Laboratory Evaluation of Children With Rheumatic Disease

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Diagnoses of rheumatologic diseases in children are based on clinical assessment of the history and physical examination. This is evident by the emphasis placed on clinical parameters in the classification criteria of diseases such as systemic lupus erythematosus,[1] Behçet's disease,[2] psoriatic arthritis,[3] and many others. However, laboratory tests also play a major role in the evaluation and care of children with suspected or confirmed rheumatologic illness. They are used as screening tools, to assist in diagnosis, to help monitor the status of established disease, and to assess for treatment complications.

Screening tests are often employed when a child presents with vague complaints, such as arthralgia, fatigue, or fever. Abnormal results increase suspicion of an inflammatory process, which at this point may be still undefined. More specific laboratory studies may help support a diagnosis. Examples of these are antinuclear antibodies in suspected systemic lupus erythematosus or elevated angiotensin-converting enzyme levels in suspected sarcoidosis. Laboratory tests are used to assess disease activity. For example, decreased complement levels in systemic lupus erythematosus or increased antineutrophil cytoplasmic antibody values in Wegener's granulomatosis may suggest disease exacerbation. Finally, routine laboratory tests, including complete blood cell counts, urinalyses, and renal and hepatic functions, are performed periodically to monitor for drug-related toxicities.

This article reviews specific laboratory studies frequently obtained for children with suspected rheumatologic illness and discusses laboratory findings in specific diseases. The laboratory approach to various rheumatologic scenarios found in primary pediatric practice is also presented.

EDUCATIONAL OBJECTIVES

1. Review laboratory findings associated with specific pediatric rheumatic diseases.
2. Critically interpret laboratory results with special awareness of false-positive results encountered in commonly ordered analyses.
3. Recognize the values and limitations of laboratory assessment in the diagnosis of pediatric rheumatic diseases.

SPECIFIC LABORATORY STUDIES

Acute Phase Reactants

Acute phase proteins are plasma proteins that fluctuate in response to inflammation (Table 1).[4] Synthesis of acute phase proteins, which takes place primarily in the liver, is affected by cytokines. Cytokine production, primarily by macrophages and monocytes, is triggered by a

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variety of conditions, including infection, autoimmune disease, and malignancy. Interleukin-6, interleukin-1–beta, and tumor necrosis factor–beta are potent inducers of acute phase proteins. The most common acute phase protein tests are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

ESR. Acute phase proteins, primarily fibrinogen, interact with erythrocyte membranes to cause clumping of the cells and thereby affect the rate at which they fall through plasma. The ESR has been used for more than 50 years in many clinical settings with extensive reports in the literature. Problems with the ESR include its relatively slow change related to patient condition and the influence of various clinical conditions on results. The ESR may increase with pregnancy, renal failure, and anemia, and it may decrease with congestive heart failure, cryoglobulinemia, and hypofibrinogenemia.[5]

CRP. The serum CRP level increases rapidly after tissue injury or inflammation. Values are quantitative and can be reported either as mg/L or mg/dL, so care must be taken when comparing values from different laboratories. An advantage over the ESR is that it changes more quickly in response to improvement or deterioration of a patient's inflammatory condition. Also, the CRP level is not affected, as is the ESR, by the clinical situations noted above. Although some have recommended that the CRP replace the ESR, the latter still has popular and clinical value. For example, in systemic lupus erythematosus, the ESR more accurately reflects disease activity. The CRP level is often normal in patients with active systemic lupus erythematosus, and its increase may suggest infection.[6]

TABLE 1

Response to Inflammation of Selected Acute Phase Proteins

Proteins that increase in response to inflammation
C-reactive protein
Fibrinogen
Plasminogen
Ferritin
Complement levels
Ceruloplasmin
Haptoglobin
Hemopexin
Granulocyte colony-stimulating factor
Interleukin-1 receptor antagonist
Serum amyloid A
Alpha-1 antitrypsin
Proteins that decrease in response to inflammation
Albumin
Insulin-like growth factor 1
Transferrin
Alpha-fetoprotein

Rheumatoid Factor

Rheumatoid factor is an immunoglobulin directed against the Fc portion of IgG. In clinical practice, IgM rheumatoid factor is generally measured, although IgG and IgA isotypes have been detected. A variety of techniques are used to detect IgM rheumatoid factor, including latex fixation, sheep red cell agglutination, enzyme-linked immunosorbent assay (ELISA), and nephelometry. Higher titers of rheumatoid factor are associated with more severe joint disease, extra-articular features, and disability. Rheumatoid factor is detectable in approximately 85% of adults with rheumatoid arthritis. However, it is found in less than 10% of children with juvenile rheumatoid arthritis, usually in older children with polyarticular disease . Therefore, it is a poor screening test for juvenile rheumatoid arthritis.[7] Children with rheumatoid factor–negative juvenile rheumatoid arthritis rarely convert to rheumatoid factor–positive disease. Children with rheumatoid factor–positive juvenile rheumatoid arthritis frequently have aggressive joint disease and extra-articular manifestations that resemble the course of adults with rheumatoid factor–positive arthritis.

Rheumatoid factor is frequently found in other rheumatologic diseases, including systemic lupus erythematosus and scleroderma, and may also be found in patients with infection, especially subacute bacterial endocarditis and hepatitis B and C (Table 2).[8]

Antinuclear Antibodies (ANAs)

ANAs are autoantibodies directed against various nuclear components. The classic screening

TABLE 2

Selected Conditions in Which Rheumatoid Factor May Be Elevated

Rheumatic diseases
Rheumatoid arthritis (> 80%)
Juvenile rheumatoid arthritis (5% to 10%)
Systemic lupus erythematosus
Mixed connective tissue disease
Sjögren's syndrome
Systemic scleroderma
Mixed cryoglobulinemia
Miscellaneous illnesses
Sarcoidosis
Silicosis
Interstitial pulmonary fibrosis
Primary biliary cirrhosis
Infections
Subacute bacterial endocarditis
Leprosy
Parasitic disease
Hepatitis B and C
Parvovirus B19
Other viral infections
Malignancies
Leukemia

technique to detect the presence of ANAs is the fluorescent antinuclear antibody test. Serial dilutions of serum are incubated with a cell substrate (the HEp-2 human larynx epithelioma cancer cell line is currently used). Fluorescein-tagged anti-human IgG is added, and the pattern of fluorescence and the serum titer at which the fluorescence disappears are reported. Various fluorescence patterns are recognized, with homogenous (or diffuse) and speckled most common (Figure A–C). The patterns are not as specific for detecting the various ANA subtypes (see below) as are specific tests, such as the currently available ELISA and immunoblotting techniques. Many laboratories now report an ANA index, which is a less expensive screening test. When results of this test are positive, the standard immunofluorescent test should be performed to confirm and quantify results.

ANA titers of 1:40 or greater are considered positive. The ANA screening test is sensitive: 98% to 99% of patients with systemic lupus erythematosus have positive results.[9] However, the test is exceedingly nonspecific. Tan et al. showed that 31.7% of healthy adults (20 to 60 years old) had positive ANA test results of 1:40, and 5% had positive results of 1:160.[10] Furthermore, the ANA test result may be positive in patients with rheumatologic diseases other than systemic lupus erythematosus, organ-specific autoimmune disease, or certain infections[11] and in patients taking specific medications (Table 3). False-positive values in children are often associated with viral illnesses.

When the results of the ANA screening test are positive, especially at a higher titer (> 1:160), and there is clinical suspicion of an autoimmune disease, testing for specific ANAs may be indicated. Many of these antibodies are described below.

Anti–Double-Stranded DNA. These autoantibodies are assayed by various techniques, including the Farr, crithidia (Figure D), and ELISA methods.[12] They are specific for systemic lupus erythematosus, and are present in approximately 40% of patients at the onset of systemic lupus erythematosus and 70% of patients during the course of their disease.[13] They are implicated in the pathogenesis of this disease because they are found in immune complexes, especially in the kidneys. A decrease in the anti–double-stranded DNA titer or quantitative value is often associated with decreased disease activity.

Anti-Histone Antibodies. These are nonspecific antibodies seen in systemic lupus erythematosus, but are often associated with drug-induced lupus when found as the main antibody in a patient with systemic lupus erythematosus.

Extractable Nuclear Antigens. Antibodies to extractable nuclear antigens are non-histone antibodies associated with systemic lupus erythematosus and mixed connective tissue disease. Anti-Sm is specific for systemic lupus erythematosus, although it is not sensitive, being present in only 20% of patients.[13] Presence of high titers of anti-U1 ribonucleoprotein in the absence of anti–double-stranded DNA or anti-Sm is associated with the diagnosis of mixed connective tissue disease.[14]

Other Non-Histone Antibodies. Anti-Ro or anti–SS-A is associated with Sjögren's syndrome and may be present in systemic lupus erythe-

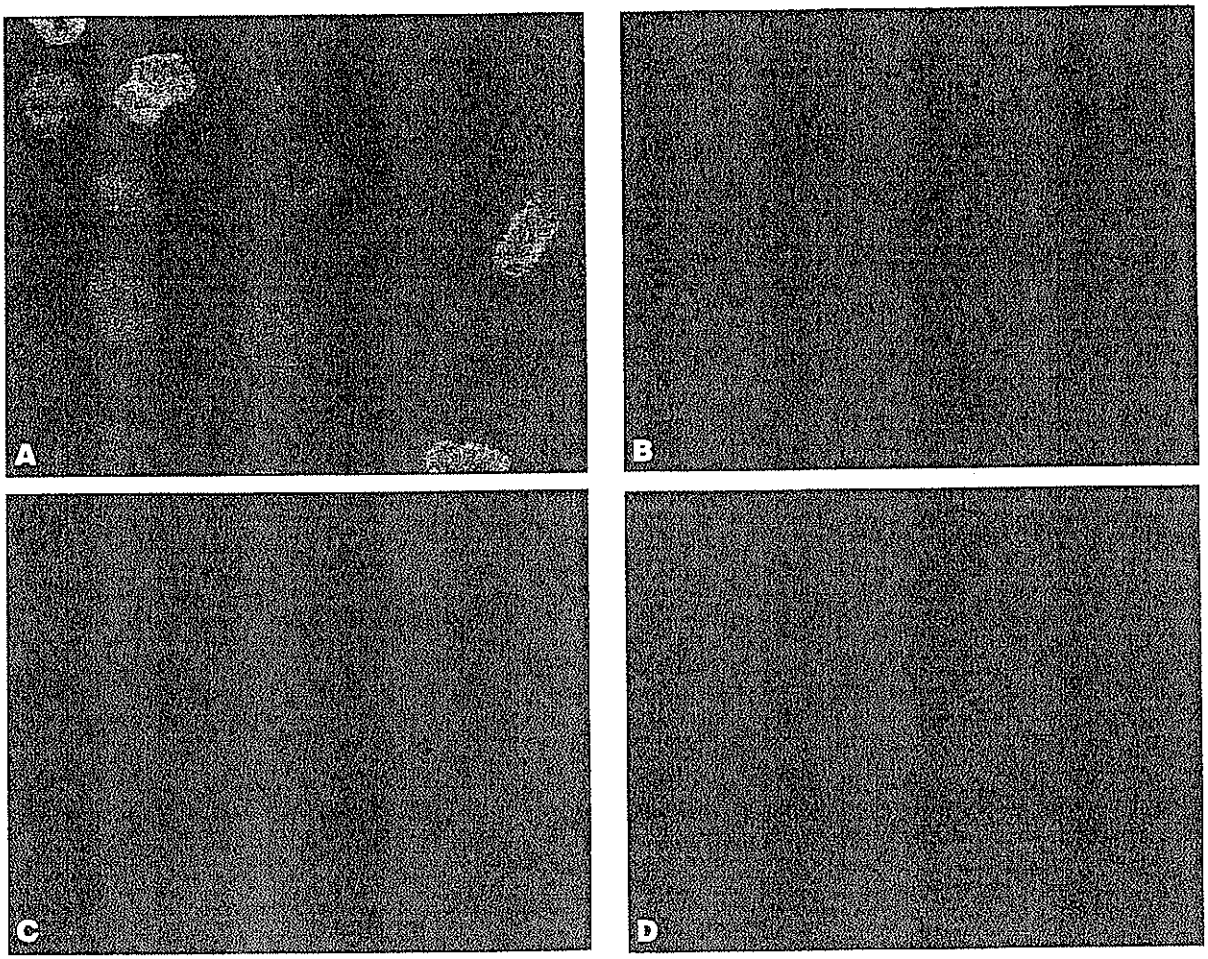

Figure. Indirect immunofluorescent patterns of antinuclear antibodies (ANAs) on HEp-2 cell line and of anti–double-stranded DNA by crithidia. (A) Homogenous or diffuse staining of ANAs, often seen in the presence of antihistone antibodies, anti–double-stranded DNA, or both. (B) Speckled pattern indicative of autoantibodies directed against Sm and U1 ribonucleoprotein. The speckled pattern for SS-A and SS-B is less coarse. (C) Anti-centromere pattern with staining of the interphase nuclei, characteristically seen in limited scleroderma (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia). (D) Demonstration of anti–double-stranded DNA using the protozoa *Crithidia luciliae*. The kinetoplast at the base of the flagellum consists only of double-stranded DNA, and therefore immunofluoresces in the presence of anti–double-stranded DNA and is specific for this autoantibody. (Courtesy of Dr. Mary Smaron and Scott Matushek, University of Chicago Laboratories.)

matosus. It may be positive even in the absence of a positive result on ANA testing. It is strongly associated with neonatal lupus syndrome and is implicated in the pathogenesis of congenital heart block in this entity. Anti-La or anti–SS-B may be positive in systemic lupus erythematosus and Sjögren's syndrome. It is also associated with neonatal lupus syndrome, although it is not present as frequently as anti-Ro or anti–SS-A (75% vs > 90%).[15]

Anti-Scl70 is seen in approximately 25% of adults with progressive systemic sclerosis, but is uncommon in children. Anti-centromere antibodies are specific for CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), which is a variant of scleroderma. Anti–Jo-1 antibodies are found in approximately 20% of adults with dermatomyositis or polymyositis, but rarely in children (< 5%).[13]

Complement

The complement system consists of more than 30 plasma and membrane proteins that serve as promoters of inflammatory response and augment or "complement" humoral immunity.

TABLE 3

Selected Conditions in Which Antinuclear Antibodies May Be Positive

Healthy individuals
Increased frequency with aging
Females more than males
Systemic autoimmune disease
Systemic lupus erythematosus
Mixed connective tissue disease
Scleroderma
Polymyositis
Dermatomyositis
Sjögren's syndrome
Rheumatoid arthritis
Juvenile rheumatoid arthritis
Organ-specific autoimmune disease
Autoimmune hepatitis
Primary autoimmune cholangitis
Autoimmune thyroid disease
Drugs
Procainamide
Hydralazine
Isoniazid
Minocycline
Penicillamine
Quinidine
Anticonvulsants
Diltiazem
Chlorpromazine
Methyldopa
Infections
Epstein–Barr virus
Tuberculosis
Subacute bacterial endocarditis
Malaria
Hepatitis C

Complement components are often decreased in active systemic lupus erythematosus as systemic consumption outstrips production. The most frequently assayed components are C3 and C4. A decrease in levels may precede or accompany an increase in systemic lupus erythematosus disease activity, especially nephritis.[16] Depressed complement levels are not unique to systemic lupus erythematosus, but may also be seen in rheumatoid vasculitis, subacute bacterial endocarditis, and post-streptococcal glomerulonephritis, reflecting immune complex formation. C3 and C4 are also acute phase reactants and their levels may increase during infection and other inflammatory conditions that do not involve immune complexes. Therefore, a rapid improvement in complement levels in a patient with active systemic lupus erythematosus may reflect the presence of infection rather than a quieting of disease.

The total hemolytic complement (CH_{50}) screens the entire complement pathway. It is usually decreased in active systemic lupus erythematosus, but may be falsely low because of improper handling of the specimen, which should be kept on ice or frozen until assayed. Because of specimen instability, it is not monitored frequently in systemic lupus erythematosus. However, it is a valuable screening test for inherited complement deficiencies. If the CH_{50} level is extremely low or zero, the absence of specific complement components should be suspected. Complement deficiencies of C1q, C4, and C2 (the most common complement deficiency) are associated with increased risk of autoimmune disease, especially systemic lupus erythematosus.[17] Deficiencies of terminal complement components (C5-9), which form the membrane attack complex, are associated with frequent infection by *Neisseria* species.

Antiphospholipid Antibodies

Antiphospholipid antibodies are a heterogeneous group of antibodies directed against phospholipids or plasma proteins bound to phospholipids. Their presence is associated with an increased risk of thrombosis (both arterial and venous) and other clinical manifestations of antiphospholipid syndrome, such as increased fetal loss, thrombocytopenia, and hemolytic anemia. Antiphospholipid antibodies are detected frequently in patients with systemic lupus erythematosus and other rheumatic diseases, and they are present in individuals without systemic lupus erythematosus who have primary antiphospholipid syndrome.[18] Antiphospholipid antibodies are occasionally found in healthy individuals (transiently in those taking certain medications or having particular viral infections) and in patients with human immunodeficiency virus

who have opportunistic infection,[11] but they are only rarely associated with thrombosis in these situations. Four main antiphospholipid antibodies have been used in clinical assessments.

False-Positive VDRL. This occurs because the substrate used in the reaction contains the phospholipid cardiolipin. Results of specific confirmatory tests for syphilis are negative. Because this test has low sensitivity and specificity, it is no longer routinely used to assess for the presence of antiphospholipid antibodies.

Lupus Anticoagulants. This is a misnomer because these antibodies are not found exclusively in systemic lupus erythematosus, nor do they act clinically as anticoagulants. Lupus anticoagulants prolong in vitro clotting assays, such as the activated partial thromboplastin time, as the antibody interferes with the assay. Addition of normal plasma does not correct the abnormality because the prolongation is not due to factor deficiency.

Anticardiolipin Antibodies. An ELISA technique is used to detect the isotypes (IgG, IgM, and IgA) of anticardiolipin antibodies. High titers of IgG anticardiolipin antibodies are more frequently associated with antiphospholipid syndrome than are the other isotypes. Anticardiolipin antibodies associated with infection are generally of the IgM isotype.

Anti–β2-Glycoprotein 1 Antibodies. β2-glycoprotein binds phospholipid and is a natural inhibitor of coagulation and platelet aggregation. Antibodies directed against this glycoprotein inhibit its anticoagulant effect.

Antineutrophil Cytoplasmic Antibodies (ANCAs)

The presence of ANCAs is sought in patients suspected to have a systemic vasculitis. These antibodies are directed against granule components of neutrophils. An indirect immunofluorescent technique identifies two distinct staining patterns: perinuclear (pANCA) and cytoplasmic (cANCA). The ELISA identifies the target antigens of these antibodies, myeloperoxidase for pANCA and proteinase 3 for cANCA.

Results of pANCA testing are frequently positive in patients with microscopic polyangiitis (typically a small vessel vasculitis with renal and pulmonary involvement) and Churg–Strauss syndrome. It may also be found in several other inflammatory conditions, including inflammatory bowel disease (especially ulcerative colitis), primary sclerosing cholangitis, and rarely in rheumatoid arthritis, classic polyarteritis nodosa, and Kawasaki disease. This makes pANCA a relatively nonspecific test with limited usefulness.

The cANCA test is specific for Wegener's granulomatosis (> 80%). However, it is less sensitive, because patients with limited involvement or inactive disease may be negative for cANCA. Increasing titers may be associated with disease exacerbation.[19]

Genetic Tests

The major histocompatibility complex genes located on chromosome 6 encode for human leukocyte antigen (HLA) class I and class II molecules. These genes are associated with a variety of rheumatologic diseases. HLA B27, a class I antigen, is frequently found in patients with spondyloarthropathy, occurring in approximately 90% of white children with ankylosing spondylitis compared with 8% of the general population.[20] It is also found with increased frequency in reactive arthritis secondary to enteric infections or chlamydia. The prevalence of HLA B27 in African Americans and Asians is much lower than that in whites. The presence of HLA B27 supports a diagnosis of a spondyloarthropathy but does not establish or eliminate this diagnosis, which is based primarily on clinical parameters.

Class II antigens are associated with systemic lupus erythematosus, adult rheumatoid arthritis, and juvenile rheumatoid arthritis. HLA DR2 and DR3 increase the risk of systemic lupus erythematosus in whites, whereas DR2 and DR7 are associated with systemic lupus erythematosus in African Americans. In adults and children with rheumatoid factor–positive rheumatoid arthritis, DR4 is frequently found. The two DR4 alleles, Dw4 and Dw14, are particularly associated with rheumatoid factor–positive disease. In children with pauciarticular juvenile rheumatoid arthritis, DR8 and DR5 are found more frequently. Currently, class II antigen testing is used primarily in research and is not indicated for clinical practice.

During the past few years, exciting progress

TABLE 4

Laboratory Studies in Children With Juvenile Rheumatoid Arthritis (JRA)

Laboratory Study	Systemic	Polyarticular JRA	Pauciarticular JRA
Hemoglobin	↓↓	Normal or ↓	Normal
White blood cell count	↑↑	Normal	Normal
Platelets	↑↑	Normal or ↑	Normal
Erythrocyte sedimentation rate	↑↑	Normal or ↑	Normal or ↑
Rheumatoid factor	Negative	5% to 10%	Negative
Antinuclear antibody	Negative	30% to 40%	40% to 60%

has been made in the identification of gene mutations associated with hereditary periodic fever syndromes. Genetic studies can now be performed with excellent sensitivity to confirm diagnostic suspicions, which are based on a patient's clinical course and ethnicity.

Familial Mediterranean fever is caused by mutations in the MEFV gene, located on the short arm of chromosome 16. This gene, expressed predominantly in mature polymorpholeukocytes, encodes for pyrin, a protein thought to be involved in the downregulation of mediators of inflammation. Certain mutations may be associated with the risk of amyloidosis.

Hyper-IgD syndrome is caused by mutations in the mevalonate kinase gene located on the long arm of chromosome 12.

Tumor necrosis factor receptor–associated periodic syndrome is caused by mutation in the TNFRSF1A gene. It is located on the short arm of chromosome 12 and encodes the 55-kDA receptor for tumor necrosis factor.[21]

Synovial Fluid Assessment

In pediatric rheumatologic diseases, the main reason to evaluate synovial fluid is to rule out infection. Fluid should be sent in a heparinized tube for cell counts, Gram stain, cultures, and glucose. In a bacterial process, the white blood cell count is usually 50,000 to 300,000/mm^3 with more than 80% neutrophils.[22] The white blood cell count is usually less than 50,000/mm^3 in arthritis secondary to tuberculosis or Lyme disease. In the latter, results of polymerase chain reaction testing for *Borrelia burgdorferi* may be positive in the synovial fluid, but polymerase chain reaction testing of synovial tissue has a much higher yield. In juvenile rheumatoid arthritis, the synovial fluid often has a white blood cell count of 15,000 to 30,000/mm^3 with approximately 75% neutrophils.[22] Rarely, crystals may be seen, consistent with a metabolic disease such as gout.

LABORATORY EVALUATION IN SPECIFIC RHEUMATOLOGIC DISEASES

Juvenile Rheumatoid Arthritis

Laboratory assessment of the child with probable juvenile rheumatoid arthritis is helpful to rule out other possible diagnoses and to support clinical suspicions. No laboratory studies are diagnostic for juvenile rheumatoid arthritis. Many children with pauciarticular and polyarticular juvenile rheumatoid arthritis have normal laboratory profiles, whereas those with active systemic onset juvenile rheumatoid arthritis should have notable changes in their complete blood cell count and elevation of acute phase reactants (Table 4). A child thought to have systemic onset juvenile rheumatoid arthritis who does not have an elevated white blood cell count or platelet count should be evaluated for malignancy or macrophage activation syndrome, a rare complication seen in systemic onset juvenile rheumatoid arthritis. Children with pauciarticular juvenile rheumatoid arthritis and a positive result on ANA testing are at increased risk of uveitis.

Systemic Lupus Erythematosus

Of the 11 diagnostic criteria for systemic lupus erythematosus, only 4 involve laboratory abnormalities.[1] These include positive ANA results, positive anti–double-stranded DNA or anti-Sm or antiphospholipid antibodies (lupus anticoagulant

or anticardiolipin antibodies) results, cytopenias, or urinary abnormalities (urinary protein > 0.5 g/d or cellular casts). In addition to these studies, many other laboratory tests are often obtained for a patient with highly suspected or newly diagnosed systemic lupus erythematosus to further define the extent of organ system involvement. These include liver and renal function tests, serum albumin, ESR, CRP, direct Coombs' test, thyroid function studies, complement levels (CH50, C3, and C4), SS-A, SS-B, rheumatoid factor, and anti–β2-glycoprotein 1.

Dermatomyositis

The laboratory hallmark of juvenile dermatomyositis is muscle enzyme elevation. It is important for diagnosis and also useful for assessing response to treatment. At diagnosis, more than 90% of patients have an increase in at least one of four muscle enzymes: creatine kinase, aldolase, serum glutamic-oxaloacetic transaminase (SGOT), and lactate dehydrogenase.[23] All should be checked initially to understand which enzymes may be most helpful in monitoring the patient's course. Creatine kinase and aldolase are more specific to muscle and tend to be used more often than SGOT and lactate dehydrogenase. ESR and CRP may be elevated in active disease. The ANA test result may be positive. Myositis-specific antibodies, such as Mi-2 and Jo-1, are rarely found in patients with juvenile dermatomyositis.

MISCELLANEOUS PEDIATRIC RHEUMATOLOGIC DISEASES

Psoriatic Arthritis

ANA is present in 30% to 60% of children with psoriatic arthritis. Acute phase reactants and platelets may be elevated. Patients may have a mild anemia.

Polyarteritis Nodosa

Marked elevation of ESR and CRP is common in polyarteritis nodosa. Anemia, leukocytosis, and thrombocytosis are expected. Hematuria and proteinuria are frequently seen.

Henoch–Schönlein Purpura

Serum IgA is increased in approximately 50% of patients with this disease.[24] Platelet and white blood cell counts may be elevated. Urinalysis may show microscopic hematuria and proteinuria, which is usually mild but can be severe.

Wegener's Granulomatosis

cANCA and anti-proteinase 3 antibodies are usually present in active disease. The results of urinalysis are often abnormal, with proteinuria, hematuria, and red cell casts. Anemia may be significant. Increases in platelet count, ESR, and CRP are common.

Sarcoidosis

Angiotensin-converting enzyme, produced by the epithelioid cells of sarcoid granulomas, is elevated in more than two-thirds of patients with sarcoidosis. Hypercalcuria and hypercalcemia occur frequently. Other nonspecific laboratory findings may be increased immunoglobulin levels, eosinophilia, and elevated acute phase reactants.

Behçet's Disease

Laboratory studies are particularly unhelpful in this disease. Antiphospholipid antibodies are occasionally found. Serum levels of circulating immune complexes, immunoglobulins, and acute phase reactants may be elevated.

Systemic Sclerosis

Results of ANA testing are usually positive, predominantly in speckled or nucleolar patterns. Although anti-Scl70 is found in approximately 25% of adults,[25] it is less frequent in childhood systemic sclerosis. Other laboratory findings may include anemia, abnormal results on urinalysis, and elevated muscle enzymes.

SPECIAL CLINICAL SETTINGS

The Child With Musculoskeletal Pain

Children with musculoskeletal pain of unknown etiology often have screening studies performed, such as a complete blood cell count, ESR, or CRP. If these results are normal, then suspicion of a serious inflammatory process is lessened. However, because most pediatric rheumatologic illnesses are diagnosed clinically, normal results do not rule out disease. The laboratory approach to the child with one painful joint is dif-

ferent from that to the child with polyarticular or diffuse pain complaints.

The differential diagnosis for a child with one involved joint includes injury, focal infection, bony tumor, pauciarticular juvenile rheumatoid arthritis, psoriatic arthritis, and other entities. Work-up should include a radiograph to evaluate for a tumor or other bony process. If there is concern of an infection, synovial fluid may be obtained. Lyme titers may be sent if the child has been in an endemic area. If the child's course is suggestive of pauciarticular juvenile rheumatoid arthritis or psoriatic arthritis, ANAs should be checked.

The differential diagnosis for the child with polyarticular complaints includes postinfectious arthritis, polyarticular juvenile rheumatoid arthritis, systemic lupus erythematosus and other autoimmune illnesses, spondyloarthropathy, malignancy, and other diseases. Laboratory work-up may include ANA, rheumatoid factor, streptococcal antibody titers (both ASO and anti-DNase B), Epstein–Barr virus titers, and other studies depending on clinical suspicions based on the history and physical examination. Patients with certain malignancies, especially leukemia, may present with musculoskeletal pain and other physical and laboratory findings suggestive of diseases such as systemic lupus erythematosus or juvenile rheumatoid arthritis. If a patient's presentation is atypical for rheumatic disease and if any concerns regarding malignancy exist, then uric acid and lactate dehydrogenase testing should be done and bone marrow and special radiologic studies may need to be performed.

The Child With a Positive ANA Test Result

Referrals are commonly made to the pediatric rheumatologist for the evaluation of the child with a positive ANA test result. If the titer is low, especially 1:160 or less, and the child has negative results on history and physical examination, no further work-up is indicated. Titers of 1:320 to 1:640 may warrant further evaluation, especially if the review of systems or the examination is concerning. Titers of this level (or lower) are often seen in juvenile rheumatoid arthritis and psoriatic arthritis. Performing a complete blood cell count and ESR or CRP for these patients is appropriate. Epstein–Barr virus titers could be checked because this infection has been associated with medium to high titers of ANA. If there is concern of multisystem disease, especially if the ANA is 1:1,280 or greater, evaluation of specific ANA, complement levels, urinalysis, and other studies may be indicated.

CONCLUSION

Laboratory evaluation of the child with suspected rheumatic disease is a valuable addition to the clinical assessment. Specific laboratory results can lessen or increase concerns of the presence of a rheumatologic process. Results may support one's working diagnosis and also help to fulfill diagnostic criteria for certain diseases. But laboratory tests should not be used alone to confirm or exclude a rheumatic diagnosis. Also, it is important to recognize that commonly used tests (eg, ANA and rheumatoid factor) often yield positive results in patients with nonrheumatic diseases. This is critical to avoid misdiagnosis and inappropriate treatment, as well as to provide direction for further evaluation of the patient.

During the past few decades, much progress has been made in understanding the immunologic processes and the genetics of various rheumatology illnesses. As more knowledge is gained in these areas, it is likely that laboratory studies will be developed that will be more specific and diagnostic for rheumatic diseases.

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Our goal is to provide an educational review of a different topic each month. Please take a minute to jot down your ideas and fax this page to our editorial office. Let us know what *you* want to know.

You may also take this opportunity to consider whether you'd like to serve as a guest editor, putting together an issue on the topic of your special interest or expertise. Fax us a proposal if you feel up to the challenge of guest editorship.

I'D LIKE TO SEE *PEDIATRIC ANNALS* COVER THESE TOPICS:

1.

2.

3.

COMMENTS:

YOUR NAME AND FAX NUMBER (OPTIONAL):

Fax this page to *Pediatric Annals*, Executive Editor, at 856-848-6091.
Thank you for participating!