analysis, in the JIA patients with uveitis, 20% developed cataracts, 19% developed glaucoma,

and 16% developed band keratopathy (13). The identification of effective treatments for JIA-associated uveitis that are able to avoid or minimize the eye damage associated with chronic steroid treatment and chronic inflammation of the eyes is an important and unsolved problem at this time.

OUTCOME

In a recent meta-analysis of outcome studies in children with chronic idiopathic arthritis, only 2 of the 21 studies reviewed used the JIA classification criteria (15). In a summary of published outcome studies, more than 30% of people with childhood-onset idiopathic chronic arthritis (most frequently classified as having one of the JRA subtypes) had significant functional limitations after 10 or more years of follow-up (16). Twelve percent were in Steinbrocker classes III (limited self-care) or IV (bed or wheelchair bound) 3 to 7 years after disease onset, but 48% were classified in class III or IV 16 or more years after disease onset (7). Active synovitis can be detected in 30% to 55% of the patients 10 years after disease onset (16). In a longitudinal study of JRA patients referred to a pediatric rheumatologist within the first 6 months of disease onset, 28% of the pJRA, 54% of the poJRA, and 45% of the sJRA patients demonstrated either erosions or joint-space narrowing on standard radiographs during follow-up (16). In an analysis of outcome studies published after 1994 that are thought to reflect the positive impact of at least some of the recent therapeutic advances, only 40% to 60% of the JIA patients demonstrated either inactive disease or remission, and on average 10% demonstrated severe functional limitation (Steinbrocker functional class III or IV) (17).

Mortality estimates have ranged from 0.29 to 1.10 per 100 patients. These estimates represent a mortality rate 3 to 14 times greater than the standardized mortality rate for a similarly aged US population (16).

The outcome for JRA patients with uveitis has significantly improved over the past several decades, but is still associated with an unacceptably high rate of ocular complications. In the most recent study of ocular outcomes, at a mean follow-up of 9.4 years since onset of eye disease, 85% of patients had normal visual acuity but 15% had significant visual loss, including 10% who were blind in at least one eye (7).

SUMMARY

Juvenile idiopathic arthritis is the most common chronic arthritis in children, the most common inflammatory rheumatic disease in children, and still a cause of significant morbidity and increased mortality. Each of the JIA categories has characteristic manifestations, complications, and outcomes. Familiarity with the different types of JIA will facilitate earlier diagnosis, awareness of potential problems, and, initiation of proper treatment.

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CHAPTER 7

Juvenile Idiopathic Arthritis
B. Pathology and Pathogenesis

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- Juvenile idiopathic arthritis (JIA) is an umbrella term for a heterogeneous group of childhood onset, inflammatory forms of arthritis.
- T-cell and cytokine profiles vary according to the JIA subtype.
- Gene variations in the human leukocyte antigen (HLA) region of chromosome 6 are associated with different types of subtypes of JIA except systemic-onset JIA.

Juvenile idiopathic arthritis (JIA) is the umbrella term for a heterogeneous group of childhood onset arthritides lasting more than 6 weeks. The current international classification system proposed by International League of Associations for Rheumatology (ILAR) (1) defines clinical differences between the groups. However, within each group there is also a clinical spectrum of disease duration and severity. Some of this may be defined by genetic markers/susceptibility genes. This chapter aims to describe common and discriminative features between the groups from the pathological and genetic points of view.

OLIGOARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Children with oligoarticular JIA have four or fewer joints affected at the onset of disease. There are two recognizable clinical subtypes with different disease courses: persistent oligoarthritis (PO) and extended oligoarthritis (EO). Oligoarthritis patients have milder disease and many have spontaneous remission. In addition, all patients in this group can have anterior uveitis.

The Synovium and Synovial Fluid

There is no distinction in the histology of the synovial tissues in inflamed joints, whether adult onset or childhood onset; that is, there is infiltration of lymphocytic and monocytic cells as well as abundant neutrophils. However, there are differences in the types of T cells and the cytokines produced between the JIA subtypes.

The immunohistochemistry of the synovial membranes of a mixed group of JIA patients were examined for cytokine production by T cells and a type 1 immune response was found (2). Furthermore, the analysis of synovial fluid (SF) T-cell markers has shown that the difference between T cells in PO and EO is the presence of regulatory T cells in the milder PO, consistent with the current hypothesis that there is a better balance of the immune system in the milder disease (3).

Laboratory Findings

In monoarthritis and mild PO patients, there is often no sign of acute phase response in the serum, such as a raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). In the more severe cases and in EO patients, the ESR and CRP are raised. Rheumatoid factor is not present, but low titer antinuclear antibodies (ANA) are frequently seen. There are no other autoantibodies.

Uveitis

The anterior uveitis that is found in JIA patients is particularly indolent and predominantly affects the anterior uveal tract, with cells visible in the anterior chamber of the eye on slit lamp examination. The pathogenesis is not clear and there are differences between the clinical nature of the inflammation in this and the other types of uveitis, such as sarcoid, Behçets, and infection-related types. Studies reported that a positive ANA was a risk factor/associated marker, but

when using more sensitive tests for ANA, such as the use of Hep2 cells in the test, the correlation is less strong.

Inflammatory Cytokines and Joint Damage

There have been many studies that measure various inflammatory and anti-inflammatory cytokines in the serum and synovial fluid of oligoarticular JIA, and these studies have often been limited by the technical problems of sample collections and the assays themselves. For example, interleukin 1 (IL-1) and tumor necrosis factor (TNF) are easily degraded ex vivo and levels of IL-6 and TNF are often increased during the blood clotting procedure. There are some consistent findings, however. TNF and its natural inhibitor, soluble TNF receptors (TNFR), are usually found in synovial fluid, along with IL-6 and IL-18 and a number of chemotactic factors, such as macrophage inhibitory protein-1 alpha (MIP-1 alpha), all of which will attract lymphocytes, monocytes, and neutrophils to the synovium. Joint damage is less in the PO versus polyarticular JIA and one current hypothesis is that insufficient inhibition of proinflammatory cytokines can prolong disease, thus leading to more damage. Consistent with this hypothesis is the observation in the study of Rooney and colleagues (4), where the authors showed a higher sTNFR/TNF ratio (sTNFR is a natural inhibitor of TNF) in the SF of the PO patients versus polyarticular JIA patients.

Damage to cartilage and bone erosion are both seen in JIA, but the rate and degree of damage, as seen on radiological imaging, is less in PO. There is often uneven local acceleration of growth of epiphyses in the inflamed area, leading to growth deformities.

Genetic Predisposition

There is good evidence that there is a strong genetic component to oligoarticular JIA. In the biggest collection of affected siblings with JIA, known as affected sibling pairs (ASP), a high proportion of the ASP show concordance of disease onset type (53% of the ASPs were concordant for the oligoarticular onset type). In addition, there is a strong autoimmune disease background in the family history of the ASP. These observations suggest a strong genetic background to this group of diseases (5). Approximately 17% of the risk of a sibling developing JIA has been estimated to be due to the influence of a region on chromosome 6 (6p), where the HLA are found (5). There was significant sharing of HLA-DR alleles (6) in the ASPs with respect to onset type and disease course in the oligoarticular group. The HLA genes are classically found significantly associated with autoimmune diseases, and the replication of disease association in different populations shows that the associated genes mentioned above are likely to contribute to pathology by modifying adaptive immunity responses. These consist of the presentation of protein fragments to the effector arm of the immune system (T and B lymphocytes) via these HLA molecules, causing the lymphocytes to become activated, divide and multiply, and differentiate into further subtypes. Further linkage analyses of the ASP have confirmed the contribution of genes in this region of the chromosome, as well as many other possible regions (7).

Nonhuman leukocyte antigen genetic polymorphisms associated with oligoarticular JIA include protein tyrosine phosphatase N22 (PTPN22) (8), a TNF haplotype (9), SLC11A1 (10), and a genetic variant of macrophage inhibitory factor (MIF) that may determine levels of MIF production (11). IL-10 is a cytokine that suppresses the expression of proinflammatory cytokines and its production is genetically determined by a particular genetic variant of IL-10. Crawley and colleagues showed the association of this genetic variant of IL-10 with the more severe EO subtype (12) and also showed that low IL-10 production is inherited from the parents in the EO patients (13). Thus, a complex inheritance pattern is emerging of genes that confer different levels of risk to the child and which may lead to differing disease course and severity.

Cause of the Disease

The prevailing hypothesis is that given a specific autoimmune genetic background, diverse stimuli can trigger the disease. Indeed, many JIA patients will have a history of upper respiratory infections or, sometimes, vaccinations preceding the onset of arthritis. The composite genetic background in the individual will determine the severity of the arthritis. The true extent of the contribution of different areas of the genome is still being characterized. There is no single microorganism that has been implicated to be the cause of oligoarticular JIA.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

This group of patients represents approximately 10% of all JIA in Caucasian series. Its proportion is reported to be greater in other ethnic groups, such as the Japanese and Chinese. There is a wide spectrum of disease severity.

Laboratory Findings

There are no specific laboratory tests for systemic JIA (sJIA), but there are characteristic patterns of laboratory abnormalities. There is typically a very high level

of CRP, high ESR, neutrophilia, thrombocytosis, and a hypochromic, microcytic anemia. Liver enzymes and coagulation screen might be abnormal in the more severe cases and in the complication often seen in severe sJIA, macrophage activation syndrome (MAS). The factors that have the most specificity in the diagnosis of MAS, as distinct from a flare of sJIA, have been identified to be decreased platelet count, fibrinogen, high ferritin, raised liver enzymes, and decreased white blood cell count (14). Confirmation of MAS with a bone marrow aspirate, or trephine biopsy makes the diagnosis. There are no autoantibodies or rheumatoid factor (RF) detectable in JIA serum and complement levels are normal or high. Immunological abnormalities include the presence of polyclonal hypergammaglobulinemia, raised proinflammatory cytokines, such as IL-1, IL-6, IL-18, and TNF, as well as chemokines, such as IL-8 (CXCL8) in the serum or plasma (15–17). Occasionally a fulminant presentation of sJIA can take the form of MAS and polyarthritis with aneurysms in medium-sized arteries, demonstrable by angiography.

Apart from severe joint destructions in patients at the more severe end of the spectrum, secondary complications include MAS, generalized osteoporosis, growth retardation/failure, and amyloidosis. All of these features suggest generalized and systemic inflammation affecting all parts of the body, not just the joints.

Pathogenesis

Infectious agents have often been reported as having triggered the onset of the disease, but there is no single agent that can be identified as the culprit in microbiological and virological examinations. In fact, by definition, sJIA is not an infectious disease because a negative septic screen is necessary for diagnosis. The frequent association of the complication MAS with severe sJIA is unusual and research, so far, shows reversible defects in natural killer (NK) cell activity, as well as reversible expression of the perforin gene on NK cells (18,19). These defects may be part of the pathology of sJIA and triggering of disease flares by infectious agents would suggest that the mechanisms for ridding the child of these agents are defective, NK cell function being one of them.

There is some evidence that genetic predisposition to sJIA comprises at least part of the etiology of sJIA. There are very few sibling pairs with this type of JIA in a large sibling pair cohort from North America (5). Despite earlier reports of associations with different HLA alleles in small cohorts, these results were not replicated in other case control studies. Furthermore, there is no association between HLA and sJIA in a larger cohort of UK Caucasians, in sharp contrast with other types of JIA, where there are multiple reports of disease association with HLA (20).

On the other hand, non-HLA genes, such as the gene encoding macrophage migration inhibitory factor (MIF), have been shown to be associated with JIA as a whole (10), but in particular, a MIF single nucleotide variant that correlated with higher MIF levels in serum and synovial fluids has been found to be associated with sJIA (21). Another non-HLA genetic variant, the 174G-allele of IL-6, found to correlate with significantly higher serum IL-6 levels, has been confirmed as a susceptibility gene for sJIA by family studies (22,23). These genes code for proteins that can be grouped broadly as proinflammatory according to their effects and many hypothesize that such genetic variants predispose the patient to a more than usually vigorous inflammatory response to stimuli, such as infectious agents. Secretion of IL-1 beta, another major proinflammatory cytokine, has also been found to be high in patients with sJIA (24). Open-label pilot trials of biologic agents blocking the signaling of IL-1 and IL-6 have shown highly encouraging results (24–26). Such putative genetic imbalances echo the more recent discovery of genetic defects in innate immunity and anti-inflammatory pathways in the autoinflammatory syndromes. Examples of these autoinflammatory syndromes are familial Mediterranean fevers (FMF), hyperIgD or familial Dutch fevers, Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous arthropathy syndrome (CINCA, also known as NOMID), and familial Hibernian fever or tumor necrosis receptor–associated periodic fever syndromes (TRAPS). sJIA can also be regarded as an autoinflammatory syndrome from the clinical picture of generalized inflammation, as well as its association with certain pro- and anti-inflammatory gene variants.

POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

These are usually chronic and severe conditions that require disease-modifying therapies. There are two subgroups as defined by ILAR: RF negative and RF positive.

Rheumatoid factor positive polyarticular JIA is similar to adult-onset rheumatoid arthritis (RA) with severe widespread erosive joint disease. The similarities between juvenile- and adult-onset RA include the presence of rheumatoid factor, as well as other more specialized antibodies, such as anti-cyclic citrullinated peptides (anti-CCP) and anti-Bip, and association with certain HLA genes. Caution has to be made in the diagnosis of this in children, because RF can be transiently raised due to infection. The ILAR definition clearly stipulates that the classification is made only if there are two positive results found at least 3 months apart.

Rheumatoid factor negative polyarticular JIA is by far the most common and is heterogeneous in terms of age of onset as well as disease course. Many of the younger patients also have anterior uveitis, similar to oligoarticular JIA patients and, similarly, it is often associated with a positive ANA. The histology of the synovium is similar to oligoarthritis, but there may be subtle differences in the proportion of T-cell subsets (3) and cytokine production (4).

Infections can trigger its onset, but there often appears to be no external trigger. Thus, genetic predisposition also contributes to the pathogenesis of this group. The HLA-DRB1*0801 gene variant, found to be associated with oligoarthritis, is also associated with polyarticular JIA, but there are other different genetic associations, as seen in a genomewide linkage study performed in the North American ASP cohort (20). These are preliminary data that will need to be refined and worldwide collaboration among groups working on JIA genetics are being proposed to resolve these questions.

ENTHESITIS-RELATED ARTHRITIS AND PSORIATIC ARTHRITIS

These arthritides are classified using clinical criteria and, as yet, not much is known in terms of pathogenesis. In the enthesitis-related arthritis (ERA) subtype, some of the patients will develop sacroiliitis and spondylitis in late teenage or adult years. Many of these will have a positive HLA-B27, which is significantly associated with adult ankylosing spondylitis. Current hypothesis for the pathogenesis for ERA is defective presentation of microorganisms from the gut by the HLA-B27 molecule to the immune system (27). Other non-HLA genes may modify the clinical presentation of the disease, including the IL-1 gene cluster (28,29).

The pathogenesis of psoriatic arthritis is unknown. The genetic component has, so far, been shown to be that of psoriasis itself, that is, HLA-Cw6 (30), but why a minority of psoriasis patients have arthritis and what determines the age of onset is currently unclear.

SUMMARY

Gene variants in the HLA region of chromosome 6 are associated with JIA, except for sJIA, similar to other autoimmune diseases. The gene variants appear to be different in each clinical subtype and this may constitute the reason for the differences in the clinical spectrum. Modifying influences from non-HLA genes also contribute to the clinical spectrum. sJIA is a systemic inflammatory disease and pathological and genetic studies, so far, suggest that this may be better classified as an autoinflammatory syndrome, with genetic variations in genes within the inflammation networks that predispose the patient to a proinflammatory state.

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CHAPTER 7

Juvenile Idiopathic Arthritis
C. Treatment and Assessment

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- Most patients with juvenile idiopathic arthritis (JIA) do not achieve a remission and require long-term treatment.
- Discovery and use of new therapies such as methotrexate and biologics have improved the outcome of JIA.
- Evidence-based guidelines are available for the treatment of some subtypes of JIA.
- Assessment tools have improved the documentation of individual and clinical trial outcome.

RATIONALE OF CURRENT TREATMENT APPROACH

The medical treatment of juvenile idiopathic arthritis (JIA) has changed dramatically over the past 15 years. This change has been related to data showing that most children never achieve a long-term remission, and thus the burden of disease to the patient, family, and, ultimately, society is enormous. Until 1990, treatment was based on the pyramid approach beginning with various nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids and gradually advancing to other medications. Studies in the late 1980s indicated that previous assumptions on the course and outcome of JIA were incorrect. Radiologic joint damage, previously thought to develop late in the disease course, occurs in most patients with systemic and polyarthritis within 2 years and in oligoarthritis within 5 years (1). Early cartilage damage, often in the first year of disease, was demonstrated using magnetic resonance imaging (MRI).

The assumption that JIA will usually resolve by adulthood also was found to be incorrect. Studies have shown that between 50% to 70% of patients with poly- or systemic arthritis and 40% to 50% of patients with oligoarthritis will continue to have active disease in adulthood. Only a few patients seem to achieve long-term, medication-free remission (1–3). Between 30% to 40% of patients have significant long-term functional disabilities including unemployment, and between 25% to 50% need major surgery, including joint replacement (2).

Juvenile idiopathic arthritis is associated with a mortality rate of 0.4% to 2%, about three times the standardized mortality rate for the US population. Most deaths are in patients with systemic arthritis, with amyloidosis (almost exclusively in Europe) and the macrophage activation syndrome being the main causes (1).

The outcome of uveitis has improved significantly in recent years, but there is still a high prevalence of ocular complication and vision loss. Five to 16% of patients have significant visual deficits, and even blindness, and 16% to 26% develop cataracts, 14% to 24% develop glaucoma, and 11% to 22% develop band keratopathy (4).

Several predictors of a poor outcome can help determine patients requiring early aggressive therapy. Patients with polyarthritis and positive rheumatoid factor (RF), antibodies to cyclic citrullinated peptides anti-CCP), the presence of human leukocyte (HLA)-DR4, nodules, and early-onset symmetric small joint involvement have a worse prognosis. Patients with systemic arthritis who are corticosteroid dependent for control of systemic symptoms and have a platelet count >600,000 after 6 months of disease have a worse outcome.

MEDICAL TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS

Nonsteroidal Anti-Inflammatory Drugs

Only about 25% to 33% of JIA patients, mainly those with oligoarthritis, respond well to NSAIDs (5). A 4- to 6-week trial of an individual NSAID is necessary to assess its efficacy. Because NSAIDs do not alter the disease course or prevent joint damage, they are used more to treat pain, stiffness, and the fever associated with systemic arthritis. No individual NSAID has been shown to have a clear advantage over others in treating arthritis. Some patients not responsive to one NSAID may respond to another (Tables 7C-1 and 7C-2).

Nonsteroidal anti-inflammatory drugs approved by the Food and Drug Administration (FDA) for JIA and currently available on the market in the United States include naproxen, ibuprofen, meloxicam, and tolmetin sodium. Liquid preparations are available for the former three. For reasons of compliance it is preferable to use an NSAID which is administered only once or twice per day. Thus, the need to administer aspirin three times per day, to monitor serum levels, and the association of aspirin with the Reye syndrome have largely resulted in other NSAIDs replacing aspirin in treating JIA.

Serious gastrointestinal (GI) adverse effects are rare, although many children develop GI symptoms. In order to prevent these symptoms, NSAIDs should be administered with food. GI symptoms can be treated by changing NSAIDs or by using H2 blockers or proton pump inhibitors. Mild elevations of liver enzymes are common. Other adverse effects include pseudoporphyria, most often associated with the use of naproxen in fair-hair Caucasians, and central nervous system effects, including headaches and disorientation, especially from indomethacin. Renal adverse effects are uncommon in children, but are more frequent during concurrent use of more than one NSAID. The issue of cardiovascular adverse effects has not been formally studied but there are no case reports of these events in children with JIA treated with NSAIDs.

Corticosteroids

Due to many deleterious effects, especially the effect on bone and growth, the use of systemic corticosteroids for JIA should be minimized. There is no evidence that systemic corticosteroids are disease modifying. The main indications for systemic use of corticosteroids are uncontrolled fever, serositis, and the macrophage activation syndrome in systemic arthritis. Another indication

TABLE 7C-1. MAJOR MEDICATIONS AND INDICATIONS FOR TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS.

MEDICATION	ARTHRITIS SUBTYPE	INDICATION
NSAIDs	All types	Symptomatic: pain, stiffness
Intra-articular corticosteroids	All types, mainly oligoarthritis	Injection of few swollen joints
Systemic corticosteroids	Systemic, polyarthritis	Fever, serositis, bridging medication, macrophage activation syndrome
Methotrexate	All types, less effective in systemic	Disease modifying
Sulfasalazine	Oligoarthritis, polyarthritis, enthesitis-related	Disease modifying
Leflunomide	Polyarthritis	Disease modifying
Cyclosporine A	Systemic	Macrophage activation syndrome, steroid sparing
Thalidomide	Systemic	Possibly anti-TNF
Anti-TNF (etanercept infliximab, adalimumab)	Polyarthritis, enthesitis-related (less effective in systemic)	Biologic modifying
Anti–IL-1 (anakinra)	Systemic	Biologic modifying
Anti–IL-6 (tocilizumab)	Systemic	Biologic modifying (currently not available outside studies)
IVIg	Systemic	Steroid sparing

ABBREVIATIONS: IL, interleukin; IVIg, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor. Hydroxychloroquine, gold, and penicillamine not effective in JIA. Abatacept, rituximab, and minocycline not studied in JIA.

TABLE 7C-2. DOSES AND ADVERSE REACTIONS OF MAJOR MEDICATIONS USED TO TREAT JUVENILE IDIOPATHIC ARTHRITIS.

MEDICATION	DOSE	MAIN ADVERSE REACTIONS
NSAIDs		GI, liver enzymes, headaches, interstitial nephritis
Naproxen	7.5–10 mg/kg (max 500 mg) twice daily	As above, pseudoporphyria
Ibuprofen	10–15 mg/kg (max 800 mg) 3–4 times daily	As above
Meloxicam	0.25–0.375 mg/kg (max 15 mg) once daily	As above
Methotrexate	10–15 mg/m^2/week (parenteral if >12.5 mg/m^2)	GI, mouth sores, liver enzymes, cytopenia
Sulfasalazine	15–25 mg/kg (max 1500 mg) twice daily	GI, rashes, cytopenia
Leflunomide	<20 kg: 10 mg every other day 20–40 kg: 10 mg/day >40 kg: 20 mg/day	GI, liver enzymes
Etanercept	0.4 mg/kg (max 25 mg) SC injection twice weekly	Injection site reaction, UR symptoms, infections
Adalimumab	24 mg/m^2 (max 40 mg) SC injection every other week	Injection site reaction, UR symptoms, infections
Infliximab	3–6 mg/kg, intravenously at weeks 0, 2, and 6, then every 6–8 weeks	Infusion reactions (allergic), infections
Anakinra	1–2 mg/kg/day (max 100 mg) SC injection	Injection site reaction, UR symptoms, infections
Triamcinolone hexacetonide	For large joints 1 mg/kg (max 40 mg) IA injection	Subcutaneous atrophy

ABBREVIATIONS: GI, gastrointestinal; IA, intra-articular; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous; UR, upper respiratory.

is use as a bridging medication until other medications become effective. In some patients, periodic intravenous pulses of corticosteroids (30 mg/kg/dose, maximal 1 g) are used instead of high dose daily oral corticosteroids, although there are no controlled studies showing fewer adverse effects of this modality in children.

There is excellent evidence for the efficacy of intra-articular injections of corticosteroids, mainly in patients with oligoarthritis. Several studies have shown that as many as 70% of patients with oligoarthritis do not have reactivation of disease in the injected joint for at least 1 year and in 40% for more than 2 years (6). MRI studies have shown a marked decrease in synovial volume after injection without a deleterious effect on the cartilage. One study reported significantly fewer patients with leg length discrepancies when intra-articular corticosteroid injections are used early (7). The efficacy is less in other JIA subtypes, especially systemic arthritis.

There are few adverse effects associated with these injections. One that can be seen is the development of periarticular subcutaneous atrophy. This may be preventable by injecting small amounts of saline while withdrawing the needle following the injection and by applying pressure to the injection site. Repeated injections over time to an individual joint have not been found to be associated with joint or cartilage damage.

Several controlled studies, including a study of simultaneous injections of bilateral inflamed joints in individual patients, have found that the long-acting triamcinolone hexacetonide was more effective and had a longer effect than other forms of injectable corticosteroids (8). Younger children and children needing multiple joint injections usually require sedation during the procedure.

Methotrexate

The use of methotrexate (MTX) is the cornerstone of the medical management plan for most patients with JIA and polyarthritis (9). The initial dose is 10 mg/m^2/week given orally or parenterally. If not effective the MTX dose should be increased to 15 mg/m^2/week and given parenterally (10). There is no additional advantage in giving higher doses.

The efficacy of MTX differs by the subtype of JIA, with the greatest efficacy seen in patients with extended oligoarthritis, while less effective in systemic arthritis (11). MTX may slow the radiologic damage progression rate as demonstrated in two small series.

Because food decreases the bioavailability of MTX, it is advised to give MTX on an empty stomach. MTX at doses ≥12 mg/m^2 should be given parenterally, because oral MTX is not absorbed well at those doses.

In order to decrease adverse effects of nausea, oral ulcerations, and perhaps liver enzyme abnormalities, MTX should be administered with folic acid (1 mg/day) or folinic acid, 25% to 50% of the MTX dose, given 24 hours after MTX administration.

Nausea and other GI symptoms are frequent. Strategies to decrease the severity of these phenomena include taking MTX before bed, switching the mode of administration (oral to parenteral) and using anti-emetics. Some children develop a psychologic aversion to MTX that can be alleviated by teaching relaxation or self-hypnosis techniques.

The collective long-term experience of MTX use for JIA remains one of remarkable safety. Tests to monitor for MTX toxicity, complete blood counts, liver enzymes, and renal function are recommended at least every 3 months (12). While mild elevations of liver enzymes occur frequently through the course of treatment, no cases of severe, irreversible liver fibrosis have been reported in JIA. Thus, routine liver biopsies are not recommended (13). Pulmonary toxicity and severe infections are extremely rare in children. Children should avoid live vaccinations while using MTX but other vaccinations can be given and seasonal influenza vaccine is recommended. If possible, children should receive varicella vaccine prior to starting MTX. MTX should be skipped during an acute infection, especially Epstein–Barr virus (EBV; see below). While rare case reports of lymphoma have been reported, current data do not suggest that the rate of malignancies is greater than in the general child population. Some of the lymphomas developed in association with EBV infection.

Other Disease-Modifying Antirheumatic Drugs and Immunosuppressive Medications

Sulfasalazine and leflunomide may be alternatives to methotrexate. A controlled study showed that sulfasalazine is effective in the treatment of oligo- and polyarthritis; the effect may persist for years after sulfasalazine is discontinued (14). Sulfasalazine may also slow the progression of radiologic damage (15). Sulfasalazine seems to be most effective in older males with oligoarthritis, representing, perhaps, children with enthesitis-related arthritis. Adverse reactions were frequently reported, especially rashes, GI symptoms, and leukopenia, frequently necessitating discontinuation of sulfasalazine. Adverse effects may be especially severe in patients with systemic arthritis. Leflunomide was shown to be effective in polyarthritis, although in a controlled study significantly more responders were found in patients receiving MTX (16).

Cyclosporine A may be more beneficial for fever control and corticosteroid dose reduction than for the treatment of arthritis in patients with systemic arthritis and may be especially effective in patients with the macrophage activation syndrome. Thalidomide may be effective in the treatment of refractory systemic arthritis, both for systemic features and arthritis. In addition to the teratogenic effect, careful observation for the development of peripheral neuropathy is necessary (17).

Most controlled studies in children did not find hydroxychloroquine, oral gold, D-penicillamine, or azathioprine to be effective in the treatment of JIA (5). There are no controlled studies of minocycline use or of combination disease-modifying antirheumatic drugs (DMARD) therapy with or without MTX in JIA.

Biologic-Modifying Medications

Anti-Tumor Necrosis Factor Medications

Recent studies have shown these medications to be highly effective in patients with polyarthritis, including patients who failed MTX. There are three anti-tumor necrosis factor (TNF) medications: etanercept, a soluble TNF receptor, and two anti-TNF antibodies, infliximab, based on a mouse protein, and adalimumab, a humanized protein. Trials of all three medications have shown similar efficacy, but currently etanercept is the only drug approved by the FDA (18). More than 50% of patients have a response greater than the American College of Rheumatology (ACR) Pediatric 70 level for all three medications. Anti-TNF medications also appear to be highly effective in enthesitis-related arthritis (juvenile spondyloarthropathy) but are significantly less effective in systemic arthritis (19). Infliximab is more effective than etanercept for JIA-related uveitis (20,21). It is still not clear whether the combination of anti-TNF and MTX is more effective than either alone but initial data support the use of combination therapy. Anti-TNF medications may slow radiologic damage progression and may increase bone density.

Adverse effects of etanercept are generally mild, mainly injection site inflammation for etanercept and adalimumab and infusion-related allergic reactions for infliximab. To prevent or minimize infliximab allergic reactions, premedication with acetaminophen, diphenhydramine, and, occasionally, hydrocortisone are sometimes needed. Other common mild adverse effects include upper respiratory infections and headaches. However, some patients develop severe adverse effects including neurologic (demyelinating diseases), psychiatric, severe infectious (especially related to varicella), cutaneous vasculitis, pancytopenia, and development of other autoimmune diseases (18,19). One case of each of tuberculosis and histoplasmosis have been reported in the use of anti-TNF medications for JIA.

No cases of malignancy have been reported in children. Adult screening guidelines for tuberculosis, at a minimum using purified protein derivative (PPD) skin testing prior to anti-TNF therapy, are adopted in pediatric practice.

Other Biologic-Modifying Drugs

Interleukin (IL)-1 Receptor Antagonists

Initial very promising results using anakinra, an IL-1 receptor antagonist, for systemic arthritis have been reported for both the systemic and articular components, including patients not responsive to anti-TNF medications. IL-1 appears to be a major mediator of inflammation in systemic arthritis (22). Anakinra is less effective for polyarthritis than anti-TNF medications.

Anti-Interleukin-6 Receptor Antibody

Interleukin 6 is also an important cytokine in the pathogenesis of systemic arthritis. Two open series of 29 patients with systemic arthritis given intravenous tocilizumab, an anti-IL6 receptor antibody, reported significant improvements in the majority of the patients as soon as after the second dose (23). Tocilizumab is still under study.

Intravenous Immunoglobulin

Two controlled studies did not find intravenous immunoglobulin (IVIg) to be effective in the treatment of the arthritis component of systemic and polyarthritis JIA. There may be more benefit for IVIg for the treatment of the systemic features of systemic arthritis.

Other Medications

There are no reports or studies in JIA of new medications found to be effective in rheumatoid arthritis, including rituximab (anti-CD20 mature B-cell antibodies) or abatacept (anti-CD28, T-cell co-stimulator antibodies).

Autologous Stem-Cell Transplantation

In patients with longstanding and unresponsive systemic and polyarthritis JIA there may be a role for autologous stem-cell transplantation (ASCT) (24). However, there is a significant mortality rate associated with ASCT (15%), thus ASCT must still be regarded as an experimental procedure in JIA.

EVIDENCE-BASED GUIDELINES FOR THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS SUBTYPES

Suggested treatment guidelines were published based on a systematic review of the controlled studies done in JIA (25). Thirty-six controlled trials were identified, 30 of them were double blind. This brief summary of the recommendations emphasizes that the treatment plan needs to be individualized based on the arthritis subtype.

Oligoarthritis

Only a minority of patients respond completely to NSAIDs. In those not responsive or patients presenting with flexion contractures, intra-articular corticosteroid injections, especially triamcinolone hexacetonide, are effective for most patients. Patients not responsive to corticosteroid injections or with extended oligoarthritis or small joint involvement should be treated as patients with polyarthritis.

Polyarthritis

Nonsteroidal anti-inflammatory drugs are mostly not effective as disease-modifying medications and are used mostly as symptomatic treatment. MTX should be started early, initially at 10 mg/m^2/week, and if not effective increased to 15 mg/m^2/week, given parenterally. Alternatives include sulfasalazine and leflunomide. If not effective, anti-TNF medications should be used.

Systemic Arthritis

There is a particular lack of evidence for systemic arthritis. NSAIDs and systemic corticosteroids are often needed for symptomatic (fever, serositis) relief. Intra-articular corticosteroid injections, MTX, and anti-TNF medications appear to be less beneficial than in other JIA subtypes, both for the systemic and arthritis components. Among the medications currently available there may be an advantage to using anakinra as a first-line corticosteroid-sparing medication. IVIg may have some benefit as a corticosteroid-sparing effect on the systemic component. Treatment for the macrophage activation syndrome includes high dose intravenous corticosteroids pulses and if not rapidly effective cyclosporine should be added. Tocilizumab, still available only in research trials, shows initial promise.

Enthesitis-Related Arthritis

Sulfasalazine may be beneficial, particularly for older males with peripheral arthritis. Anti-TNF medications are highly effective.

Psoriatic Arthritis

There are no studies of the treatment of psoriatic arthritis in children. The presentation of psoriatic arthritis can be as oligo-, poly-, and enthesitis-related arthritis and until other evidence is reported should be treated as the parallel JIA subset.

Uveitis

The treatment of uveitis should be directed by ophthalmologists with experience in treating this disorder with the guidance of pediatric rheumatologists experienced in managing immunosuppressive and biologic-modifying medications. Usually, initial treatment consists of topical corticosteroid drops. Subtenon corticosteroid injections may also be beneficial. Immunosuppresive therapy should be started early in patients with severe uveitis or in those who become corticosteroid dependent. MTX is the most common medication used (21,26). For patients not responsive to MTX, infliximab, but not etanercept, appears to be effective (19,20).

OTHER FACETS OF TREATING JUVENILE IDIOPATHIC ARTHRITIS

The medical treatment of JIA, while most important, is only one facet of JIA therapy. A multidisciplinary team incorporating pediatric rheumatologists, ophthalmologists, orthopedic surgeons, dentists, physical and occupational therapists, dietitians, social workers, psychologists, and educational and vocational counselors are involved in treating patients with JIA.

Many patients continue to have pain despite adequate disease control with modern medications and often pain is not adequately treated. Patients should receive adequate pain medications, including narcotics if necessary. Other pain modalities should be considered, including physical therapy, physical measures like heat or cold, splints, orthotics, acupuncture and massage, and various behavioral and stress-reducing techniques.

A critical part of the treatment regimen is physical therapy. The main purposes of physical therapy are to maintain range of motion of the affected joints, improve muscle strength, prevent deformities, and to correct or minimize damage and loss of function. Methods used include guided and home exercise programs for range of motion and muscle strengthening exercises, splints, orthotics, and various modalities to decrease pain. Aquatic exercise is often tolerated more than land exercises, especially in patients with significant lower extremity arthritis. Splints are used for knee flexion contractures. Some patients with persistent knee contractures may benefit from serial casting. Orthotics are often used for ankle or subtalar arthritis or for foot deformities in order to decrease pain when walking, improve gait, as an arch support for flatfoot, and to minimize pressure on metatarsal heads, thus preventing the formation of callus or subluxations of the toes. Patients with leg length discrepancy occasionally need shoe lifts in the shorter leg.

The role of occupational therapy is to maintain and improve the normal life function. Techniques used include hand exercises; wrist, hand and finger splints; teaching joint protection techniques; and fitting various aids for daily activities. These depend on the extent of the disease and include aids for writing, dressing (also shoes), eating utensils, adapting bathrooms and other household equipment for patients with arthritis, and mobility aids, if needed (canes, walkers, wheelchairs). Heat pads or bottles, bathing, and paraffin baths may help decrease morning stiffness.

Dietary consultation may be needed because some patients with significant arthritis have anorexia and lack adequate growth from several factors, including active disease, arthritis of the temporomandibular joint, and various medications (NSAIDs, methotrexate). Dietary consultation is also important for patients treated with corticosteroids in preventing excessive weight gain, hypertension, and bone loss, and includes advice on adequate calcium and vitamin D intake.

Physical activity is encouraged but should be tailored by the degree of arthritis and the joints involved. Children are encouraged to set their own limits but should not persist in an activity that causes pain in an arthritic joint. In general, activities that are less weight bearing, such as swimming and cycling, are preferred, but most sports that do not involve significant contact (football, hockey, wrestling, boxing) are tolerated. Patients with neck arthritis need to limit activities that can result in cervical spine damage (diving, certain types of jumping).

It is important to discuss school issues with the patients, family, and, if needed, school officials. In general, patients with JIA attain similar school achievements as healthy students. However, JIA patients are often absent due to flares, infections, and visits to physicians and other therapists. Patients may arrive late to school due to morning stiffness. Gym performance, moving from class to class, and writing may be affected. Children with uveitis may need adjustments due to visual difficulties. Common school adjustments include allowing elevator use, more time to get from class to class, stretching in class, more time to write tests, computer

use, having a second set of books, and gym modifications. In the United States, the Americans with Disability Act (504 plan) mandates allowing for every child to receive education in the least restrictive environment. In more severe cases a formal individualized educational plan (IEP) can be employed (see Chapter 7D).

As in any chronic disease, especially one with chronic medication use, psychological support is often needed. Patients and families should be encouraged to seek support early before a crisis occurs. This support is often needed to deal with medication issues such as body image changes from corticosteroids, nausea from methotrexate, or to increase compliance with the medication regimen (see Chapter 7D for a discussion of adherence). Social workers can assist with the financial burden caused by the disease and the cost of medications.

An important issue is the transition to adulthood, including transition of medical care to adult rheumatologists, education, and vocational planning. These issues should start to be discussed and planned well in advance of the youth's 18th birthday. Data show that transition to adult health care results in improved outcomes if the transition is planned and the disease is well controlled at the time of the transfer to the adult rheumatologist (27). A transition policy has been adopted by the major primary care physician groups (American Academy of Pediatrics, American Academy of Family Physicians, and the American College of Physicians) (28) and there are special medical issues for the young adult who has grown up with JIA.

Patient advocacy groups, such as the Juvenile Arthritis Alliance, sponsored by the Arthritis Foundation, can also give support. The Arthritis Foundation supports regional and national meetings, arthritis camps, educational materials, newsletters, and discussion forums on JIA (http://www.arthritis.org). Other important sources of educational material on JIA include the American College of Rheumatology (http://www.rheumatology.org) and the Pediatric Rheumatology International Trials Organization (PRINTO; http://www.printo.it). The latter site has information on JIA in more than 30 languages.

TOOLS TO ASSESS JUVENILE IDIOPATHIC ARTHRITIS OUTCOMES

Several assessment tools have been developed for the purposes of following individual patients as well as for clinical trials and outcome studies (Table 7C-3). These tools assess various domains of JIA. A validated comprehensive global disease activity scale has not been developed yet. Disease activity tools commonly used include active joint count (joints with swelling or tender/pain on motion), joints with limitation of motion, and acute phase reactants, for example, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). It is important to note, however, that many patients with active arthritis have normal acute phase reactants. Subjective, but well-validated global assessment tools include visual analog scales used by physicians and parents.

TABLE 7C-3. ASSESSMENT AND OUTCOME MEASURE TOOLS FOR JUVENILE IDIOPATHIC ARTHRITIS.

DOMAIN	ASSESSMENT TOOLS
Disease activity	Active joint count, acute phase reactants
Global assessment	Physician, patient visual analog scale
Functional assessment	Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Functional Assessment Report (JAFAR), Juvenile Arthritis Functional Status Index (JASI)
Quality-of-life assessment	Childhood Health Questionnaire (CHQ), Peds-Quality of Life (QOL)—rheumatology subset, pain visual analog scale
Radiologic damage	Poznanski, Dijkstra scores
Disease-related irreversible damage	Juvenile Arthritis Damage Index (JADI)
Clinical trial outcome measures	American College of Rheumatology (ACR) Pediatric 30, criteria for inactive disease or clinical remission

Several functional assessments tools have been developed (29). These include the Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Functional Assessment Report (JAFAR), and Juvenile Arthritis Self-Report Index (JASI). These tools have all been validated, and are reliable, sensitive to change, include items applicable to all children with JIA at all ages, and are easy to use and score (except the JASI, which is limited to children >8 years old and is very lengthy). Most are completed by parents and/or patients. These tools provide an overall functional assessment by a composite score and also enable determination of particular functional deficits. The CHAQ, translated and validated in more than 30 languages, is the most commonly used. Various studies did not find significant differences between the measures, thus all appear valid for use in clinical practice and trials. There are several problems with the functional assessment tools, especially a ceiling effect in patients with mild oligoarthritis and minimal functional problems.

Most functional tools do not address issues of overall quality of life (QOL), especially general health and psychosocial issues related to JIA (29). These are most commonly assessed in JIA by use of the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and the Childhood Health Questionnaire (CHQ). The CHQ also allows comparisons between diseases for research studies. It has been translated and validated in more than 30 languages and is the most used tool. In the United States, there is also widespread use of the Pediatric Quality of Life generic questionnaire and the rheumatology module (PedsQL-RM).

Until recently the only radiologic assessment tool was the Poznanski scale that looked at wrist damage by comparing the ratio of the length of the carpus bones to the length of the second metacarpal bone. A more comprehensive scale was recently developed and validated by the Dutch JIA Study Group (15). The Dijkstra composite score is based on inflammation (swelling, osteopenia), damage (joint space narrowing, cysts, erosions), and growth abnormality subscores for 19 joints or joint groups.

Most recent clinical trials for JIA have used the well-validated ACR Pediatric 30 scale as the primary outcome measure of responsiveness (30). This scale, developed in 1997, defines patients as responders or nonresponders. This scale was modified for defining disease flares necessary for some clinical trials of rapidly acting biologic-modifying medications utilizing a withdrawal design, that is, patients defined as responders in the open phase of the trial were randomized to continue the medication or to receive placebo. Due to the advent of potent biologic-modifying medications, rheumatologists no longer aim only for improvement, but aspire to induce remission. Preliminary criteria defining clinical remission of all JIA subtypes on and off medications were defined and validated in a large series of patients (3,31).

A global damage assessment tool, the Juvenile Arthritis Damage Index (JADI), was recently developed and validated (32). The JADI includes two components. The JADI-A assesses articular damage based on persistent findings of joint contractures, deformities, or major surgery in 36 joints or joint groups lasting at least 6 months and not related to active arthritis. The JADI-E assesses extra-articular damage to the eyes, skin, nonarticular musculoskeletal system, endocrine system, and secondary amyloidosis.

SUMMARY AND FUTURE RESEARCH

The development of new therapies has markedly increased our ability to effectively treat children with JIA. Indeed, there are indications that patients treated aggressively early in the disease course with MTX and/or biologic-modifying medications appear to improve significantly faster than patients treated later in the disease course. However, recent sobering studies have shown our inability to induce long-term, medication-free remission in most patients. There also is a lack of evidence-based medicine in the treatment of some JIA subtypes. Controlled studies for new medications for systemic arthritis, including anti–IL-6 receptor antibodies, new anti–IL-1 medications, and thalidomide or other combinations are necessary. Studies of new medications shown to be effective in rheumatoid arthritis, such as abetacept and rituximab, need to be studied in polyarthritis.

A high priority for investigation should be the early effect of aggressive therapy on the disease course, including the potential use of remission induction therapy that could include combining various methods of administering corticosteroids with MTX and a biologic-modifying medication to be followed with step-down maintenance therapy in both poly- and systemic arthritis. While intuitively logical in the short term, these protocols need to be validated for long-term effects as well as for potential increases in adverse reactions. The results of these studies should fill gaps in evidence-based guidelines in order to assure quality care of children with arthritis. New outcome tools will enable us to study the long-term disease-modifying effects of MTX and biologic-modifying medications on remission rates, radiologic changes, functional capabilities, and the prevention of irreversible articular and extra-articular damage.

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CHAPTER 7

Juvenile Idiopathic Arthritis
D. Special Considerations

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- Youth with juvenile idiopathic arthritis (JIA) require special attention to managing growth abnormalities, both local and general, as well as osteopenia.
- Adherence to medical regimens is often suboptimal and can be improved by paying attention to educational, organizational, and behavioral approaches
- Management of youth with JIA should take in account the psychological, educational, and transition to adulthood issues to maximize their outcome.

Many rheumatic diseases that occur in adults also affect children, albeit less frequently. Additionally, some diseases such as systemic-onset or pauciarticular pattern of juvenile rheumatoid arthritis occur predominantly in children. In all of these diseases, the clinical manifestations are often impacted by the child's growth and development.

EXAMINATION

Performing a valid and complete examination on a child who is ill or in pain can be difficult. Yet an accurate exam is necessary if the correct diagnosis is to be made. Children at different ages and developmental levels respond differently to examination. Rheumatic disease manifestations can also vary with age. It may be helpful to keep certain guidelines in mind. Height and weight should be obtained at each visit and these growth parameters plotted on an appropriate growth chart. Inadequately controlled disease or medication side effects can impair normal growth.

In infants and toddlers, observation skills are particularly important. By looking for movements that cause pain or irritability as well as lack of movement of any joint, one can ascertain much before the patient is ever examined. Using toys, talking, and keeping eye contact with the child may help alleviate the child's fear. Having the child sit on the parent's lap and even having the parent assist with the examination may make a more thorough examination possible. Swelling can be subtle in a chubby child and careful attention to range of motion is critical. A single swollen digit may be the only sign of arthritis.

Most school-aged children like to actively participate in the examination, particularly if they are in comfortable clothing such as T-shirt and shorts. It is generally best to examine any painful area last, after completing the general and remainder of the musculoskeletal examination. In addition to joint examination, careful attention should be paid to gait, leg length, and muscle strength. Having a child perform a sit-up or climb a few stairs can be a helpful screen for muscle weakness.

In adolescents, the examination itself is not difficult but relating to the patient can be. It is again important that the patient is as comfortable as possible and that rapport is established with the adolescent, not just the parent. In situations where the parent continues to dominate the interactions, it may be helpful to ask to speak to the adolescent alone. The examination should include a scoliosis screen as part of the musculoskeletal examination.

GROWTH

Juvenile rheumatoid arthritis (JRA) is a chronic disease and has long been known to affect growth of the child. Historically, this clinical effect was noted by Still in 1897 and later described by Kuhns in 1932. Its cause is multifactorial, including not only the disease itself but medication side effects, nutrition, and mechanical problems. The roles of growth hormone and insulin-like growth factors are gradually being elucidated, as described below.

General

It is clear that the onset subtype of JRA is important, with little or no general adverse effect on growth seen in the pauciarticular group. However, this group may have severe local growth disturbances at the sites of inflammation, particularly leg length discrepancy and mandibular asymmetries.

Patients with polyarticular and systemic disease who have never received corticosteroid therapy may have general growth retardation, generally related to the severity and duration of disease. In one study, one fourth of both disease groups lost greater than 1 height Z score over the 14-year follow-up period (1). [Z score = $(X_1 - X_2)$/SD, where X_1 = subject's measurement, X_2 = mean of the reference population for age and gender, and SD = standard deviation of the mean for the reference population.] Growth impairment was generally not severe except in a small number of systemic patients. Height velocity during puberty was especially vulnerable. The degree of catch-up growth was unpredictable.

In another study with 64 prepubertal children with primarily mild pauciarticular and polyarticular JRA, growth velocity decreased in the first year of disease postdiagnosis and then increased to normal range with treatment and 4-year follow-up. The greatest effect on velocity was seen in children with more severe polyarticular disease. There were only two systemic patients in the study (2). A long-term follow-up study of adults who had JRA and had received corticosteroids showed reduced final height and arm-span (3).

Local

Local growth disturbances occur as a result of inflammation and the accompanying increase in vascularity, which may result in either over- or undergrowth of the affected bone. Examples of local growth abnormalities are the following: (1) The hip is a frequently involved joint in JRA and occasionally this leads to a small femoral head within a larger acetabulum. This was noted in five patients undergoing hip arthroplasty. The small size was thought to be secondary to destruction of the articular cartilage (4). Of note, all patients had disease onset prior to age 3. (2) The knee is the most frequently involved joint in JRA and persistent synovitis, particularly in an asymmetric fashion, can lead to significant leg length discrepancy. The distal femoral epiphysis accounts for approximately 70% of femoral growth, so persistent inflammation leads to overgrowth on the involved side in a child whose epiphyses have not yet closed. Often the medial side predominates, leading to additional knee valgus. Increased use of intra-articular steroids may reduce this risk and appears to have a low level of adverse effects (5). (3) Micrognathia and malocclusion are known as common sequelae of JRA. Unilateral disease may lead to chin deviation. Sixty-nine percent of youth with polyarticular and systemic disease had orthodontic abnormalities (6). Polyarticular patients often have small, short facies with underdeveloped mandibles. These consequences of temporomandibular joint (TMJ) arthritis are difficult to treat. Magnetic resonance imaging (MRI) may detect early changes. Orthodontic consultation is recommended. Corticosteroid injection may be helpful in selected patients and costochondral grafts have been used in severely affected patients. (4) Other sites frequently involved include the wrist, with undergrowth of the ulnar head, and the vertebrae, with undergrowth of the cervical spine.

Osteopenia and Osteoporosis

Osteopenia is low bone mass for age and the child with JRA is at great risk for failure to achieve adequate postpubertal bone mass. The introduction of dual-energy x-ray absorptiometry (DXA) has enabled assessment of osteopenia and has led to realization of the magnitude of the problem. Both the cortical appendicular skeleton and the axial trabecular bone are affected, but the cortical to a greater degree (7). Osteopenia appears to correlate with disease activity and severity (7). Other factors, including decreased physical activity, immobility, decreased sun exposure, and decreased dietary intake of calcium and vitamin D, are additional contributing factors. Peak bone mass is normally reached during adolescence and this achievement is important to minimize future risk for osteoporosis and fractures. Often in JRA the bone density fails to undergo expected pubertal increase. Significant axial osteopenia of lumbar spine and femoral neck was found in patients with polyarticular disease (8). In a 2-year prospective, controlled study in early juvenile idiopathic arthritis (JIA; includes JRA, psoriatic arthritis, and ankylosing spondylitis), moderate reduction of bone mass gain, bone turnover, and total lean body mass was observed (9).

Therapy includes weight-bearing exercise, appropriate nutrition, calcium and vitamin D supplementation, and, most importantly, adequate disease control with suppression of inflammation. Early study of bisphosphonate therapy in children with rheumatic disease has been encouraging but not without adverse effects (10). Behavioral intervention may also be helpful in increasing calcium intake (11).

In addition to generalized osteopenia, involved joints often show local juxta-articular demineralization even on early radiographs. Patients may benefit from DXA monitoring at selected intervals.

Endocrine Factors

Osteocalcin

Low levels of osteocalcin, along with decreased bone mineral content, were found in children with active inflammation but both parameters were normal in children with inactive disease (12). Osteocalcin levels in patients with heights less than the third percentile were below normal, suggesting decreased osteoblast activity (13). In this study, osteocalcin levels correlated with decreased insulin-like growth factor 1 (IGF-l) levels. However, these patients were also on corticosteroid therapy, which can decrease osteocalcin levels.

Insulin-like Growth Factor 1

Insulin-like growth factor 1 is a peptide produced in the liver and is the main periperal mediator of growth hormone. It promotes collagen formation. Serum levels of this peptide have been reduced in most JRA studies, especially in systemic disease (14). Levels appear to correlate with the degree of inflammation as measured by acute phase reactants. Levels returned to normal with recombinant growth hormone (rGH) therapy in one study (13).

Interleukin 6 (IL-6)

This cytokine is markedly elevated in systemic disease and appears to correlate with the degree of inflammation. Studies in transgenic mice show that IL-6 mediates a decrease in IGF-1 production, which might represent a mechanism by which chronic inflammation affects growth (15).

Vascular Endothelial Growth Factor

This factor is a mitogen for vascular endothelial cells and a mediator of vascular permeability. Serum levels correlate with disease activity in polyarticular JRA and may play a role in inflammation that could affect growth (16).

Growth Hormone

Children with JRA and short stature have low human growth hormone (hGH) secretion and some had inadequate or no response to exogenous hGH administration, suggesting an additional defect in the response pathway or growth hormone insensitivity (17). Other studies have shown levels not significantly different from controls (13).

Growth Hormone Therapy

In one study, 14 children with JRA on corticosteroid therapy received 1.4 IU rGH/kg/week with a partial response. The mean height velocity increased from 1.9 to 5.4 cm/year with an accompanying 12% increase in lean body mass. However, at the end of 1 year the height velocity decreased to pretreatment levels (18).

In another study, rGH increased height velocity during the year of therapy (mean, 3.1 cm/year) but the long-term effect was unknown. There was no correlation between growth hormone secretion and rGH therapy response, raising the question of a target cell defect or peripheral defect regarding growth hormone mediation. Fifty percent of the children in this study had borderline or poor caloric intake (13). Growth hormone therapy may be beneficial in some patients but the response is unpredictable. In a 4-year study of growth hormone therapy in children with polyarticular or systemic disease receiving corticosteroids, improvement of 1 SD was seen in bone mineral content compared to controls (19).

Thyroid Disease

Other endocrine disease may affect both symptoms and growth. Stagi and colleagues found an increased prevalence of autoimmune thyroiditis, subclinical hypothyroidism, and celiac disease in children with JIA (20). In a separate study, antithyroid antibodies were found in a higher frequency in children with arthritis, especially pauciarticular disease, than in the general population (21). These findings suggest that careful monitoring of thyroid function in children with arthritis is indicated.

Nutrition

Adequate nutrition, both caloric and protein, are critical to optimize growth in children with JRA. Up to 30% of children with JRA have some growth abnormality (22). Using anthropometric measurements, up to 40% have poor nutritional status and muscle mass is frequently low. Protein stores as well as specific nutrients such as iron, selenium, vitamin C, and zinc have been reported as low (23). In a recent study, undernutrition was present in 16% of the children with arthritis, including those with pauciarticular disease (24). Inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF) likely modulate some of the nutritional abnormalities. In addition, some patients have mechanical feeding problems related to jaw or upper extremity disease. Aggressive early therapy and use of newer biologic agents, such as anti-TNF agents, can dramatically improve individual patient's nutritional status and growth. However, long-term studies are not yet available.

Monitoring of serial weights during clinic visits should be routine. Dietary logs, nutrient analysis, and consultation with a dietitian is needed for a child with continued poor weight gain. Nutritional supplementation may be beneficial, as may behavioral therapy.

EYE DISEASE

Inflammatory eye disease, especially uveitis, occurs with increased frequency in children with arthritis. Reported incidence varies from 5% to as high as 50%, but recent studies show an incidence of 12% to 25% (25,26). The known risk factors include age <6 years at disease onset, pauciarticular pattern of disease, and antinuclear antibody (ANA) positivity. Current guidelines for frequency of ophthalmologic examination are available (27). As uveitis can develop after the onset of arthritis, ongoing monitoring is important. Long-term outcome for adult patients with childhood-onset uveitis is still poor, with visual acuity impaired in 40%, poor in 20%, and lost in 10% (28). Current arthritis therapeutic regimens, especially methotrexate and anti-TNF agents, appear effective in uveitis. Therefore, the outcome of uveitis with onset in the past 5 to 10 years will likely be much better than the existing reports (see Chapter 7A for more information) (29).

ADHERENCE

Optimal treatment of pediatric rheumatic disease often requires complex therapeutic strategies that can be both confusing and time consuming to patients and their families. Strategies often involve a coordinated list of activities, including taking regular medication, complex exercise regimens, dietary modifications, regular clinic visits and laboratory tests for monitoring the patient, and, in some children, wearing of therapeutic splints. This is complicated by the fact that there is often delayed benefit for good compliance. It is easy to understand why adherence to these regimens is often compromised. In fact, estimates are that only 50% to 54% of patients with chronic pediatric disease adhere adequately with their recommended therapy (30). In JRA, the medication adherence was found to be of similar frequency, ranging from 38% to 59% (31). In a study of prednisone therapy in children with systemic lupus erythematosus (SLE) or dermatomyositis, compliance ranged from 33% to 78%, which is similar to that reported in pediatric cancer patients (32). Surprisingly in the prednisone study, two thirds of patients overmedicated themselves, possibly when they felt poorly. Adherence with exercise regimens are likely to be lower than with medication, ranging from 47% to 67% by parent report (33). One must also differentiate between complete nonadherence and periodic nonadherence.

The consequences of nonadherence are multiple, not only for the patient but also for the health care system. The patients' risk for disease complications and long-term sequelae are generally increased with noncompliance. Poor or dishonest communication between patient and physician or health care provider also stresses the relationship and may lead to needless changes of medication or unnecessary testing. All of these are inefficient and lead to increased health care costs.

Factors Affecting Adherence

Many factors may impede adherence. These can generally be grouped into three categories: (1) factors relating to the disease; (2) factors related to the patient and family; and (3) those related to the regimen itself. There is no typical noncompliant patient and no consistent correlations with obvious demographic factors. However, certain states that lead to noncompliance have been reported (33) and are included in Tables 7D-1 and 7D-2.

Factors Related to Treatment Regimen

The health care provider can increase the likelihood of good adherence by making the treatment regimen as simple as possible and by anticipating some of the

TABLE 7D-1. ADHERENCE: FACTORS RELATING TO PATIENT/FAMILY.

1. Negative reactions from the child, including complaints, refusal, discomfort, or embarrassment, or more general oppositional behavior.
2. Lack of understanding of the disease and treatment, especially in younger children.
3. Misunderstanding of the disease and treatment.
4. Lack of patient autonomy and low self-esteem.
5. Dissatisfaction with the provider or the therapeutic intervention.
6. Inadequate family resources.
7. Language barriers.
8. Family instability or disagreement.
9. Other family demands, for example, parental illness.
10. Parental resentment or anger over the illness.
11. Family's coping abilities and strategies.

TABLE 7D-2. ADHERENCE: FACTORS RELATED TO DISEASE.

1.	Duration, often prolonged with unpredictable exacerbations—compliance tends to decrease over time.
2.	Age of onset—younger patients are less compliant.
3.	Asymptomatic periods. When a patient is asymptomatic or in remission, there is often a temptation to discontinue medication because the patient feels well. This is enhanced by a commonly seen delay in therapeutic response of days to weeks and also by the delay in occurrence of negative effects (recurrence of symptoms) with missed medication.
4.	Severity of disease—no clear correlation with compliance.

known negative factors, including bad-tasting medication, dosing frequency, forgetting (exercise vs. medication), high cost, complexity, delay in therapeutic response, and transportation concerns. Exercise regimens may be especially problematic because the child may experience discomfort and express anger or resentment toward the parent.

Children with chronic disease may be asked to alter their lifestyle in a way that restricts their sports interests or peer-related social activity or reduces their leisure time. Such changes are especially difficult for active children and adolescents. Parental supervision and appropriate involvement are critical in providing the children with needed support. Delay in receiving or lack of subspecialty care and implementation of appropriate therapeutic regimens may also contribute to poor functional outcomes.

Assessment of Adherence

Assessment of adherence can be direct or indirect. Indirect means include parental observation, self-report, medication diary, prescription renewals, and presence of predictable side effects. Direct means include pill count, measurement of laboratory parameters such as drug levels, and electronic devices that record and store the time and date a pill container is opened (34).

Improving Adherence

Strategies used to improve compliance can be categorized into three types: educational, organizational, and behavioral. These can be used singly or in combination (33).

Educational strategies include providing information, helping prioritize, re-education, written handouts, reminder systems, community and national resources, positive feedback, and appropriate discipline techniques. Information should be age, culture, and language appropriate and take into account the child's cognitive abilities. It is important not to overwhelm the family early in the process.

Organizational strategies include counseling, increasing supervision, decreasing complexity, decreasing costs, and increasing palatability of medication. The regimens should fit into the family daily routine as much as possible. Therapeutic exercise and play can often be combined.

Behavioral strategies can include self-management training to increase self-esteem, training for parents to deal with oppositional behavior, and monitoring adherence and using reinforcement or a reward system for good adherence. Reinforcement programs are time consuming and require parental training but can improve adherence (33). Reward systems where tokens are exchanged for privileges can be successful. The child's responsibilities for the treatment regimen should increase as the child gets older but parents should not completely withdraw their supervision.

Regular clinic visits are important to re-educate and reinforce adherence strategies and adapt treatment. They also help build and maintain a cooperative and trusting relationship between clinician and patient. Visits should allow enough time for adherence discussion and reinforcement. Good documentation is also important to facilitate monitoring of adherence. The clinician must relate to the child, who needs to be an active partner in his or her treatment program. Judgmental attitudes are not helpful. A multidisciplinary team approach is optimal. Further studies are needed to identify children and families at high risk for nonadherence, further define successful family coping mechanisms that can be taught and reinforced, and to evaluate strategies for improving compliance.

PSYCHOSOCIAL AND EDUCATIONAL ISSUES

Chronic disease has a major impact on the development and daily functioning of a child as well as on the family. Unfortunately, there are few and often contradictory studies on the nature of the impact and the contributing factors. Different assessment methods, varying population size, and a mixture of disease subtypes, particularly with JRA, contribute to the different conclusions. Some epidemiological studies concluded that there is more risk for psychosocial problems in JRA patients (35), others less (36). A controlled study used self-report questionnaires combined with personal interviews to study children (age 7–11) and adolescents (age 12–16) with arthritis (37). Self-esteem, perceived competence, and body image were similar to healthy controls. The arthritis patients did have less energy to participate in social activities and adolescents received more emotional support from family, peers, and professionals.

The amount of support received correlated positively with disease severity. Other studies showed that children with chronic illness do not have a higher incidence of psychiatric disease nor is there any correlation between psychological test scores and disease functional measurements (38).

Family Impact

Long-term psychosocial outcome appears to be favorable overall. Chronic family difficulties predicted psychosocial functioning in patients with JRA in a 9-year follow-up study, without correlation with disease activity (39). The most frequent psychiatric disturbance on follow-up was anxiety disorder. No children had depressive disorder and 15% had mild-to-moderate impairment in psychosocial functioning (39).

Positive family factors may play an important role in the child's ability to cope with chronic illness. In one study a highly cohesive family structure correlated with a high level of social adjustment in children with JRA (37). An environment with flexibility, individual freedom, and an emphasis on self-mastery appears optimal. Family coping skills can be enhanced by educational programs such as those sponsored by the Arthritis Foundation, and by retreats or workshops directed by professionals (40). These also can reduce family stress and improve parent–child relationships.

Pain

Inadequate attention is often given to pain in children with arthritis. Young children usually do not verbalize discomfort or pain and even the older child may have become accustomed or tolerant to a certain level of pain. Tools are available to help the clinician ascertain the child's perception of pain and can be used as serial measurements. The Pain Coping Questionnaire has been validated in children and adolescents and is good at assessing the child's pain coping strategies. It is simple and applicable over a wide age range (41). Less coping effectiveness has been related to higher levels of pain. Use of the Visual Analogue Scale of Pediatric Pain Questionnaire is also a simple tool that can be used during clinic visits to monitor pain levels in patients at risk. Higher patient perceived pain intensity correlates with higher incidence of depressive and anxiety symptoms (42).

School and Educational Achievement

Many factors affect school attendance but it is generally high except for more severely affected patients. In one study, school absence was associated with decreased adherence with physical therapy and the presence of psychological problems but not with age or duration of illness (43). School problems for children with arthritis include handwriting, opening doors, lateness to class, physical education participation, carrying books, fatigue, absences, and inadequate understanding by teachers and peers. School success is critical to the normal development of the child and school status and educational progress should be assessed regularly at clinic visits. In a controlled study of 44 adults with JRA surveyed 25 years after disease onset, there were equivalent levels of educational achievement, income, and insurance coverage but lower rates of employment, daily energy levels, and exercise tolerance (44).

During the past decade, the overall prognosis for children with rheumatic disease has steadily improved. However, for optimal treatment and outcome attention must be given to their special needs.

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