Chronic Musculoskeletal Pain in Children: Part II. Rheumatic Causes

JENNIFER L. JUNNILA, M.D., M.P.H., *Army Medical Department Center and School, San Antonio, Texas*
VICTORIA W. CARTWRIGHT, M.D., M.S., *Madigan Army Medical Center, Tacoma, Washington*

Primary care physicians should have a working knowledge of rheumatic diseases of childhood that manifest primarily as musculoskeletal pain. Children with juvenile rheumatoid arthritis can present with painless joint inflammation and may have normal results on rheumatologic tests. Significant morbidity may result from associated painless uveitis, and children with juvenile rheumatoid arthritis should be screened by an ophthalmologist. The spondyloarthropathies (including juvenile ankylosing spondylitis and reactive arthritis) often cause enthesitis, and patients typically have positive results on a human leukocyte antigen B27 test and negative results on an antinuclear antibody test. Patients with acute rheumatic fever present with migratory arthritis two to three weeks after having untreated group A beta-hemolytic streptococcal pharyngitis. Henoch-Schönlein purpura may manifest as arthritis before the classic purpuric rash appears. Systemic lupus erythematosus is rare in childhood but may cause significant morbidity and mortality if not treated early. Nonsteroidal anti-inflammatory drugs and physical therapy may be useful early interventions if a rheumatic illness is suspected. Family physicians should refer children when the diagnosis is in question or subspecialty treatment is required. Part I of this series discusses an approach to diagnosis with judicious use of laboratory and radiologic testing. (Am Fam Physician 2006;74:293-300. Copyright © 2006 American Academy of Family Physicians.)

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This is part II of a two-part article on musculoskeletal pain in children. Part I, "Initial Evaluation," appears in the July 1, 2006, issue of *AFP*.

When a rheumatic cause of musculoskeletal pain in children is suspected, the primary care physician should develop an appropriate differential diagnosis; establish the most likely diagnosis, if possible; and begin initial treatment. Part I of this series[1] outlines a primary care approach to evaluating and diagnosing the child with musculoskeletal pain and discusses malignancy, benign nocturnal limb pains of childhood, and benign hypermobility syndrome. This article, part II of the series, addresses initial treatment of rheumatic disease and discusses the most common specific rheumatic conditions of childhood that manifest as musculoskeletal pain. Key features of these conditions are summarized in *Table 1*.[2-5]

Nonrheumatic causes of musculoskeletal pain—including sprains and strains, patellofemoral pain syndrome, stress fractures, and osteochondrosis—are much more common than rheumatic causes. Physicians must also be alert to the possibility of arthralgias secondary to malignancy. Dermatomyositis should be considered in any child with characteristic rash, arthritis, and weakness. Inflammation of the intervertebral disks (diskitis), spondylolysis with or without spondylolisthesis, and malignancy should be included in the differential diagnosis of back pain in children. Many inherited disorders with nonarticular manifestations (e.g., hemophilia, sickle cell disease) may present with arthritis or periarticular pain. Other rare causes of musculoskeletal pain in children include myofascial pain and chronic recurrent multifocal osteomyelitis.[6]

The American College of Rheumatology has published a consensus statement that provides referral guidelines for children with suspected rheumatic disease *(Table 2)*.[7] Children who should be referred include those with an unclear diagnosis and those who require long-term management of a diagnosed rheumatic condition. Although the effects have not been well studied in children, better outcomes with early referral have been demonstrated in adults with rheumatic disease.[8,9]

Initial Treatment

In the child with musculoskeletal pain suspected to be caused by a rheumatic condition, treatment should begin with administration of a nonsteroidal anti-inflammatory drug (NSAID); for example, ibuprofen (Motrin), at a dosage of 30 to 40 mg per kg per day in three

doses, or naproxen (Naprosyn), at a dosage of 10 mg per kg per day in two doses.[10,11] NSAIDs should be taken consistently for the anti-inflammatory effects to manifest. However, NSAIDs alone typically are not as effective for analgesia if synovitis is persistent. Subspecialists may initiate further treatment with immunosuppressants or cytotoxic agents. Intra-articular corticosteroids may be used as definitive therapy for monarthritis.[12] Systemic corticosteroids usually are reserved for patients with systemic symptoms that cannot be controlled by NSAIDs, after infection and malignancy have been ruled out. Additional treatment may include physical therapy aimed at maintaining range of motion.

Juvenile Rheumatoid Arthritis

The classification of juvenile rheumatoid arthritis, or juvenile idiopathic arthritis, has been revised in the past few years,[13] but the disease will be discussed here using the older American College of Rheumatology criteria.[14]

The estimated prevalence of juvenile rheumatoid arthritis is about one per 1,000, but worldwide it probably is underdiagnosed.[15,16] In one epidemiologic study[17] that included a physical examination by a pediatric rheumatologist, nine cases of chronic arthritis were identified in a group of 2,241 twelve-year-old children—a prevalence of four per 1,000.

Children with juvenile rheumatoid arthritis affecting a lower extremity typically present with a limp. The classic signs of inflammation are present in variable degrees; joints may be warm and swollen but not red or hot. Pain can be absent or mild in proportion to the amount of inflammation.[18] Joint pain has a high negative predictive value for inflammatory rheumatic disease in children: in one study,[19] 99 percent of children with pain as an isolated complaint did not have inflammatory disease. When pain was one of several reasons for referral, 91 percent of children did not have inflammatory disease. In addition, of 1,000 children visiting a primary pediatric practice with a complaint of pain, none was diagnosed with an inflammatory disease.[20]

The primary morbidity associated with juvenile rheumatoid arthritis is caused by idiopathic inflammatory eye disease. Uveitis occurs in approximately 10 to 30 percent of children with arthritis and usually is asymptomatic.[21] The pathogenesis of uveitis associated with juvenile rheumatoid arthritis is unknown, but the condition is more common in girls and in those with a positive antinuclear antibody (ANA) test result.[22]

The criteria for a diagnosis of juvenile rheumatoid arthritis are chronic arthritis lasting six weeks in at least one joint and exclusion of other causes of symptoms, or a classic clinical scenario suggestive of systemic-onset juvenile rheumatoid arthritis. There are three subtypes of juvenile rheumatoid arthritis—pauciarticular, polyarticular, and systemic-onset—distinguished by the number of joints involved during the first six months after onset. The associated morbidities and prognosis are different for each subtype.[23,24]

Juvenile rheumatoid arthritis is a diagnosis of exclusion; Lyme disease, leukemia, infection of bone or joint, psoriasis, inflammatory bowel disease, streptococcal infection, bleeding disorder, and vasculitis must be ruled out as causes of joint disease. Laboratory tests neither rule in nor rule out

juvenile rheumatoid arthritis: the diagnosis essentially is clinical. An elevated ANA titer is not a diagnostic criterion for juvenile rheumatoid arthritis, but it can be an indication for uveitis screening because patients with a positive ANA result are at greater risk of developing silent uveitis.[22,25] Erythrocyte sedimentation rate can be normal despite marked involvement of arthritis.

A study[26] published in 2003 found that although only 4 percent of family physicians felt up to date on the latest advances in juvenile rheumatoid arthritis treatment, only 32 percent referred all patients with juvenile rheumatoid arthritis to subspecialists for diagnosis and disease management. Access to subspecialists, insurance considerations, and geographic factors may impact this decision, but if possible, children with a presumptive diagnosis of juvenile rheumatoid arthritis should be referred to a subspecialist such as a pediatric rheumatologist for assistance with ongoing management.[7] An ophthalmologist should screen all children with arthritis for silent uveitis to help prevent associated morbidity.[22]

Spondyloarthropathies

The spondyloarthropathies are a group of conditions characterized by the classic clinical triad of arthritis, enthesitis (inflammation and tenderness at sites of tendon insertion), and the presence of human leukocyte antigen B27 (HLA-B27). The most common spondyloarthropathies are ankylosing spondylitis, reactive arthritis (Reiter syndrome), psoriatic arthritis, and the arthritides of inflammatory bowel disease. The overall prevalence is estimated to be two per 1,000.[3]

Although psoriatic arthritis is uncommon in childhood, the diagnosis is straightforward with the simultaneous presence of psoriasis and arthritis. Arthritis may be the initial manifestation of inflammatory bowel disease; therefore, any child with arthritis who has chronic or recurrent abdominal pain, weight loss, or lack of appropriate weight gain should be evaluated thoroughly. Children with one of the spondyloarthropathies, with the exception of psoriatic arthritis, most often have negative test results for ANA and

rheumatoid factor. The HLA-B27 test has a sensitivity of 84 percent and a specificity of 96.5 percent for spondyloarthropathy, corresponding to positive and negative likelihood ratios of 24 and 0.16, respectively.[27]

ENTHESITIS

Enthesitis typically manifests as ankle pain, heel pain, Achilles' apophysitis, and back or hip stiffness. Enthesitis may be present alone or with arthritis, as in seronegative arthritis enthesopathy, a syndrome seen in approximately 20 percent of children with rheumatic disease.[28] Enthesitic pain typically is worse at the end of the day after vigorous activities, but usually it does not limit activities. Children with enthesitis may have symptoms for several years before seeking treatment, and there may be a family history of similar complaints. Most children with enthesitis have remission of symptoms without any further progression of disease. Some children with enthesitis and a positive HLA-B27 test result or concomitant arthritis develop a spondyloarthropathy.

> The primary morbidity associated with juvenile rheumatoid arthritis is caused by idiopathic inflammatory eye disease.

JUVENILE ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is present in approximately one per 1,000 women and two per 1,000 men,[3] although the prevalence in children is expected to be much lower because of the natural course of the disease. Clinical features of juvenile ankylosing spondylitis include lumbar back pain, prolonged morning stiffness that improves with exercise, and arthritis of one or more peripheral joints. Classification criteria are based on the typical presentation and use clinical findings such as spinal pain, arthritis, or enthesitis; presence of HLA-B27; family history of similar disease; and associated symptoms such as uveitis or colitis.[29] Onset usually occurs in late childhood or adolescence, and a much higher occurrence is found in boys. The most common extra-articular involvement is symptomatic uveitis.

Laboratory tests have few distinguishing features for the diagnosis of juvenile ankylosing spondylitis and should not be

TABLE 1

Common Rheumatic Conditions of Childhood That Manifest as Musculoskeletal Pain

Condition	Clinical findings
Acute rheumatic fever or streptococcal infection–related arthritis	Migratory arthritis two to three weeks after streptococcal pharyngitis; age of onset usually school age, with distribution proportionate to risk for streptococcal infection Persistent arthritis may indicate streptococcal infection–related arthritis.
Benign hypermobility syndrome	Intermittent pains at night; age of onset usually three to 10 years, more common in girls
Benign nocturnal limb pains of childhood ("growing pains")	Cramping lower-leg pain in the evenings or nights; age of onset is three to 10 years
Henoch-Schönlein purpura	Rash, abdominal pain, often triggered by upper respiratory tract infection; age of onset typically school age, median is four years.
Juvenile rheumatoid arthritis	Three subtypes distinguished by the number of affected joints: *Pauciarticular:* Limp with nonpainful joint swelling involving four or fewer joints; age of onset usually younger than eight years *Polyarticular:* Joint swelling involving five or more joints, diminished use; bimodal age distribution, one to six and 11 to 16 years *Systemic-onset:* Daily fevers with high spikes, recurring evanescent erythematous rash, variable joint involvement, hepatosplenomegaly, generalized lymphadenopathy; age of onset varies
Malignancy (osteosarcoma, rhabdo-myosarcoma, leukemia, lymphoma)	Painful joints, bone pain, constitutional symptoms; no age predominance because clinical presentations vary
Spondyloarthropathies	
Arthritis with enthesitis	Ankle pain, heel pain, Achilles' apophysitis, back or hip stiffness; pain typically worse at the end of the day
Ankylosing spondylitis	Lumbar back pain and stiffness in young men; usually age 13 or older
Reactive arthritis (Reiter syndrome)	Painful joint with swelling following gastrointestinal or genitourinary infection; usually age 13 or older
Psoriatic arthritis	Psoriatic rash
Arthritides of inflammatory bowel disease	Chronic or recurrent abdominal pain, weight loss or lack of appropriate weight gain, malaise
Systemic lupus erythematosus	Painful, typically symmetrical arthritis; more common in adolescents and in girls

ANA = antinuclear antibody; ESR = erythrocyte sedimentation rate; CBC = complete blood count; HLA = human leukocyte antigen.

Information from references 2 through 5.

relied upon.[30] Definitive diagnosis requires radiologic evidence of sacroiliac arthritis,[29] although sclerosis may not develop until adulthood. Magnetic resonance imaging and computed tomography are more sensitive than plain radiography and bone scan for juvenile ankylosing spondylitis.[31]

REACTIVE ARTHRITIS

Reactive arthritis describes a diverse group of aseptic inflammatory arthritides and is the most common type of inflammatory polyarthritis in males 13 years or older. It typically follows a gastrointestinal infection or nongonococcal urethritis. Diagnosis is made

Physical examination findings	Associated findings
Characteristic rash; carditis is a serious complication; chorea is a late finding and can occur years after the illness.	Evidence of antecedent streptococcal infection (see Table 3)
Evidence of hypermobility (i.e., hyperextended metacarpophalangeal joints, elbows, or knees)	Must rule out other disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome, Down syndrome); positive family history common
Normal during and after episode	Laboratory tests and radiography usually unnecessary; results generally normal
Purpuric rash, nonspecific swelling	Hematuria and proteinuria if renal involvement; check for hypertension; urinalysis at least monthly for six months to evaluate for renal involvement
Swelling/synovitis, rash, constitutional symptoms; uveitis usually insidious and found only on routine eye screening, although patients may present with pain, redness, photophobia, or visual changes	Laboratory testing not helpful: rheumatoid factor, ANA, and ESR results may be normal; CBC may be abnormal in systemic disease. An elevated ESR is worrisome for other diagnoses, such as malignancy[2] or infection.
Ill appearance, malignant effusions, joint swelling	CBC abnormal (any cell line), or paradoxical inflammation with normal platelets and elevated ESR[3]; radiographs may show abnormalities
Inflammation and tenderness at sites of tendon insertion	Positive family history common
Painful iritis common	HLA-B27 result usually positive; ANA result often negative; platelet count and ESR can be elevated
Acute, asymmetric, lower-limb arthritis typical; painful iritis/conjunctivitis classic	HLA-B27 result usually positive; ANA result often negative
Arthritis may precede psoriasis; dactylitis may occur.	HLA-B27 result often positive
Large-joint arthritis	HLA-B27 result often positive; ANA result often negative
Rash, arthritis, lymphadenopathy, central nervous system–related symptoms	High titers of ANA (typically > 1:640)[4]; presence of anti–double-stranded DNA; presence of anti-Smith antibodies; presence of anticardiolipin antibodies (in up to 65 percent of children with the disease)[5]; possible presence of lupus anticoagulant and antiphospholipid antibodies; cytopenias; low serum complement levels (falling serum complement levels [C3, C4, or both] may signal worsening disease and precede flares of renal involvement); nephritis

clinically with inflammatory arthritis and a history of recent infection, after exclusion of other causes of arthritis such as streptococcus or septic arthritis. Laboratory studies may be inconclusive but should be used according to the history and clinical findings—for example, an antistreptolysin-O antibody test in the setting of a possible streptococcal infection (to rule in or out a diagnosis of infectious arthritis), or synovial fluid culture analysis if the joint is red, hot, and swollen—because reactive arthritis and septic arthritis can be clinically indistinguishable.[32]

Symptoms of reactive arthritis tend to

TABLE 2

Indications for Referral in the Child with Suspected Rheumatic D

TABLE 3

Clinical Features of Acute Rheumatic Fever

Evidence of antecedent group A streptococcal infection
Throat culture positive for group A streptococcal infection
Positive result for rapid streptococcal antigen test
High or rising titer of antistreptococcal antibodies

Major manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

Minor manifestations
Arthralgia
Fever
Elevated erythrocyte sedimentation rate or C-reactive protein level
Prolonged PR interval

NOTE: *Evidence of antecedent group A streptococcal infection with two major manifestations or one major and two minor manifestations indicates a high likelihood of acute rheumatic fever.*

Adapted with permission from Dajani AS, Ayoub E, Bierman FZ, Bisno AL, Denny FW, Durack DT, et al. Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 1993;87:303.

be self-limiting, of up to six months' duration. Even so, appropriate diagnosis and adequate treatment are important to prevent the development of long-term disability.

Acute Rheumatic Fever

The precipitating cause of acute rheumatic fever is pharyngitis caused by the group A beta-hemolytic streptococci *Streptococcus pyogenes*. The clinical manifestations typically occur two to three weeks after onset of streptococcal pharyngitis, and the inflammatory process stems from an immune reaction to the streptococcal infection rather than the effects of extracellular toxins or direct bacterial invasion.

Arthritis is the most common symptom, occurring in 49 to 78 percent of patients with acute rheumatic fever,[33,34] and typically involves large joints such as the knees, ankles, wrists, and elbows; axial disease is rare. Migratory joint disease is classic and the arthritis rarely lasts for more than one week. Inflammatory carditis is the most serious manifestation of acute rheumatic fever and may cause permanent cardiac valve disease and acute cardiac decompensation.

The modified Jones criteria help make the diagnosis of acute rheumatic fever *(Table 3)*.[35] High titers of antistreptolysin-O antibodies may provide supporting evidence of antecedent streptococcal infection. If a patient experiences no relief in their arthritis after five days of therapy with NSAIDs, the physician should consider a different diagnosis, such as poststreptococcal arthritis. Acute rheumatic fever can be prevented by appropriate antibiotic treatment of streptococcal pharyngitis.

Henoch-Schönlein Purpura

Often triggered by an upper respiratory tract infection, Henoch-Schönlein purpura is the most common systemic vasculitis in children, with an incidence of about 14 per 100,000 in school-age children.[36] The classic palpable, purpuric rash is the typical presenting complaint for most children with Henoch-Schönlein purpura, although in 25 percent of children this is preceded by arthralgia or arthritis, which also are common symptoms.[37]

Physicians should be aware of the classic triad of purpura, colicky abdominal pain, and arthritis. Other manifestations include transient hematuria, nephritis, subcutaneous edema, pulmonary hemorrhage, headache, seizures, hematemesis, intussusception, and scrotal swelling.

All children with Henoch-Schönlein purpura should have routine and microscopic urinalyses, a serum creatinine test, and a blood urea nitrogen test, because patients with renal involvement may develop renal failure. The arthritis of Henoch-Schönlein purpura does not lead to permanent sequelae and the rash resolves spontaneously. Henoch-Schönlein purpura is a self-limited disease with excellent outcomes if no renal involvement occurs.

Systemic Lupus Erythematosus

Ten to 15 percent of patients with systemic lupus erythematosus are children. The condition may affect males or females at any age and is more common among women.[3] Estimated prevalences are one per 1,000 in white women of ages 15 to 64 years and four per 1,000 in black women of the same ages; there are few data available for prevalences in persons younger than 18 years.[3] Incidence is estimated to be about four new cases per 1 million persons per year.[38]

Systemic lupus erythematosus can manifest in children as signs of arthritis as well as fever, weight loss, and malaise. The arthritis associated with systemic lupus erythematosus typically is painful (unlike the arthritis of juvenile rheumatoid arthritis) and symmetrical. The classic malar rash is present in only two thirds of children with systemic lupus erythematosus,[39] and it may be attributed to other causes; therefore, it cannot be relied upon for diagnosis. Other clinical features of systemic lupus erythematosus may include painless mouth ulcers, glomerulonephritis with hematuria and proteinuria, and coma or psychosis. Laboratory evaluation may find specific changes such as cytopenias (in 70 percent of cases), high titers of ANA, or the presence of anti–double-stranded DNA (in 73 percent of cases) or anti-Smith antibodies (31 percent).[39]

Physicians must promptly recognize when a child has a high likelihood of systemic lupus erythematosus (e.g., presence of arthritis and constitutional symptoms) and refer him or her immediately for diagnosis and appropriate intensive therapy; survival rates are excellent to satisfactory for patients who receive aggressive treatment. Daily sunscreen also should be included in the treatment plan for all children with systemic lupus erythematosus.

The Authors

JENNIFER L. JUNNILA, M.D., M.P.H., is an active-duty family physician with the U.S. Army. She is currently assigned at the Army Medical Department Center and School, San Antonio, Tex., where she is an instructor in the Interservice Physician Assistant Program. She received her medical degree from the Medical College of Wisconsin, Milwaukee, and completed a residency in family practice at Waukesha (Wis.) Memorial Hospital. She completed her master's of public health degree at the University of Washington, Seattle.

VICTORIA W. CARTWRIGHT, M.D., M.S., is Chief of Pediatric Rheumatology at Madigan Army Medical Center, Tacoma, Wash. She completed a master's degree in epidemiology at the University of Washington School of Public Health and Community Medicine, Seattle, and a fellowship in pediatric rheumatology at Children's Hospital and Regional Medical Center, University of Washington, Seattle.

Address correspondence to Jennifer L. Junnila, M.D., M.P.H., Army Medical Department Center and School, Attn: Interservice Physician Assistant Program, Fort Sam Houston, TX 78234 (e-mail: Jennifer.Junnila@us.army. mil). Reprints are not available from the authors.

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