DEFINITIONS

Chronic childhood arthritis affecting more than four joints during the first 6 months of disease is defined as polyarthritis.\(^1,2\) In the classification of the International League of Associations for Rheumatology (ILAR),\(^2\) polyarthritis is further categorized as rheumatoid factor (RF) negative if tests for RF are negative, and RF positive if RF is detected on two occasions at least three months apart (Table 15–1). Consequently, this chapter considers RF-negative and RF-positive polyarthritis juvenile idiopathic arthritis (JIA) subsets separately, as distinctive clinical entities.

RHEUMATOID FACTOR–NEGATIVE POLYARTHRITIS

Epidemiology

Polyarthritis accounts for approximately 20% of JIA patients in British and Canadian studies, and of these approximately 85% have negative tests for RF as determined by standard assays.\(^3,4\) Within the polyarthritis subset the proportion that is seronegative for RF varies in accord with population ethnicity.\(^5-8\)

Incidence and Prevalence

Incidence and prevalence data, estimated from population surveys, vary widely as a consequence of differences in case ascertainment, diagnostic and classification criteria applied, accessibility to health care, referral patterns, and genetic and ethnic characteristics of the source population.\(^9\) The incidence of chronic childhood arthritis has been estimated at 7 to 21 per 100,000 in North American and Northern European population-based studies.\(^10-15\) Prevalence rates of 121 to 220 per 100,000 have been reported; metaanalysis has indicated a chronic childhood arthritis prevalence of 132 per 100,000 in population-based studies.\(^6\) Assuming that approximately 20% of the captured populations has polyarthritis and 85% of these are RF negative, the annual incidence and prevalence figures for RF-negative polyarthritis can be estimated to be 1 to 4 per 100,000 and 21 to 37 per 100,000, respectively.

Age at Onset and Sex Ratio

Although the RF-negative polyarthritis JIA subtype can begin at any age before 16, the onset age distribution displays a biphasic tendency, with one peak at 1 to 3 years of age and another encompassing later childhood and adolescence. RF-negative polyarthritis affects girls approximately 4 times more frequently than boys.\(^3,4\) The predominance of females is greater in those with an onset age during the teenage years (female/male ratio 10:1) than in those with a younger onset age (female/male ratio 3:1).

Geographic and Racial Distribution

JIA occurs worldwide but prevalences vary widely among geographical regions. Both RF-negative and RF-positive polyarthritis are overrepresented in some Native North American populations.\(^6\) Among a group of 113 children with polyarthritis from Saskatchewan, Canada, 31 (27.4%) were Native Canadians compared with the general Native Canadian population of 14.9%. Of the 31 children with polyarthritis, 17 (54.8%) were RF negative and 14 (45.2%) were RF positive, indicating a relatively higher proportion of RF-positive polyarthritis in this population than in the nonnative population. Oen and Cheang\(^6\) reported that polyarthritis accounted for a higher proportion of East Indian (61%), and North American Indian (64%) children with chronic arthritis, compared with caucasian children (27%). Saurenmann and colleagues\(^4\) analyzed ethnicity as a risk factor for JIA in a multiethnic cohort. Among 223 children with RF-negative polyarthritis, no significant differences in percentages of European and non-European patients were found. However, the Native Canadian Indian population had a high relative risk (3.2) of developing RF-negative polyarthritis.

Etiology and Pathogenesis

The etiology of polyarthritis is unknown. Like many rheumatic diseases, JIA is believed to have complex origins that include interactions among an array of susceptibility genes and as yet unidentified exogenous factors. Environmental and lifestyle influences have been proposed as factors promoting arthritis in the context of genetic vulnerability. Within the group of RF-negative polyarthritis, variations in clinical characteristics, courses, and outcomes suggest that this JIA class is more heterogeneous.
than the collective name suggests. Consequently, within this JIA subset, etiologies and pathogenic processes are likely varied.

As with other JIA subtypes, immune and inflammatory responses that characterize polyarthritis exhibit a predominantly proinflammatory profile during active disease and a regulatory, antiinflammatory profile during inactive disease.\(^{16,17}\)

No cytokine or chemokine response patterns in either blood or synovial fluid are unique to RF-negative polyarthritis. De Jager and colleagues\(^{16}\) noted comparable plasma level increases in interleukin (IL)-6 and -12, and chemokine C-C motif ligand (CCL)3, C-X-C motif ligand (CXCL)9, and CXCL10 in a small group of children with RF-negative polyarthritis (10 patients) and oligoarthritis with a polyarticular course (5 patients). In this same group synovial fluid levels of certain cytokines (IL-6 and IL-15) and chemokines (CCL12, CCL3, CCL11, CXCL8 and CXCL9) were higher in synovial fluid than in plasma. Increased levels of IL-17 have been found in seronegative polyarthritis (as well as in enthesitis-related arthritis) and are considered to be of potential pathogenic importance by promoting other proinflammatory cytokines and enhancing matrix metalloproteinases production, leading to cartilage degradation.\(^{18}\) CCL20 derived from synovial fluid mononuclear cells was increased in children with polyarthritis (including those with extended oligoarticular JIA); the enhanced production was attributed to the hypoxic synovial environment.\(^{19}\) The hypoxic synovial environmental also has been suggested as a factor that promotes increases in intraarticular vascular endothelial growth factor and osteopontin, which enhance angiogenesis in synovial tissue in children with RF-negative polyarthritis and extended oligoarthritis JIA subsets.\(^{20}\)

### Genetic Background

Evidence supporting a genetic influence in the pathogenesis of JIA includes ethnic variability in the incidence of certain JIA subsets, female preponderance, increased sibling recurrence rates of the same JIA subtype,\(^{21}\) and associations with both human leukocyte antigen (HLA) and non-HLA genes.

#### Human Leukocyte Antigen Genes

Genes both within and outside the major histocompatibility complex (MHC) have been evaluated for their contribution to genetic susceptibility to JIA. The HLA class I A2 allele confers susceptibility in RF-negative polyarthritis, as do the class II alleles DRB1*08, DQA1*04 and DPB1*03.\(^{22}\) These HLA-related profiles are distinct from those characterizing RF-positive polyarthritis\(^{22}\) and support the view that children without RF have a discrete disease that is different, at least genetically, from that of children with RF. Furthermore, some of the HLA alleles that confer susceptibility to RF-negative polyarthritis (A2, DRB1*08 and DQA1*04) also confer susceptibility to the oligoarthritis JIA subtype,\(^{22}\) suggesting that children with RF-negative polyarthritis are more allied genetically with the oligoarthritis JIA subtype than with RF-positive polyarthritis.

#### Non-HLA Genes

The TRAF1/C5 region located on chromosome 9q33-34 encodes the tumor necrosis factor (TNF) receptor-associated factor 1 and the complement component 5.\(^{23}\) In RF-negative polyarthritis patients, there is a significant increase in the A allele of a single nucleotide polymorphism (SNP) in the TRAF1/C5 region when compared with controls.\(^{23}\) Homozygotes for the susceptibility allele (AA) have an odds ratio (OR) of 2.51 (95% CI 1.23 to 5.14) compared with the homozygotes of the protective allele (GG), whereas heterozygotes have an OR of 1.50 (95% CI 0.81 to 2.77). In extended oligoarthritis (defined as the accumulation of more than 4 joints after 6 months from onset) and RF-positive polyarthritis, a trend towards an increased A allele frequency is observed (49% and 50% respectively, versus 41% in controls), suggesting a possible association of the allele with the polyarticular phenotype in general rather than with the RF-negative polyarticular subset specifically.\(^{23}\)

The protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) gene codes for lymphoid-specific phosphatase, which modulates antibody-mediated T cell activation. A missense SNP in the gene coding for PTPN22 reduces the ability to downregulate T cell activation and has been associated with JIA.\(^{24,25}\) Among the JIA subsets the strongest association of this SNP is with RF-negative polyarthritis.\(^{25}\) However, the association of the PTPN22 gene with JIA has not been found consistently,\(^{26,27}\) possibly a reflection of ethnic differences in the study populations.
The SLC11A1 (solute carrier family 11 member 1) gene regulates macrophage-mediated resistance to certain intracellular pathogens and is associated with susceptibility to certain infectious diseases and possibly, JIA. The SLC11A1 locus appears to exert an independent effect on JIA susceptibility, but in patients with RF-negative polyarthritis the locus appears to have an enhancing effect on disease susceptibility with the HLA-DRB1 locus.

Clinical Manifestations

In children with RF-negative polyarthritis articular disease predominates; extraarticular features are infrequent and are less severe than in those who are RF positive. Variations in onset ages, clinical and serological manifestations, and courses suggest the RF-negative class of polyarthritis comprises at least several different clinical entities. For example, some patients with RF-negative polyarthritis have a young onset age and positive tests for antinuclear antibody (ANA) and uveitis; apart from the number of involved joints, therefore, they are clinically indistinguishable from some patients with the oligoarthritis JIA subtype.

Joint Disease

Onset of arthritis may be acute, but it is more often insidious, with progressive involvement of additional joints. Morning stiffness or gelling after inactivity, indicative of active arthritis, may persist for hours, or occasionally all day. The arthritis may be remittent or indolent. The joints are swollen as a result of synovial hypertrophy and intraarticular fluid and may be warm but are generally not tender or red. Among children with RF-negative polyarthritis knees, wrists and ankles are the most commonly affected joints both at initial presentation and throughout the disease course. Small joint involvement of the hands or feet may occur early or late in the course of the disease; the second and third metacarpophalangeal (MCP) and proximal interphalangeal joints are most commonly affected. The distal interphalangeal joints are seldom affected in children with polyarthritis at onset. The temporomandibular joint (TMJ) is commonly affected in children with a polyarticular disease course regardless of onset subtype; children with the RF-negative polyarthritis are more likely to have TMJ involvement, particularly at long-term follow-up, than those who are RF positive. The earlier age at onset, when the TMJ might be more vulnerable to degradation processes, is thought to be the reason for the greater prevalence of involvement in the RF-negative group compared with the RF-positive group. Cervical spine involvement is not commonly recognized early in the course of RF-negative polyarthritis either clinically or radiographically. However, reduced range of motion of the cervical spine, particularly loss of extension, can occur later in the course of RF-negative polyarthritis and ankylosis of the apophyseal joints of the second and third vertebrae can be demonstrated radiographically (Fig. 15–1).

In children with RF-negative polyarthritis, the number of affected joints tends to be less and the pattern of involvement more asymmetrical than in RF-positive polyarthritis (Fig. 15–2). In RF-negative disease, involvement of wrists and small joints of the hands is less frequent than in RF-positive disease. Clinical signs of hip involvement are present in fewer than 20% of children with RF-negative polyarthritis at onset, but progressive radiographic abnormalities of the hip joint become evident with longer term following (Fig. 15–2). Oen and colleagues reported that radiological signs of hip joint involvement (early joint space narrowing and eventual growth abnormalities) were more likely to occur in RF-negative than RF-positive polyarthritis; the tendency
for RF-negative polyarthritis to have its onset at a younger age than it does in RF-positive disease might be a factor contributing to the higher prevalence of growth changes in the seronegative group.

In a small subset of RF-negative patients with polyarthritis, clinical signs of joint effusion and synovial hypertrophy are absent, although these children have joint stiffness and progressive joint contractures associated with laboratory indicators of inflammation. These children have been described as having “dry synovitis.” Ostrov has proposed preliminary criteria for dry synovitis as follows: Joint pain and stiffness reported in the patient history for at least 3 months, minimal joint effusion, minimally palpable synovial tissue on examination that is associated with morning stiffness for greater than 1 hour, loss of range of motion (with or without contractures) of involved joints detected on physical examination, and improvement in the symptoms and physical findings with appropriate medical treatment. This uncommon subset of polyarthritis can be considered a variant of RF-negative polyarthritis, although it has also been suggested to be a forme fruste of scleroderma. There is insufficient information about dry synovitis to definitively define its prevalence, clinical features, course, and response to treatment.

Systemic Manifestations

Systemic manifestations in children with seronegative polyarthritis are unusual but can include fatigue and growth failure. Low-grade fever seldom occurs.

Fatigue is a common symptom in children with polyarthritis and can be present even in the absence of active joint disease. Ringold and colleagues studied fatigue in 60 children with polyarthritis, of whom 24 (41.2%) were RF negative, using the PedsQL Multidimensional Fatigue Scale, which includes assessment of general fatigue, sleep/rest fatigue, and cognitive fatigue domains. Both children and their parents/proxies reported lower scores in all domains compared with controls. Factors contributing to fatigue can include pain and stress, decreased muscle mass, low aerobic and anaerobic capacity, a higher exercise heart rate, and the presence of anemia. Ward and colleagues did not find that sleep disturbances contributed to fatigue in a group of 70 children with JIA of whom 40 (50.7%) had the polyarthritis subtype.

Growth disturbances are common in JIA. In children with polyarthritis height-for-age Z scores (an expression of the number of standard deviations from the normal mean) may decline in the first several years of disease but tend to return to normal with longer term follow-up. In those children without RF, the negative deviation is less marked and less prolonged than in those with RF, although the difference tends to be significant only with longer disease duration. Low growth velocity tends to correlate with disease severity and activity and with the number of involved joints.

Extraarticular Manifestations

NODULES

Subcutaneous nodules occur rarely (<1%) in RF-negative polyarthritis. There is insufficient information to know the frequency with which subcutaneous nodules might eventually develop in the seronegative polyarthritis JIA group.

UVEITIS

After oligoarticular JIA (which accounts for more than one-half of JIA patients affected by uveitis), chronic asymptomatic uveitis is most common in the RF-negative polyarthritis group. Approximately 15% of children with RF-negative polyarthritis have uveitis, and children with RF-negative polyarthritis account for approximately 20% of all JIA uveitis patients. Sabri and colleagues reported that 32 of 142 JIA patients with uveitis (22.5%) had RF-negative polyarthritis; none of the children with RF-positive JIA had uveitis. As with the oligoarthritis JIA subgroup, uveitis in RF-negative polyarthritis tends to be associated with younger onset age and a positive test for ANA (see Chapter 20).

CARDIOVASCULAR AND PULMONARY DISEASE

RF-negative polyarthritis is not typically associated with overt cardiovascular pathology. Bharti and colleagues reported that children with arthritis, regardless of onset subtype, had significantly greater left ventricular volumes and other abnormalities suggesting abnormal left ventricular diastolic relaxation. However, patients with polyarticular disease had better diastolic left ventricular filling than did those with systemic or oligoarticular arthritis. The authors suggest that significantly higher blood pressure and heart rates in juvenile arthritis might account for the observed diastolic functional changes. They also speculate that subclinical diastolic dysfunction observed in children with juvenile arthritis might portend overt cardiovascular disease later in life. Knook and colleagues demonstrated lower 1-second forced vital capacity and peak expiratory flows in a group of 31 children with chronic arthritis, of whom more than two-thirds had RF-negative polyarthritis. These abnormalities were attributable to impairment in respiratory muscle strength rather than intrinsic restrictive or obstructive lung disease.

Differential Diagnosis

The differential diagnosis for a child with polyarthritis includes other rheumatic diseases, infection, other inflammatory conditions, malignancies, and metabolic and genetic disorders.

Rheumatic Diseases

The onset of polyarthritis in a girl later in childhood or during adolescence should suggest the possible diagnosis of systemic lupus erythematosus (SLE) (see Chapter 21). The arthritis of SLE may mimic that of JIA, although it is nonerosive and less likely to be deforming; the presence of other clinical hallmarks and a positive test for anti–double-stranded DNA antibodies establishes the diagnosis of SLE. SLE may develop years after the initial diagnosis of RF-negative polyarticular JIA.

The differential diagnosis of RF-negative polyarthritis also includes enthesitis-related arthritis (ERA) (see Chapter 17). Predominant involvement of large joints of the
lower extremities and the presence of enthesitis supports the diagnosis of ERA, although enthesitis can occur, albeit uncommonly, in other types of JIA.\textsuperscript{48}

Scleroderma begins insidiously with joint contractures of the small joints of the hands, mimicking features of polyarthritis but ordinarily without associated signs of intraarticular swelling. Arthritis may occur in childhood dermatomyositis but can be distinguished from JIA by clinical manifestations such as rash and muscle weakness.

**Infections**

Septic arthritis affecting multiple joints is unusual; only 3\% of the 63 children with septic arthritis reported by Al Saadi and colleagues\textsuperscript{49} had more than one involved joint. Elwood and colleagues\textsuperscript{50} reported the case of a child with longstanding polyarthritis who, while receiving immunosuppressive therapy for treatment of her arthritis, developed multifocal septic arthritis due to group A beta-hemolytic streptococcal infection. Lyme disease may be polyarticular, but it can usually be differentiated from RF-negative polyarthritis by its intermittent pattern of arthritis activity and the accompanying cutaneous, neurological, and cardiac abnormalities (see Chapter 39). Arthritis caused by *Neisseria gonorrhoeae* may have an early migratory polyarticular phase.\textsuperscript{51}

Reactive polyarthritis in response to infection in the respiratory, gastrointestinal, or genitourinary tracts can ordinarily be distinguished from JIA polyarthritis by a limited duration of the disease and associated clinical manifestations\textsuperscript{52,53} (see Chapter 39). Group A beta-hemolytic streptococcal throat infection can be associated with acute, painful, nonerosive, migratory polyarthritis (see Chapter 40).

**Malignancy**

Malignant infiltration of bone or synovium can mimic polyarthritis, although in most instances the malignant focus is in juxtaarticular bone rather than in the joint. (see Chapter 46). However, joint swelling can occur in acute lymphoblastic leukemia as a result of leukemic infiltration of the synovium. Involvement in malignancy tends to be oligoarticular rather than polyarticular.\textsuperscript{54} In addition to the systemic manifestations of malignancy, there may be moderate to severe anemia or elevation of an ESR that is out of keeping with other features of their disease.

**Other Inflammatory Conditions**

Arthritis associated with inflammatory bowel disease (see Chapter 19), or sarcoidosis (see Chapter 35) should be considered in the differential diagnosis of RF-negative polyarthritis. Sickle cell disease in the very young child causes diffuse, symmetrical swelling of the hands and feet (hand-foot syndrome) that may mimic true arthritis (see Chapter 41). Hypermobility syndromes, mucopolysaccharidoses, familial hypertrophic synovitis,\textsuperscript{55,56} familial arthritis and camptodactyly,\textsuperscript{57} familial osteochondritis dissecans,\textsuperscript{58} Stickler syndrome,\textsuperscript{59} velocardiofacial syndrome,\textsuperscript{60} Turner syndrome,\textsuperscript{61} and relapsing polychondritis\textsuperscript{62} are rare causes of disease that may suggest a diagnosis of polyarticular JIA.

**Laboratory Examination**

The laboratory provides evidence of inflammation, is useful in excluding other diagnoses, and is important in classification, prognosis, and guiding therapy.

**Indicators of Inflammation**

Children with polyarthritis typically have moderate elevations of ESR and C-reactive protein. Many have elevated white blood cell counts and platelet counts and a normocytic hypochromic anemia characteristic of chronic inflammation.

**Autoantibodies**

**RHEUMATOID FACTORS**

RFs are antibodies that bind to the CH2 and CH3 domains of the Fc portion of human or animal immunoglobulin (Ig) G (IgG). Customarily, RF is detected by particle agglutination assays such as latex fixation or nephelometric techniques that preferentially detect pentameric IgM RF. Approximately one-third of children with polyarthritis who do not have IgM RF detectable by agglutination methods have IgM RF detected when using a more sensitive enzyme immunoassay (EIA).\textsuperscript{63-68} RF detected by either technique is associated with deforming joint disease, joint space narrowing, and joint erosions.\textsuperscript{64,69} Furthermore, children with IgM RF-negative polyarthritis, as determined by conventional methods, can have “hidden RFs.” The hidden IgM RF is 19S IgM RF, which, because it is bound to IgG in the serum being tested, cannot generate a response in the standard agglutination assay until it is acid eluted from the IgG. Up to 85\% of children with polyarticular disease have been reported to have such antibodies, which are associated with active disease.\textsuperscript{70-72}

IgA RF, alone or in combination with IgM RF, has been associated with active disease or severe disability in polyarthritis.\textsuperscript{64,73} Using EIA, Gilliam and colleagues found IgA RF in 4 of 23 (17.4\%) and IgM RF in 9 patients (39.1\%) with RF-negative polyarthritis.\textsuperscript{64} Both IgA and IgG RFs are associated with joint space narrowing and joint erosions, although the correlation is substantially less than with IgM RF. Application of more sensitive methods, such as EIA, suggests the possibility that some “RF-negative” polyarthritis patients might be more appropriately assigned to the RF-positive polyarthritis category. Anti-citrullinated protein antibodies (ACPA) are found in 0\% to 17\% of children with RF-negative polyarthritis.\textsuperscript{64,74,75}

**ANTINUCLEAR ANTIBODIES**

ANA are present in approximately one half of children with RF-negative polyarthritis, typically in low to medium titers (1:80 to 1:640).\textsuperscript{76,77} In a group of 68 children with RF-negative polyarthritis reported by Ravelli and colleagues, 33 (48.5\%) were ANA positive.\textsuperscript{77} The group of ANA-positive RF-negative polyarthritis patients was not significantly different from the group with oligoarthritis with respect to age at first presentation, sex ratio, frequency of symmetrical arthritis, or prevalence of uveitis. Furthermore, the number of involved joints with limited range of motion was greater in the ANA-negative
group than the ANA-positive group. These observations suggest that ANA positivity, irrespective of JIA onset subtype, distinguishes a relatively homogenous group characterized by early onset, female predominance, asymmetric arthritis, and an increased risk of chronic uveitis. Thus, RF-negative polyarthritis, when associated with a positive ANA test, is more likely oligoarticular JIA than is ANA-negative polyarthritis. The antigenic specificities of ANA in JIA are generally unknown. Antibodies to individual histones and to histone-histone and histone-DNA complexes are occasionally, but inconsistently, found.

SYNOVIAL FLUID ANALYSIS

Synovial fluid analysis in RF-negative polyarthritis reveals a nonspecific inflammatory reaction that is not clearly distinguishable from that found in other JIA subtypes. In children with polyarthritis (including those with extended oligoarthritis), polymorphonuclear neutrophil counts in synovial fluid tend to be higher than in persistent oligoarticular disease but not significantly different from counts in systemic JIA or enteroarthritis. Cytokine, chemokine, and proteome profiles in synovial fluids are not well enough defined to be of practical clinical utility.

Radiological Examination

In radiographs taken within 2 years after disease onset, joint space narrowing (including decreased joint space, ankylosis, and carpal collapse) was demonstrated in 12% of one group of 39 children. Radiographs (obtained at last follow-up, a median of 6.5 years after onset) showed joint space narrowing in 43%. Erosions and growth abnormalities likewise increased with time (Chapter 10).

Pathology

Although the synovial membrane is the principal site of pathology in JIA, there is little substantive information about the histopathological and immunopathological characteristics of JIA joint tissues. The limited information available suggests that the histological appearance of the synovium is similar for all JIA subtypes, although greater hypervascularity in the polyarthritis group relative to ERA, psoriatic arthritis, and oligoarthritis has been noted.

Treatment

As with all forms of chronic childhood arthritis, RF-negative polyarthritis requires a multifaceted approach to management. The mainstays of treatment include early and judicious use of pharmacotherapy, physical and occupational therapy, and promotion of healthy lifestyles, including optimizing nutrition and physical activity. Achieving and sustaining complete disease control is no longer an unrealistically achievable objective.

Medical Management

Initial treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is appropriate. Naproxen or ibuprofen is most commonly used in North America, but indomethacin is favored by some pediatric rheumatologists in Europe and elsewhere. Some physicians combine initial NSAID therapy with a disease-remitting agent, usually methotrexate. In any event, failure of NSAIDs to control the disease within 6 to 8 weeks should prompt the addition of methotrexate. Methotrexate is usually given by mouth initially, in dosages of 10 to 15 mg/m²/week. In the absence of an adequate response, the dosage can be increased to 15 to 20 mg/m²/week, preferably administered subcutaneously. The response to methotrexate is usually excellent. For patients unresponsive to or intolerant of methotrexate, leflunomide is an alternate option, although there is insufficient information to evaluate leflunomide’s role in RF-negative polyarthritis specifically.

Anti-TNF agents are effective in treating children with polyarthritis who are unresponsive to methotrexate or leflunomide alone, although there is little information to indicate that RF status correlates with responsiveness.

Glucocorticoids are important as intraarticular therapy. Breit and colleagues reported a longer median duration of response to intraarticular triamcinolone hexacetonide in children with juvenile chronic arthritis who were RF negative (105 weeks) than in those who were RF positive (63 weeks). Glucocorticoids have a limited role as systemic therapy in polyarthritis, although judicious use of systemic steroids as a bridging agent can be considered until disease-modifying agents begin to have their effect. Drugs such as gold compounds and penicillamine are seldom used since the advent of generally safer and more efficacious pharmacotherapeutic options. Although hydroxychloroquine is at times used in RF-negative polyarthritis as an adjunctive agent, often in combination with methotrexate, there is little evidence to support its efficacy.

Exercise and Physical and Occupational Therapy

There is ample evidence indicating that regular participation in physical activity by children with JIA is beneficial. Although functional impairment generally correlates with the extent and severity of articular disease, poor fitness also occurs even in those with mild symptoms and persists even after disease remission.

Both aerobic and anaerobic exercise capacity is decreased in children with polyarthritis compared with oligoarticular disease; those with RF-positive polyarthritis are somewhat more limited than those with RF-negative disease (see Chapter 12).

Notwithstanding the advantages of active exercise, it is important to have a carefully designed passive therapy program. Children tend to function within the range of motion they have, not the range they should be trying to achieve. Focused physical therapy should be instituted as soon as the degree of inflammation subsides sufficiently to facilitate the child’s cooperation. Physical therapy aimed at restoration of normal range of motion can be facilitated by pretreatment with an analgesic such as acetaminophen and the application of heat or ice. Major contractures are often more amenable to therapy after intraarticular injection of triamcinolone hexacetonide.
Surgery
The need for surgical management is less common now than in the past as a consequence of more effective medical management. Nonetheless, some children with resistant or untreated disease will require joint replacement of hips, knees or, occasionally, small joints of the hands. Such procedures are seldom needed in childhood, but in adults with long-standing disease of juvenile onset they add greatly to function and quality of life. Prior to surgical procedures, the child with polyarthritis should be thoroughly evaluated for conditions that might increase risk. In polyarthritis, for example, cervical spine and temporomandibular joint involvement pose potential added anesthetic risks, immunosuppression can increase risks of perioperative infection, and poor bone quality can compromise the integrity of joint implants.

Course of the Disease and Prognosis
RF-negative polyarthritis is a chronic disease, lasting years or decades. Oen and colleagues reported that only 25% of 80 children with RF-negative polyarthritis diagnosed between 1977 and 1994 and followed for at least 5 years had gone into remission by age 16 years. Furthermore, children who had not gone into remission by this age were likely to have ongoing active arthritis into their late 20s or early 30s. These data suggest that RF-negative polyarthritis continues to be associated with substantial morbidity and functional disability in most affected children.

RHEUMATOID FACTOR–POSITIVE POLYARTHRITIS
RF-positive polyarthritis is defined by ILAR criteria as arthritis cumulatively affecting 5 or more joints during the first 6 months, in the presence of two positive tests for RF performed at least 3 months apart. In addition, exclusion criteria specified in the ILAR criteria must be applied (see Table 15–1).

The RF-positive polyarthritis subtype of JIA shares a similar clinical phenotype, serology, and immunogenetic profile with that of adult rheumatoid arthritis, and both can occur in the same family. In European populations, approximately 15% of children with polyarthritis are RF positive, representing approximately 3% of the JIA population.

Epidemiology
Incidence and Prevalence
The wide variations in reported incidences of RF-positive polyarthritis probably reflects differences in patient selection and geographical origin contributed to by both genetic and environmental influences. The reported frequencies of RF-positive polyarthritis range from 51% in a series of Native Canadian Indian children to 17% of East Indian, 14% of African-American, 12.5% of Japanese, 0.2 to 5% of European, and 1% of American children and adolescents with chronic arthritis. There is limited published information about incidence and prevalence rates for the RF-positive polyarthritis onset subtype. Estimated incidence rates of 0.3 to 0.5 per 100,000 person-years at risk have been reported or can be calculated from publications from Europe. In comparison, incidence estimates as high as 12.3 can be calculated from published data for East Coast Alaskan Indian children and 8.1 per 100,000 person-years at risk for Native Canadian Indian children in Manitoba. Similarly, estimates of point prevalence of 0 to 6.7 in Europe and 54 per 100,000 at risk for Manitoba Canadian Indian children can be calculated from published data.

Age at Onset and Sex Ratio
The mean age at juvenile onset of RF-positive polyarthritis is 9 to 11 years; range is 1.5 to 15 years. Affected girls outnumber boys from 4 to 13 to 1 in large series.

Etiology and Pathogenesis
As with other JIA subtypes, the etiology of RF-positive polyarthritis remains unknown. Whether there is a role of RFs or ACPA is speculation, but in adults these antibodies have been demonstrated years before the onset of overt rheumatoid arthritis, suggesting that they may have a pathogenic role. Clinical disease may not occur until ACPA are deposited in synovium, a process that is facilitated by immune complexes formed by RF. There are no comparable data for children. An analogous pathway likely applies to children with RF-positive polyarthritis, but triggers for citrullination may differ in the pediatric population.

Genetic Background
HLA Genes
RF-positive polyarthritis and adult RA share genetic predispositions. HLA antigens account for an estimated one-third of the genetic risk for RA. The shared epitope (SE), a specific sequence present on a number of HLA DR antigens, is associated with increased risk for both adult RA and RF-positive JIA. The SE is found on HLA-DR4 (HLA-DRB1*0401, *0404, *0408, or *0405), DR1 (DRB1*0101), and DR14 (DRB1*1402) alleles.

Population frequencies and particular SE-bearing HLA alleles vary in different ethnic groups. Thus, RF-positive polyarthritis and RA are associated with DR4 (DRB1*04) alleles, mainly DRB1*0401 and *0404, in Caucasian populations with relative risks ranging from 3.2 to 7.2 for the former and 3.8 to 8.9 for the latter. The associated allele is DRB1*0405 in Japanese and DRB1*1402 in some North American Native populations. Double doses of the SE further increase the relative risk of the disease.

In some Native North American Indian tribes both DRB1*04 alleles and DRB1*1402 carry the SE and are associated with RA, whereas in other populations the frequency of DRB1*1402 is so high that no significant increase is found in patients with RA. In Native
Canadian Indian children the situation is more complex because both the SE and DRB1*0901 occurring together as a genotype are associated with RF-positive polyarthritis. This dual association supports the suggestion that a greater genetic influence is associated with earlier age at onset.

Population frequencies of the SE tend to correlate with frequencies of RA and RF-positive polyarthritis. For example, the frequency of the SE in Caucasian populations is 27% to 36%, whereas Native North American Indian populations with high incidence and prevalence rates of RA and RF-positive polyarthritis have frequencies of 66% to 98%.

More recently the association of the SE has been found to be limited to ACPA-positive RA. ACPA are also associated with DR4, in children with polyarthritis.

**Non-HLA genes**

Attempts to discover associations of JIA with genes outside the MHC have been hampered by the relative rarity of JIA and its respective subtypes. Detecting gene association requires stratified analyses by JIA subtype because subtype-specific associations may be masked if only the total JIA group is considered. Furthermore, because of differences in population frequencies, cases and controls need to be selected from the same population.

Associations of CTLA-4 genes with both RA and JIA are controversial. The inconsistency in observed associations of CTLA-4 with JIA might relate to the specific SNP studied, population frequencies, patient selection, and lack of power. One study found no association between CTLA-4 and JIA in a large cohort of patients as a whole but showed a borderline association with RF-positive polyarthritis. Whole genome scans in JIA have failed to reveal specific associations with RF-positive polyarthritis.

**Clinical Manifestations**

**Joint Disease**

Upper and lower extremity large and small joints are affected, as well as the cervical spine and TMJs. The thoracic and lumbar spine and sacroiliac joints are spared. Although large joints are commonly involved, the characteristic pattern is symmetrical arthritis affecting the MCP and PIP joints of the hands, the wrists, and the MTP and PIP joints of the feet. In contrast to RF-negative polyarthritis, micrognathia does not usually occur with TMJ involvement because of the later age at onset. Early limited range of motion occurs at the wrists and can eventually progress to more substantial debility and deformity (Fig. 15–3). Deformities that develop at the hands include ulnar drift at the wrists and the MCP joints and boutonnière and swan neck deformities at the fingers (Fig. 15–4). Deformities that develop at the feet include hallux valgus deformity at the first MTP joints, hammertoe, and cock-up toe deformities.

**Systemic Manifestations**

Fatigue and weight loss may occur with active disease. Fever is rare in RF-positive polyarthritis, and a rash does not occur.
Extraarticular Manifestations

Other than nodules, extraarticular disease manifestations associated with adult RA described below rarely occur in patients with RF-positive polyarthritis onset subtype, whether during childhood, adolescence, or adulthood.

NODULES

The most common extraarticular signs in patients with RF-positive polyarthritis are rheumatoid nodules (Fig. 15–5). In Ansell’s series, 30% of patients with polyarticular RF-positive arthritis had rheumatoid nodules during the first year of disease. Nodules often occur distal to the olecranon and at other bony prominences and pressure points, on flexor tendon sheaths, Achilles tendon, and on the soles of the feet. They are firm, mobile, and nontender; however, pressure of the nodule against soft tissues or bone may cause pain. The presence of rheumatoid nodules indicates a poor prognosis. Accelerated nodulosis may occur in patients on methotrexate. In this case the nodules are multiple, develop over a short time, tend to occur on the hands, and regress on discontinuation of methotrexate. This complication has been described in two children with RF-positive polyarthritis and one with systemic JIA. Methotrexate-induced nodulosis is associated with minimal discomfort and may stabilize with use of hydroxychloroquine. Nodulosis associated with methotrexate does not necessarily preclude continuation of methotrexate therapy.

Rheumatoid nodules must be distinguished from subcutaneous nodules of rheumatic fever, which are smaller, so-called benign rheumatoid nodules that are not associated with chronic arthritis, and from granuloma annulare, which are small nodules arranged in a circular pattern.

VASCULITIS

Rheumatoid vasculitis is rarely described in RF-positive polyarthritis during childhood or adolescence. In 1978, Ansell noted nailfold and extensive cutaneous vasculitis in several patients during prolonged follow-up. However, the lack of reports of this complication in recent literature may reflect improved therapies for arthritis or less severe disease, as vasculitis in adults with RA tends to occur in those with the most severe disease.

FELTY SYNDROME

Felty syndrome consists of persistent neutropenia, splenomegaly, and RA and is associated with frequent infections. The bone marrow is normocellular, and the mechanism of neutropenia is complex, involving both antigranulocyte antibodies and decreased granulopoiesis. In adults, Felty syndrome occurs in RF-positive patients with long disease duration. It has been reported rarely in adolescents with RF-positive polyarthritis and in adults who had juvenile onset disease.

CARDIOVASCULAR AND PULMONARY DISEASE

Valvular heart disease has been reported in at least eight patients with childhood-onset RF-positive polyarthritis. Aortic insufficiency is the most common lesion. Patients present with sudden onset of congestive heart failure or may deteriorate suddenly after a variable period of stability following the detection of cardiac murmurs. Valve replacement is almost always required. Cardiac symptoms may start during childhood, adolescence, or adulthood, at intervals varying from 4 to 17 years from onset of JIA. However, pathological murmurs may be detected as early as 1 year after onset. Patients with JIA who have organic cardiac murmurs should be evaluated for valvular insufficiency and monitored carefully.

Pulmonary parenchymal disease, so-called rheumatoid lung, has been reported in seven children with RF-positive polyarthritis. Two types of pulmonary involvement have been reported: lymphoid interstitial pneumonitis and bronchiolitis obliterans or bronchiolitis obliterans organizing pneumonia (BOOP). These pulmonary complications may occur during childhood and adolescence or in adulthood. The time interval between the clinical presentation of pulmonary disease and onset of JIA has ranged from 10 years before to 20 years after onset of JIA. Symptoms include tachypnea, dyspnea, a nonproductive cough, and fever. On auscultation crackles and an end-inspiratory squeak are often heard. Diagnosis is based on clinical history and findings, pulmonary function tests, chest radiographs, and high-resolution computed tomography (HRCT). Bronchoalveolar lavage and/or lung biopsy may be necessary. Pulmonary function tests show reduced lung volumes and decreased diffusion capacity. A restrictive pattern is seen when interstitial pneumonitis is present and an obstructive pattern in BOOP. Chest radiographs may be normal or may show interstitial infiltrates. HRCT abnormalities include ground glass changes suggesting inflammation, bronchiectasis, or bronchiolectasis (suggesting BOOP), and honeycombing (suggesting fibrosis). The differential
diagnosis includes drug-induced pulmonary toxicity and infection. The prognosis of rheumatoid lung is variable in children and adolescents. Although a few patients have improved with corticosteroid therapy, others have deteriorated despite corticosteroid and immunosuppressive therapy.

**Differential Diagnosis**

The differential diagnosis of polyarthritis is discussed above. Specific diagnoses to be considered in the context of RF-positive polyarthritis are connective tissue diseases, reactive arthritis, and infections, in which polyarticular arthritis and a positive test for RF may occur concurrently. Among the connective tissue diseases, SLE and overlap syndromes, including mixed connective tissue disease, are diagnostic considerations in the child or adolescent with polyarticular arthritis who has a positive test for RF. RF is positive in 10% to 30% of children with SLE and in approximately two-thirds of children with mixed connective tissue disease. RF may be present in cases of acute rheumatic fever. Tuberculosis and subacute bacterial endocarditis can be associated with arthritis accompanied by a positive test for RF.

**Laboratory Investigations**

**Indicators of Inflammation**

These are identical to those in RF-negative polyarthritis discussed earlier.

**Autoantibodies**

**RHEUMATOID FACTOR**

The classification of RF-positive polyarthritis is based on the presence of two positive tests for RF performed at least 3 months apart in a patient who has polyarticular joint involvement during the first 6 months of disease. In practice, patients with RF-positive polyarthritis are characterized by persistently positive IgM RF, generally in high titre.

**ANTICITRULLINATED PROTEIN ANTIBODIES**

In children with JIA only those with polyarthritis onset subtypes have ACPA; however, similar to adults with RA, the concordance with RF positivity is not complete. Although individual series are small (9 to 20 patients), the frequency of ACPA in RF-positive polyarthritis varies from 57% to 90% (mean 73%), and, as discussed earlier, some patients (up to 17%) with RF-negative polyarthritis have positive ACPA tests. As in adults there is an association of ACPA positivity with DR4 and erosions. Currently, it is not clear that testing for ACPA in children with polyarthritis has prognostic value greater than RF.

**ANTINUCLEAR ANTIBODIES**

Positive tests for ANA have been reported in 80% of children with RF-positive polyarthritis and 57% of those with RF-negative polyarthritis.

**SYNOVIAL FLUID ANALYSIS**

Synovial fluid analyses from patients with RF-positive polyarthritis show an inflammatory fluid not clearly differentiated from that found in other forms of JIA. Synovial fluid cell counts and proportions of neutrophils may be higher in RF-positive polyarthritis than in those with oligoarticular arthritis.

**Radiological Examination**

Most information on joint damage in RF-positive polyarthritis comes from a limited number of studies of plain radiographs of patients treated before the introduction of biological therapies. Joint space narrowing and erosions occur within the first 1 to 2 years after onset and are most frequent at the wrists, hands, feet, and shoulders. At the wrist, cartilage loss occurs at the proximal wrist joint and in the intercarpal joints, resulting in carpal ankylosis and shortening. Both erosions and cartilage loss occur more frequently in RF-positive polyarthritis than in other forms of JIA. Atlantoaxial subluxation of the cervical spine is more frequent in patients with RF.
(36% frequency) than in other patients with JRA (16%) (Fig. 15–6)166 (see Chapter 10).

**Pathology**

**Synovium**

Despite similarities in overall appearance, the cellular infiltrates may differ among various types of arthritis. For example, immunohistological examination shows a greater predominance of CD4 T cells over CD8 T cells in polyarticular JRA and RA, compared with oligoarticular JRA and juvenile spondyloarthropathies.167

**Rheumatoid Nodules**

The mature rheumatoid nodule consists of characteristic zones.168 The innermost zone is a core of necrotic tissue containing cellular material surrounded by fibrinoid, an eosinophilic material composed mainly of fibrin. The next layer is a palisade of radially arranged elongated mononuclear cells, and the outermost connective tissue layer is a vascular region containing a lymphocytic infiltrate. Lymphocytes are found both in a perivascular and/or a diffuse distribution. Immunohistological studies have shown that the palisade consists of macrophages and the majority of the lymphocytes are T cells—both CD4 and CD8, in ratios of 1:1 to 3:1.168-170 B cells and plasma cells are scarce. Dendritic cells are also found in perivascular areas or scattered in the periphery of the nodules but are rare and are not found in close proximity to T cells.169

**Cardiac Valvular Lesions**

Excised aortic valves of children with RF-positive polyarthritis who have aortic insufficiency are grossly thickened.144,151 Granulomatous, nodular lesions are often present on the valve cusps.148,150,151 Histological findings include destruction of the normal architecture of the valve, granulomas that are histopathologically similar to rheumatoid nodules, nonspecific inflammatory changes, and fibrosis.144,146,148,150,151

**Pulmonary Lesions**

Lung biopsies of patients with RF-positive polyarthritis who have parenchymal lung disease show typical findings of interstitial pneumonia and bronchiolitis obliterans.152,153,155-157 In the former the alveolar septa are thickened by a predominantly lymphocytic infiltrate. Lymphoid follicles or germinal centers, plasma cells, and histiocytes are also seen within the septae. Bronchiolitis obliterans is characterized by infiltrates of lymphocytes and plasma cells in the bronchiolar wall, destruction of the respiratory epithelium, occlusion of bronchioles with plugs of inflammatory cells and mucus, and fibrosis and obliteration of bronchioles. In BOOP granulation tissue extends into the alveolar spaces. Chronic interstitial inflammation is seen concurrently with bronchiolitis obliterans or BOOP.156,157

**Treatment**

Aggressive medical treatment of RF-positive polyarthritis is warranted because of its almost uniformly poor prognosis.88 Children with this disease should be treated with NSAIDs and a disease-modifying antirheumatic drug (DMARD) at the time of diagnosis in the absence of contraindications. Methotrexate or methotrexate in combination with hydroxychloroquine and/or sulfasalazine should be the DMARD of first choice. If there is an inadequate response after 3 months, medications should be escalated. Consideration should be given to a combination of DMARDs or substituting leflunomide for methotrexate. NSAIDs should be used as adjunctive therapy because they can help improve symptoms but do not impact substantially on the disease course. Intraarticular steroid injections should be used, particularly for large, painful joints early in the treatment regimen. Low-dose prednisone, if used at all, should be limited to a bridging period until DMARD therapy becomes effective. Failure to respond adequately despite all these measures over 3 to 6 months is an indication for biologic therapy. As for patients with RF-negative polyarthritis, the total treatment plan includes patient and parent education, physical and occupational therapy, maintenance of physical activities, and optimal nutrition, including calcium and vitamin D.

**Course of the Disease and Prognosis**

**Mortality**

In 1983 Ansell reported an 8% mortality rate among 85 patients with RF-positive polyarthritis.136 Renal amyloidosis was the cause of death in 2 patients and quadriplegia resulting from cervical spine involvement complicated by infection in another.136 In a series of 24 patients with JRA and amyloidosis from Finland, the mortality rate 15 years after the diagnosis of amyloidosis was 42%, and the cause of death was renal failure in five, infection in three, leukemia in one, and one had a perioperative death.171 However, patients who died were not listed by onset subtype. No new case of amyloidosis complicating JIA had been reported since 1991 in Finland, and the complication appears to be increasingly rare worldwide.

More recent data also indicate an increased mortality in patients with JIA.172,173 In Scotland, the standardized mortality ratio (the ratio of observed to expected deaths), derived from International Classification of Disease codes on hospital records and linkage to national death registers, was 3.39 for males and 5.09 for females with musculoskeletal and connective tissue disease are most frequently related to circulatory or respiratory causes, although no details are available. Similarly, in Rochester, Minnesota, a high mortality of 0.27 compared with an expected rate of 0.068 per 100 patient years was calculated for adults with a history of JRA.173 The causes of death were other autoimmune disorders. No subtype-specific death rates are available in either report.

**Remission**

Remission is often imprecisely defined, but patients with RF-positive polyarthritis have the lowest remission rates among children with chronic arthritis, varying from no remissions to a 5% frequency of remission, off medications during 8 to 10 years of follow-up.174,176 However, clinical remission on medications can be achieved in 65% of patients.176
Disability

Until recently patients with RF-positive polyarthritis continued to have significant disability. The frequency of patients with severe disability or in Steinbrocker functional class III (capable of limited to few or no activities of usual occupation or self-care) or IV (incapacitated largely or wholly bedridden, capable of little or no self-care) was 15% in 1976 and 1994 publications and 5% in 2002 after mean or median disease durations of 14 to 20 years.173-177,178 However, in Childhood Health Assessment Questionnaires,18% of patients had scores of >1.5, reflecting severe disability.179 These reports originated from pediatric rheumatology centers, where selection bias may be less and follow-up times shorter than in reports from adult rheumatology clinics. For example, in an adult rheumatology clinic, 38% of adult patients with RF-positive polyarthritis since childhood and with a mean disease duration of 28 years were in Steinbrocker Class III or IV, and 53% had a health assessment questionnaire score of >1.5.179 Whether these poor outcomes will continue as treatment choices improve is a subject requiring continuing investigation.

REFERENCES


Entire reference list is available online at www.expertconsult.com.