Semiology of rheumatic diseases. Acute rheumatic fever.

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Children are often poor historians, the examining physician must have a clear knowledge of the differential diagnosis when he approaches a child with limb pain. A careful history and physical examination are key to establishing the correct diagnosis. The examining physician must determine whether objective inflammation is present (pain, swelling, warmth, or limitation of motion), and if inflammation is present whether it is articular or periarticular.

A. No inflammation:

1. Growing pains: the most common and most misused diagnosis for musculoskeletal pain in childhood. True "growing pains" occur in young children peaking at four to five years of age. The pain classically occurs in the popliteal fossa. It is relieved by gentle massage or reassurance and occurs only at night. Pain during the day is not due to 'growing pains'. The condition is benign and selflimited, it does not require specific therapy, but may be relieved by NSAID.

2. Psychogenic Rheumatism: Vague joint pains and fatigue are frequent manifestations of 'somatization' disorders. The child who is unable to attend school despite a normal physical exam and laboratory evaluation is often demonstrating psychological distress. Many will respond to gentle reassurance, but in others the complaints mask a significant psychological disorder. Children with persistent complaints despite normal findings should be evaluated carefully for family problems. An immediate recommendation of psychological counseling is frequently rejected, but physicians who establish a trusting relationship with the family by thoroughly investigating the child for medical illness before suggesting a psychological origin may be able to bring about gradual resolution.

3. Reflex Neurovascular Dystrophy: This represents a more severe form of psychogenic rheumatism in which the somatization has progressed to include hyperaesthesias, often with mottled skin coloring and vascular instability. The condition often begins with a well documented injury which failed to improve. The syndrome typically occurs in 'perfect' children under excessive parental pressure. Performance activities and sexual abuse are well recognized causes of this syndrome.

B. Periarticular inflammation:

Periarticular inflammation may be the result of rheumatic disorders, but osseous disorders must be carefully excluded.

1. <u>Orthopedic disorders</u>: Acute periarticular pain may result from a fracture or osteomyelitis. Small children with fractures may not report trauma. Battering must be considered when a child presents with unsuspected fractures.

2. Neoplastic disorders: Neoplastic diseases associated with infiltration of the bone marrow include leukemia, lymphoma, and neuroblastoma. All may initially present with 'joint pains.' Disproportionate anemia, thrombocytopenia, hyperuricemia, lymphadenopathy, or hepatosplenomegaly should prompt careful evaluation including bone marrow aspiration if malignancy is suspected. Bone scans cannot be relied upon to detect leukemia.

3. Rheumatic disorders: The juvenile spondyloarthropathies often present with both articular and periarticular inflammation.

The periarticular manifestations may predominate, but articular inflammation is usually simultaneously present. Lumbar stiffness and heel pain should be specifically sought.

C. Articular inflammation:

True articular inflammation may be acute or chronic (more than three weeks in duration).

1. Acute articular inflammation

a. Infection: An acutely inflamed joint must be considered of infectious etiology until proven otherwise. Staphylococc, Streptococc, and Hemophilus influenzae are frequent causes of septic arthritis in childhood. Lyme disease is another frequent infectious arthritis where Ixodes ticks are endemic. These arthritis typically present with a single inflamed joint accompanied by fever and elevated erythrocyte sedimentation rates.

b. Reactive arthritis: Reactive arthritis may accompany or follow bacterial, viral, or fungal infection. It is usually polyarticluar and may be associated with fever, rash and systemic illness. Some cases of Lyme disease present in this manner. It may also be the presentation of meningococcemia. Toxic synovitis is the most common reactive arthritis in childhood. The typical child is three to five years of age and was well except for an upper respiratory infection in the evening prior to the onset of symptoms. The following morning he/she awakes unable to walk, with decreased range of motion in one hip. Fever is only low grade, without significant elevation of the white blood cell count, or erythrocyte sedimentation rate. Unless an experienced physician is comfortable with the clinical picture, the joint must be aspirated to rule out bacterial infection.

c. Poststreptococcal reactive arthritis deserves special consideration. In the past these children were not classified as acute rheumatic fever because they do not fulfill 2 of Jones major criteria. Children with elevated sedimentation rates and arthritis following a documented streptococcal infection should receive rheumatic fever prophylaxis. Cardiac damage has been recorded with subsequent streptococcal infections in children who did not receive prophylaxis.

C. Acute expression of a collagen vascular disease: Serum sickness, acute rheumatic fever, Henoch Schonlein purpura, and the 'chronic' collagen vascular diseases may present with the acute onset of arthritis.

2. Chronic articular inflammation:

a. Infection:

Chronicity does not exclude infection. Tuberculosis is a frequent cause of smoldering arthritis. Other bacterial infections including staphylococcal arthritis may also present with a smoldering onset. Children with established collagen vascular disease are not immune to developing complicating septic arthritis or osteomyelitis.

b. Collagen vascular diseases: All of the chronic collagen vascular diseases may occur in children. Diagnoses of gout or temporal arteritis must be regarded with extreme suspicion. They are virtually unheard of in childhood. The chronic collagen vascular diseases with findings unique to childhood include juvenile idiopathic arthritis (JIA), plant thorn synovitis, the spondyloarthropathies, Kawasaki disease, dermatomyositis, linear scleroderma, benign hypermobile joint syndrome, and certain heritable disorders.

The Collagen vascular diseases of childhood.

A. Juvenile Idiopathic Arthritis: JIA is the most common chronic synovitis of childhood. There are three subtypes which are distinguished by the number of joints involved during the first six months after onset.

1. Pauciarticular onset JIA: Pauciarticular onset JIA involves four or fewer joints. It most commonly occurs in young females, but may effect either sex. This group is divided between children who are antinuclear antibody (ANA) positive and at greater risk of complicating eye disease (iridocyclitis) and children who are ANA negative. Young females with early involvement of small joints are at high risk of progressing to polyarticular involvement with a poor prognosis. Many of these children have 'sausage digits' and probably 'psoriaform' arthritis. Adolescents with involvement of four or fewer large joints more likely have a spondyloarthropathy.

2. Polyarticular onset JIA: Polyarticular onset JIA has two distinct subtypes. Rheumatoid factor (RF) positive adolescent females have typical adult type rheumatoid arthritis with early onset. Young children with polyarticular JIA are typically rheumatoid factor (RF) negative. Both of these entities carry a guarded prognosis especially if they are associated with significant anemia and elevation of the ESR. Some children previously labeled as polyarticular JIA may have 'psoriaform' arthritis. RF may also be found in children with SLE and mixed connective tissue disease.

3. Systemic onset JIA: Systemic onset JIA presents with high spiking fevers, rash, and variable joint involvement. It occurs with a more equal sex ratio that the other forms which have a female predominance. Children with systemic onset JIA are striking for their ill appearance during episodes of fever, with a relatively benign appearance between episodes. The fleeting salmon pink rash and a temperature curve which falls to normal or below at least once each day are characteristic. While many children with systemic onset JIA do well, others develop significant internal organ involvement or progress to chronic destructive arthritis. Amyloidosis is a rare complication in the USA, but common in Europe.

B. Spondyloarthropathies: The spondyloarthropathies are a diffuse group of conditions occurring in both males and females. Their hallmark is an asymmetric large joint arthritis associated with limited lumbar flexion and tenosynovitis. These children are most often ANA negative and rheumatoid factor negative. They are at risk for acute, painful iritis, but (in general) not chronic iridocyclitis. Psoriaform arthritis is considered a spondyloarthropathy, but is recognized to have a high frequency of ANA positivity and iridocyclitis. Genetic studies to determine the relationship of psoriaform arthritis and pauciarticular JIA are in progress.

1. Ankylosing spondylitis (AS): AS is the 'classic' spondyloarthropathy. It occurs predominantly in HLA B27 positive males with abnormal limitation of lumbar flexion. Because definite AS cannot be diagnosed in the absence of radiographic sacroiliitis many children who are suspect fail to fulfill the diagnostic criteria. These children should be carried with a diagnosis of 'juvenile spondyloarthropathy'.

2. Juvenile spondyloarthropathy (SEA syndrome [seronegative enthesiopathy/arthropathy]): These are children with asymmetric large joint arthritis and enthesiopathic findings who do not meet the criteria for AnkylosingSpondylitis. They are easily differentiated from JIA by their later age at onset (usually age 10 or older), the early presence of back or hip involvement, and the frequent occurrence of asymmetric metatarsal joint pain or Achilles tendonitis. Although many of these patients are HLA B27 positive boys, girls and HLA B27 negative individuals of either sex, may be affected. It was initially thought that the majority of these children would develop classical AnkylosingSpondylitis upon reaching adulthood, but only a small percentage do so.

3. Reiter's syndrome: The full combination of arthritis, urethritis, and conjunctivitis occurs infrequently in childhood. When it does occur its manifestations are the same as those seen in adults. It is not important to differentiate children with 'incomplete' Reiter's syndrome from others with 'juvenile spondyloarthropathy,' since the therapy and prognosis are similar.

4. Psoriatic arthritis/'psoriaform' arthritis: True psoriatic arthritis with typical skin lesions and boney changes is infrequent in childhood. Some children without psoriatic skin changes present with asymmetric dactylitis (sausage digits), a family history of psoriasis in a first or second degree relative, and variable degrees of additional joint inflammation. In contrast to the other spondyloarthropathies this constellation of findings not only affects adolescents, but often occurs in young females who would otherwise be labeled as having pauciarticular JIA.

5. Inflammatory bowel disease (IBD): The arthritis accompanying inflammatory bowel disease is a typical spondyloarthropathy. Because arthritis may be the initial manifestation of IBD, any child with arthritis who develops chronic or recurrent abdominal pain should be carefully evaluated for the presence of ulcerative colitis or regional enteritis.

Dermatomyositis is an acute inflammatory condition of skin and muscle. There are several distinct subsets of children with dermatomyositis who may ultimately prove to have distinct diseases. Most often dermatomyositis presents with increasing fatigue and loss of proximal muscle strength accompanied by a heliotrope rash. In some children vasculitic lesions of the nail beds ('nailfoldcapillary dilatation) and skin overlying the proximal interphalangeal joints (Gottren's papules) are a prominent finding. Less frequently the onset of dermatomyositis can be rapid with fever, widespread vasculitic rash and profound weakness. Both rapid and gradual onset of disease are often accompanied by malaise and may be complicated by fever and severe muscle wasting.

Laboratory evaluation typically shows elevation of the CPK, SGOT, and aldolase, although in some cases only the CPK or aldolase may be abnormal. The diagnosis is suggested by marked proximal muscle weakness and confirmed by inflammatory changes in the muscle biopsy. The characteristic clinical history, however, is simply of a child who is not able to 'keep up', or who is asking to be carried more and more often. Difficulty going up and down stairs is often the manifestation which prompts the family to seek medical attention. Although not pathologically distinguishable, three distinct patterns of childhood dermatomyositis are clinically recognizable. The most common group consists of children with proximal muscle weakness, mild heliotrope rash and no findings suggestive of vasculitis. These children often have a benign illness which resolves over a four to six month period with corticosteroid therapy alone.

Children with a marked vasculitic rash, or typical findings of vascular involvement in the nail beds (nail-fold capillary abnormalities), or inflammatory papules overlying the interphalangeal joints (Gottren's papules) most often have a more chronic relapsing course. Their disease typically improves with corticosteriod or immunosuppressive therapy, but recurs. Less frequently seen are children with severe rash, markedly elevated muscle enzyme levels, but only moderate weakness. This subgroup of children is often refractory to therapy. A fourth group which may be mistakenly diagnosed as dermatomyositis consists of children who are incidentally found to have markedly elevated CPK levels (e.g. 20,000 units) when being screened for another reason. These children are not weak, do not have a heliotropic rash, and remain well without therapy. Although the precise explanation for this group is unknown, they most likely have a simple biochemical defect.

Systemic lupus erythematosus most frequently strikes females entering the second decade of life. However, it may affect children of either sex at any age. The characteristic malar rash presented in textbooks is present in only one third of cases and is often mistaken for malar flushing due to fever or other causes. Physicians who rely on its presence to suspect the diagnosis of SLE will miss the majority of cases. Definite SLE can be diagnosed whenever a child fulfills four the eleven American college of Rheumatology diagnostic criteria. It must be suspected in any child or adolescent with unexplained 'failure to thrive'. Fever, weight loss, arthralgia, and malaise are the most common presenting manifestations. However some children will present with asymptomatic hematuria or thrombocytopenia.

Most often chronically ill children present with a mild anemia, leukocytosis, and thrombocytosis. Leukopenia and/or thrombocytopenia should prompt investigation for a neoplastic process infiltrating the bonemarrow or evidence of increased peripheral destruction as occurs in SLE. A positive test for antinuclear antibodies has a very high sensitivity, but low specificity. To establish a diagnosis of SLE the clinician must seek evidence of multi-system disease. Often this takes the form of arthritis, pleural effusions, or proteinuria. The disease course of systemic lupus erythematosus may be highly variable.

Two thirds of children have evidence of renal involvement at the time of presentation and these children are at risk for progression to diffuse proliferative glomerulonephritis and ultimate renal failure. Other children may have no evidence of renal involvement and a relatively benign course. The key indicators of prognosis at the time of presentation are the presence or absence of renal involvement, the degree of anemia, and the persistance of hypocomplementemia following the intiation of therapy. Rising titers of antibodies to dsDNA and falling serum complement levels (C3, C4 or both) are often indicators of worsening disease and may precede flares of renal involvement. The key to proper therapy is prompt recognition of the patient at high risk and institution of aggressive therapy. Five and ten year survivals are excellent for those without renal disease and satisfactory for those with renal disease who are aggressively treated. Complications such as infection or stroke may strike without warning even in the absence of renal disease.

Henoch Schoenlein purpura (HSP):

The characteristic presentation of abdominal pain, a vasculitic rash over the extensor surfaces of the lower extremities and buttocks, and arthritis is easily recongized in this condition. Because HSP is most often benign physicians may forget to evaluate for the presence of renal involvement. Unfortunately renal involvement may be present in one third of cases and in a small percentage of cases will proceed to renal failure. All children with HSP should be investigated for the presence of renal involvement with a proper routine and microscopic urine analysis as well as measurement of the blood urea nitrogen (BUN) and creatinine. If any abnormalities are present this should be followed by collection of a twenty-four hour urine for protein, creatine, and creatinine clearance.

Several forms of arthritis which occur predominantly in children are not easily characterized. Recognition of these conditions is important to assure proper therapy.

A. Plant thorn synovitis: This entity results from retention of a fragment of plant material within the joint following a puncture injury. The onset of joint swelling and limitation usually occurs four to six weeks after the initial injury which may have been forgotten in the interim. The arthritis is often quite painful and unresponsive to normal measures. Proper diagnosis is often made following surgical biopsy of an intractable monoarthritis when the pathologic specimen reveals plant fibers under polarized light microscopy. Synovectomy is the treatment of choice.

B. Benign hypermobile joint syndrome: This condition typically occurs in early adolescent girls. Most often they are gymnasts who practice extensively and have great flexibility due to ligamentous laxity. As a result their joints are subjected to repeated episodes of 'microtrauma.' Acute episodes may be treated with NSAIDs, but more prolonged difficulty should prompt review of the athletic program. Osteochondritis dessicans (particularly of the knee) may present in a similar manner and can result in permanent disability in this group of patients.

C. Immunization associated arthritis: The development of a benign polyarthritis affecting primarily the small joints of the hands 10 to 14 days following rubella immunization is well documented. The arthritis is typically mild and resolves over seven to ten days with only symptomatic therapy. Similar episodes have been reported less frequently with other immunizations.

D. Arthritis associated with immunoglobulin deficiency: Children with IgA deficiency are most often asymptomatic. However, IgA deficiency occurs with a greater than expected frequency in children with arthritis. The arthritis often consists of benign recurrent joint effusions, but some children develop typical JIA. A similar benign arthritis is seen in some children with hypogammaglobulinemia. IgA deficiency will only be detected if quantitative immunoglobulins are routinely measured. Panhypogammaglobulinemia may be suspected if the total protein is decreased with a normal serum albumin.

VI. Arthritis associated with other conditions

Arthritis is a well recognized complication of vasculitis including SLE, Wegener's granulomatosis, Takayasu's arteritis, and Henoch Schonlein purpura, Kawasaki disease and juvenile onset dermatomyositis. Many inherited disorders such as hemophilia, sickle cell disease, mucopolysacharidoses, sphinoglipidoses, and epiphyseal dysplasias may present with arthritis or periarticular pain in childhood. Characteristic nonarticular manifestations usually predominate.

A. Marfans syndrome: Children with Marfans syndrome characteristically are tall with arachnodactyly. They typical have ligamentous laxity and present with complaints similar to those of the hypermobile joint syndrome. Characteristic findings are an arm span greater than their height, and leg length greater than trunk length. These children are vulnerable to dissecting aortic aneurysms. Aortic root dilatation may be evaluated by routine echocardiography.

B. Ehlers Dahnlos syndrome: Children with Ehlers Dahnlos syndrome suffer from an extreme form of hypermobile joint syndrome due to abnormal connective tissue. Recurrent joint injury secondary to chronic subluxation and characteristic 'cigarette paper' scarring are common. Milder cases which lack the cutaneous manifestations occur.

C. Cystic fibrosis: these children occasionally develop benign effusions of the large joints which will prompt rheumatologic referral. Hypertrophic osteoarthro pathy may also occur in children with cystic fibrosis.

Laboratory Evaluation of Rheumatic Diseases

The diagnosis of rheumatologic diseases is based on clinical information, blood and imaging tests, and in some cases on histology. Blood tests are useful in confirming clinically suspected diagnosis and monitoring the disease activity. The tests should be used as adjuncts to a comprehensive history and physical examination.

The value of a test in diagnosing a certain condition depends on its pretest probability. A positive test result with high pretest probability helps to make a diagnosis, but a negative test result with low pretest probability helps to rule out the diagnosis. Clinicians cannot rely heavily on blood tests in making the diagnosis of rheumatologic diseases, except for certain tests that are highly specific for certain diseases. Improper application of these tests leads to misdiagnosis, inappropriate therapy, and unnecessary health care expenses.

Acute-phase reactants

Acute-phase reactants are proteins whose plasma concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) by at least 25% during inflammatory states. The effect of inflammatory molecules such as interleukin (IL)-6, IL-1, tumor necrosis factor α (TNF-α), interferon gamma (IFN-γ), and transforming growth factor β (TGF-β) causes a change in hepatic protein synthesis collectively known as acute-phase response. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most widely measured acute-phase reactants in clinical practice.

ESR is a measure of the height of erythrocytes that fall through plasma in a Westergen or a Wintrobe tube over a period of 1 hour. ESR can be greatly influenced by the shape and number of red blood cells as well as other plasma constituents like fibrinogen, globulins, and albumins. It can be spuriously high in the absence of inflammation, as in anemia, nephritic syndrome, and hypergammaglobulinemia, and it can be spuriously normal in cryoglobulinemia and hemoglobinopathy. ESR increases steadily with age, and the upper limit varies with sex; hence, ESR is difficult to interpret compared to CRP.

The concentration of CRP in serum is more sensitive than ESR to evaluate and monitor inflammation, and it is independent of factors that affect ESR. It correlates better with disease activity, and the rise in CPR level is seen much earlier than that of other acute-phase reactants, usually 4 to 6 hours after tissue injury.

Positive Acute-Phase Reactants

$Alpha_1$-antitrypsin
Ceruloplasmin
Complement components
C-reactive protein
Ferritin
Fibrinogen
Haptoglobin
Serum amyloid A

Negative Acute-Phase Reactants

Albumin
Transferrin
Transthyretin

Both ESR and CRP levels can be elevated in a wide variety of conditions including trauma, infection, infarction, neoplasms, and inflammatory arthritis. Usually ESR and CRP levels correlate well, but in some patients levels may be discordant for reasons that are unclear. They are very useful in monitoring disease activity in rheumatologic conditions such as juvenile arthritis, polymyalgia rheumatica,and giant cell arteritis. Some studies have shown that the pretreatment ESR value is of some prognostic value in polymyalgia rheumatica. Most patients with active lupus have normal or minimally elevated CRP levels, and markedly elevated concentrations of CRP in SLE should raise a suspicion of bacterial infection. Other causes for elevated CRP in SLE patients include serositis, synovitis, and vasculitis.

Antinuclear antibodies (ANAs) directed against a variety of nuclear antigens have been detected in the serum of patients with many rheumatic and nonrheumatic diseases as well as in healthy persons. Various immunochemistry techniques are used to detect and characterize these ANAs. These methods include immunofluorescence microscopy, hemagglutination, immunodiffusion, complement fixation, and enzyme-linked immunosorbent assay (ELISA).

ANA testing is very useful in establishing a diagnosis of systemic lupus erythematosus (SLE). Nearly all patients with SLE have a positive ANA test, with a sensitivity of 93% to 95% and a specificity of 57%.However, even healthy persons can have a positive ANA test at lower titers. About 25% to 30% of healthy persons have a positive test with a titer of 1 : 40, 10% to 15% at a titer of 1 : 80, and 5% at a titer of 1 : 160 or greater. The frequency increases with age, particularly in women. ANA titer of 1 : 40 is seen in 25% to 30% of relatives of patients with rheumatologic disorders.

In addition to lupus, ANA testing is helpful in diagnosing other rheumatic diseases such as systemic sclerosis and Sjögren's syndrome. The sensitivity of ANA in diagnosing systemic sclerosis is 85% and the specificity is 54%.Although ANA is not included in the 2002 classification criteria for Sjögren's syndrome, it is found in 80% of patients with primary Sjögren's syndrome and at high titers (>1 : 320) in nearly one half of the patients.Patients presenting with Raynaud's phenomenon should also have ANA testing because a positive ANA test indicates an increased risk of developing an associated systemic rheumatic disease from 19% to 30%, whereas a negative test indicates a risk of 7%.Additionally, ANA testing helps to stratify the risk of uveitis in patients with juvenile idiopathic arthritis.

ANA can also be positive in many autoimmune disease states not associated with connective tissue diseases, such as autoimmune hepatitis, primary autoimmune cholangitis, primary biliary cirrhosis, and Crohn's disease. Other disorders associated with positive ANA titer include such chronic infectious diseases as mononucleosis, subacute bacterial endocarditis, tuberculosis, and lymphoproliferative diseases. ANA testing should be reserved for patients with high suspicion for systemic autoimmune disease, such as young women with fatigue, joint pain, and rash, and should not be used as a screening test in patients complaining of generalized fatigue and musculoskeletal pain, particularly elderly patients.

Anti-DNA Antibodies

Antibodies to dsDNA are often measured in SLE and are commonly referred to as anti-DNA antibodies. They are very useful in the diagnosis of SLE and assessment of disease activity, and they are associated with lupus nephritis.

The sensitivity of anti-dsDNA antibody for diagnosis of SLE is 57.3% and the specificity is 97.4%.These antibodies are present at some time in the course of the disease as the levels fluctuate and may be absent at times. Anti-DNA antibodies have been reported in patients with a variety of other rheumatologic and nonrheumatologic diseases including juvenile arthritis, Sjögren's syndrome, scleroderma, drug-induced lupus, Raynaud's phenomenon, mixed connective tissue disease, discoid lupus, myositis, chronic active hepatitis, uveitis, Graves' disease, and anticardiolipin antibody syndrome. Not all patients with SLE have positive anti-dsDNA antibodies; a negative test does not exclude the diagnosis of SLE. The prevalence of patients with a positive anti-DNA assay despite a negative ANA has been reported to be 0% to 0.8%. Unless there is a reasonable suspicion that the ANA is falsely negative, anti-DNA antibody testing is not generally indicated in ANA-negative patients.

Anti-Smith and Antiribonucleoprotein Antibodies

Antibodies directed against small nuclear riboprotein include anti-Smith (anti-Sm) antibody and antiribonuclear protein (anti-RNP) antibodies. They bind to related but distinct antibodies. Anti-Sm antibodies are very useful for confirming the diagnosis of SLE. A positive test result strongly supports the diagnosis, although a negative test result cannot exclude it. The sensitivity of anti-Sm antibody for diagnosis of lupus ranges from 24% to 30%, and specificity ranges from 96% to 98%.

Anti-RNP antibodies bind to protein containing U1-RNA. They coexist with anti-Sm antibodies in many patients with SLE. They have a very low sensitivity and moderate specificity for diagnosing SLE, but they are very useful in diagnosing mixed connective tissue disease. The sensitivity of anti-RNP antibodies for diagnosing mixed connective tissue disease is 71% to 100% and the specificity is 84% to 100%.

Antihistone Antibodies

Antihistone antibodies are present in more than 95% patients with drug-induced lupus and up to 80% of patients with idiopathic lupus. The more presence of antihistone antibodies does not indicate drug-induced lupus. Up to 80% of patients taking procainamide for 1 to 2 years develop positive ANAs, but most do not develop drug-induced lupus.

Anticentromere antibodies are associated with limited cutaneous systemic sclerosis, previously called CREST (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, *t*elangectasia] syndrome).They are rarely found in patients with other connective tissue diseases or in healthy persons, making them highly specific for diagnosing systemic sclerosis. The sensitivity of anticentromere antibodies for the diagnosis of limitied cutaneous systemic sclerosis is 31%, and specificity is 97%.They are very useful in distinguishing patients with limited systemic sclerosis from patients with diffuse systemic sclerosis or with primary Raynaud's phenomenon. Anti-centromes antibodies are predictive of limited cutaneous involvement or decreased likelihood of investital being displayed in systemic sclerosis.

Anti-Scl-70 antibody is also very useful in diagnosing systemic sclerosis. This antibody is seen in 20.2 % of patients with systemic sclerosis and is highly specific (100%) for diffuse disease.Anti Scl-70 and anticentromere antibodies rarely coexist in the same person. The presence of anti-Scl-70 antibodies is useful in predicting a greater likelihood for the development of diffuse cutaneous involvement and radiographic pulmonary fibrosis with an abnormal pulmonary function test.

Rheumatoid factor (RF) autoantibodies are directed against the Fc portion of IgG. The most commonly measured RF is IgM. The other RFs include IgG, IgE, and IgA.

Rheumatoid Factor Positivity in Different Diseases

Rheumatic Conditions (Sensitivity)

Cryoglobulinemia (40%-100%)
Polymyositis and dermatomyositis (5%-10%)
Juvenile arthritis (50%-90%)
Sjögren's syndrome (75%-95%)
Systemic lupus erythematosus (15%-35%)
Systemic sclerosis (20%-30%)

RF is detected in a wide variety of rheumatic and nonrheumatic conditions. It is commonly used in diagnosing juvenile arthritis. The sensitivity of RF for diagnosing juvenile arthritis is around 50% to 80%, and specificity is 85% to 90%, as reported by some studies where patients with advanced disease were tested. RF may be negative in the early stages of juvenile arthritis, and positivity increases over time.

RF alone cannot be used for diagnosis of juvenile arthritis. Around 15% to 20% of patients with juvenile arthritis never have RF positivity, and 2% to 10% of healthy persons are RF positive. Positive RF alone does not confirm juvenile arthritis and negative RF does not exclude it.RF testing must be ordered more selectively, and the best time to obtain the test may be when the suspicion of juvenile arthritis is low and a negative test would provide significant reassurance.There is a correlation between higher RF concentrations and more-severe disease and poor prognosis, but the use of RF in monitoring disease activity is unclear.

The complement system consists of plasma and membrane proteins that provide innate defense against microbial pathogens. Complement activation is usually assessed by determining the levels of individual complement components such as C3 and C4 and by quantifying the CH50 (total hemolytic complement) activity. Complement levels are measured by either functional or antigenic assays. CH50 is a useful tool for assessing allnine components of the classic pathway (C1, C2, C3, C4, C5, C6, C7, C8, and C9). CH50 is undetectable when there is complete deficiency of any individual complement component. Classic pathway activation is indicated by low levels of C3 and C4. Alternate pathway activation is indicated by low levels of C3 but normal C4.

Complement measurement is an important diagnostic tool in many connective tissue disorders. Hypocomplementemia is present in disorders associated with excessive levels of immune complexes such as SLE and cryoglobulinemia. There is a significant association between low complement levels and lupus nephropathy. A high frequency of positive ANA and anti-dsDNA in patients with primary antiphospholipid antibody syndrome with hypocomplementemia probably suggests that these patients might develop a lupus-like illness.

Antiphospholipid antibodies include antibodies directed against phospholipid-associated proteins such as cardiolipin, β_2-glycoprotein 1, and prothrombin. These antibodies are usually measured in patients with SLE, recurrent thrombosis, and recurrent fetal loss, raising the possibility of antiphospholipid antibody syndrome. The antiphospholipid syndrome is characterized by venous thrombolism, arterial thrombosis, or pregnancy morbidity (individually or in combination), together with antiphospholipid antibodies and lupus anticoagulant.

The anticardiolipin antibodies are measured by ELISA and usually include three serotypes: IgG,IgM, and IgA. These antibodies should be present in medium to high concentrations on at least two occasions about 12 weeks apart to establish a diagnosis of antiphospholipid antibody syndrome, along with some clinical criteria. A number of studies have shown that acute medical illness and infections can lead to a transient increase of the antibodies.

Summary

ESR and CRP are markers of inflammation and are elevated in inflammation. ESR can be elevated without inflammation in hypergammaglobulinemia or anemia.

CRP is a more sensitive marker of inflammation and is independent of factors affecting ESR.

Many patients with active lupus do not have elevated CRP levels; elevated CRP can suggest bacterial infection.

ANA testing is very useful in establishing a diagnosis of SLE. Nearly all patients with lupus have a positive ANA (sensitivity is 93%-95%, but specificity is 57%). Most patients with positive ANA do not have lupus, because the prevalence of lupus is low in the general population.

ANA titer is not used for assessing the disease activity in lupus. Thus, serial ANA testing is of unknown value.

Anti-DNA antibody testing is very useful in the diagnosis of SLE and is also a useful biomarker of SLE disease activity.

Anti-Scl 70 antibody is very useful in diagnosing systemic sclerosis and anticentromere antibody in diagnosing limited scleroderma. Anti-Scl 70 and anticentromere antibodies rarely coexist in the same patient.

SSA and SSB antibodies should be checked in patients with sicca symptoms. Patients with primary Sjögren's syndrome with SSA or SSB antibodies represent the most clinically and immunologically active subset. These patients need very close follow-up for development of extraglandular features.

The sensitivity of rheumatoid factor for juvenile arthritis is around 50% to 80% and specificity is 85% to 90%. It may be negative in the early stages of juvenile arthritis, and positivity increases over time.

Between 70% and 90% of patients with Wegener's granulomatosis test positive for ANCAs in the c-ANCA pattern, with antibodies directed against PR3. A negative ANCA assay does not exclude Wegener's granulomatosis.

Between 40% and 80% of patients with microscopic polyangiitis are ANCA positive and usually have the p-ANCA pattern with MPO specificity.

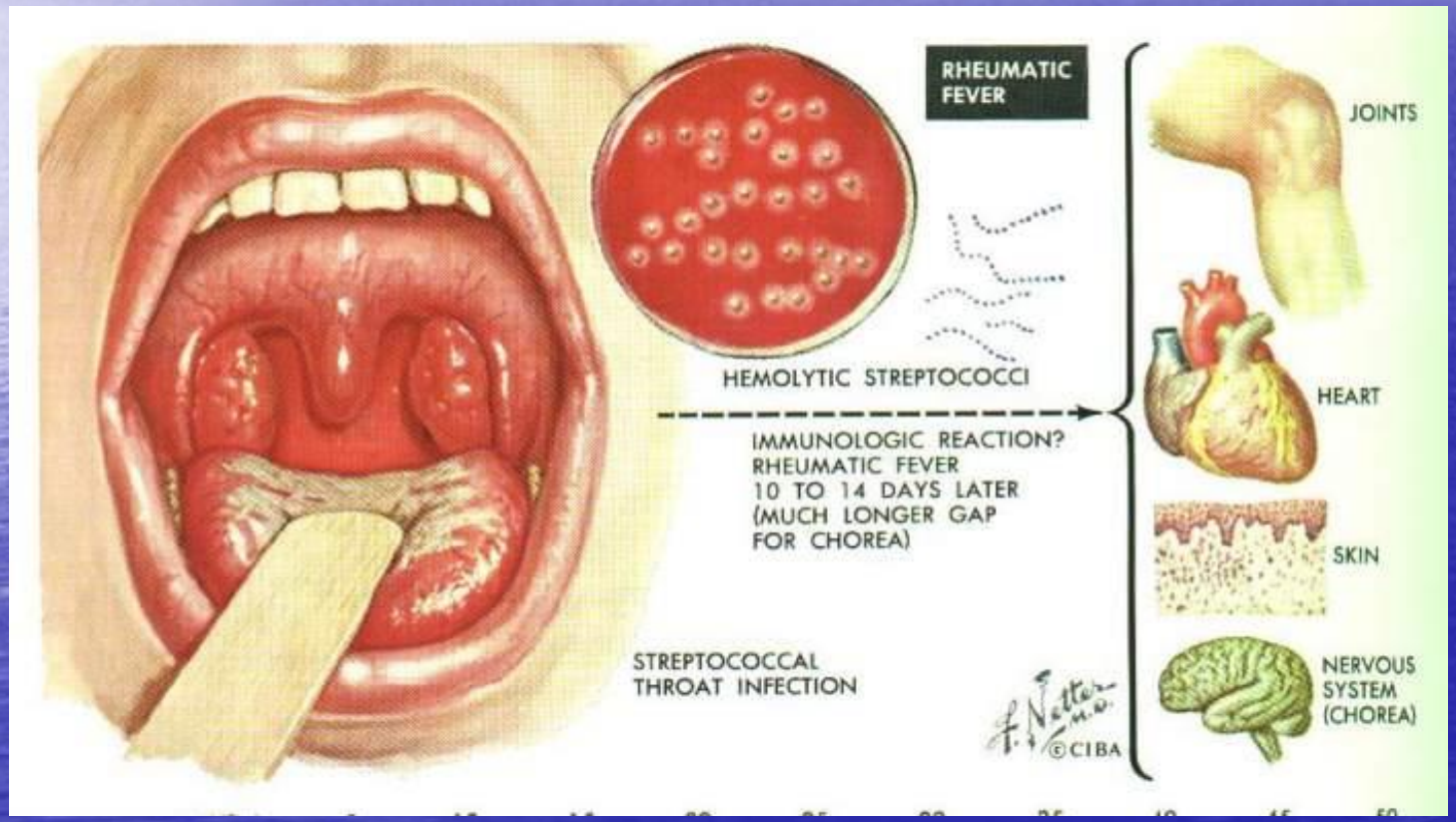
The role of sequential ANCA titers after the diagnosis is established is unclear. A recent study showed a weak association between disease activity and ANCA levels. Inherited deficiencies of complements C1, C2, and C4 predispose to SLE.

Acute rheumatic fever

Etiology

Considerable evidence supports the link between antecedent group A streptococcus pharyngitis and **acute rheumatic fever and rheumatic heart disease. As many as two** thirds of patients with an acute episode of **rheumatic fever** have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute **rheumatic fever** closely parallel that of group A streprococcus pharyngitis. Not all serotypes of group A streptococcus can cause rheumatic fever. Certain serotypes of group A streptococcus (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute **rheumatic fever** than are other serotypes.

Etiology


RHEUMATIC FEVER
HEMOLYTIC STREPTOCOCCI
IMMUNOLOGIC REACTION?
RHEUMATIC FEVER
10 TO 14 DAYS LATER
(MUCH LONGER GAP
FOR CHOREA)
STREPTOCOCCAL
THROAT INFECTION
©CIBA
JOINTS
HEART
SKIN
NERVOUS
SYSTEM
(CHOREA)

Epidemiology

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. R**heumatic heart disease remains the most common form of acquired heart disease in all** age-groups, accounting for up to 50% of all cardiovascular disease and 50% of all cardiac admissions in many developing countries. In the United States at the beginning of the 20th century, acute rheumatic fever was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. Acute rheumatic fever was associated with poverty and overcrowding, particularly in urban areas.

Pathogenesis

An **immune-mediated pathogenesis for acute rheumatic fever** has been suggested by the latent period between the group A streptococcus infection and acute **rheumatic fever** . The antigenicity of several group A streptococcus cellular and extracellular epitopes and their immunologic cross-reactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Certain rheumatogenic M proteins (M1, M5, M6, and M19) share epitopes with human myocardial proteins such as tropomyosin and myosin. The binding of an M-protein N-terminal domain to a region of collagen type IV leads to an **antibody response to the collagen, resulting in ground substance inflammation,** especially in subendothelial areas such as cardiac valves and myocardium.

Clinical Manifestations and Diagnosis

The **Jones Criteria, as revised in 2015 by the American** Heart Association, are intended for diagnosis of the initial attack of acute rheumatic fever and recurrent attacks. There are **5 major and 4 minor criteria** and a requirement of evidence of recent group A streptococcus infection. Diagnosis of a first attack or recurrent attack of acute rheumatic fever can be established when a patient fulfills 2 major or 1 major and 2 minor criteria and has evidence of preceding group A streptococcus infection. Major criteria: Carditis, Polyarthritis, Erythema marginatum, Subcutaneous nodules, Chorea. **Minor criteria: Clinical features:** Arthralgia, Fever; **Laboratory features:** Elevated acute phase reactants: Erythrocyte sedimentation rate, C-reactive protein, Prolonged P-R interval. Positive throat culture or rapid streptococcal antigen test, Elevated or increasing streptococcal antibody titer.

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as 1 or more other large joints become involved. Rheumatic arthritis is almost never deforming. Arthritis is the earliest manifestation of acute rheumatic fever and may correlate temporally with peak antistreptococcal antibody titers.

Carditis

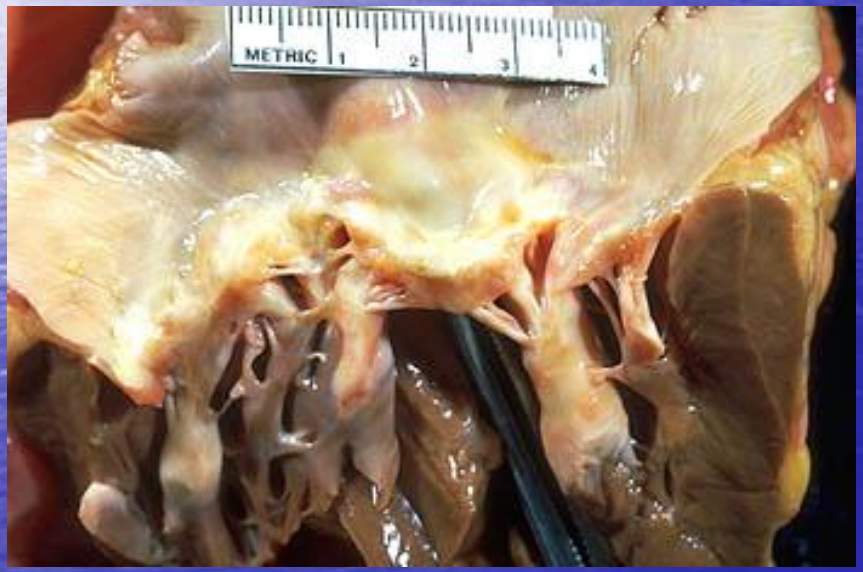
Carditis occurs in approximately 50–60% of all cases of acute rheumatic fever. **Subclinical carditis - defined as without a murmur of valvulitis but with** echocardiographic evidence of valvulitis; **Clinical carditis - with a valvulitis** murmur.

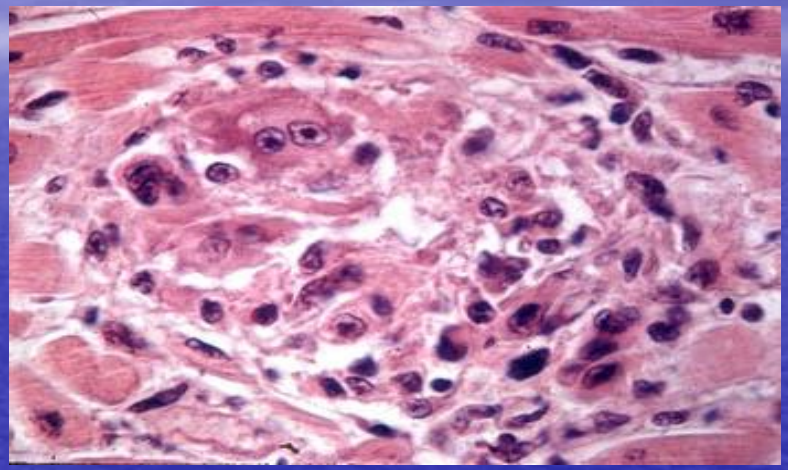
Subclinical (i.e. only echocardiographic) evidence of pathologic mitral regurgitation requires that a jet is seen in at least two views, the jet length is ≥2 cm in at least 1 view, peak jet velocity is >3 meters/second, and the peak systolic jet is in at least 1 envelope. Subclinical pathologic evidence of aortic regurgitation is similar except that the jet length is ≥1 cm in at least 1 view. Rheumatic carditis is characterized by **pancarditis,** with active inflammation of myocardium, pericardium, and endocardium. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon.

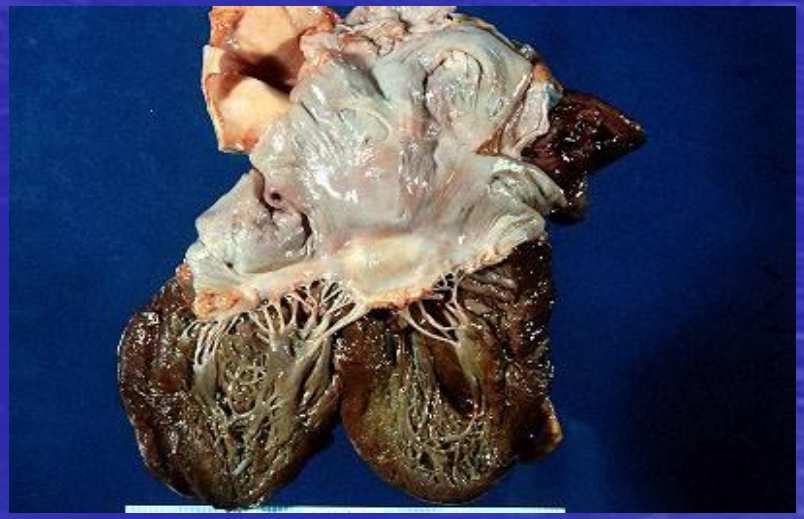
Carditis

Valvular insufficiency is characteristic of both acute and convalescent stages of acute rheumatic fever, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. **Acute rheumatic carditis usually presents as tachycardia and cardiac** murmurs. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. **Mitral regurgitation is** characterized by a high-pitched apical holosystolic murmur radiating to the axilla. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.

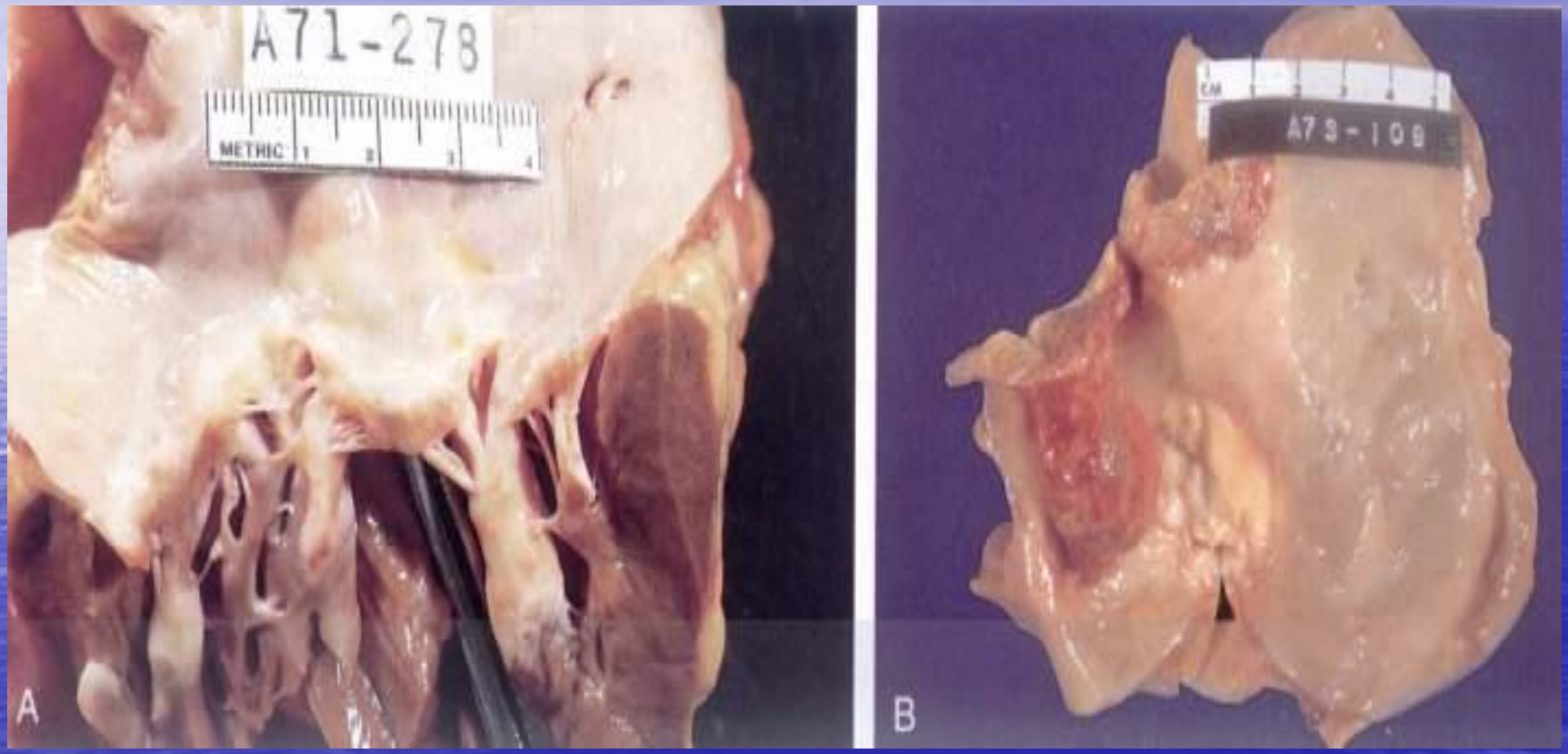
Carditis



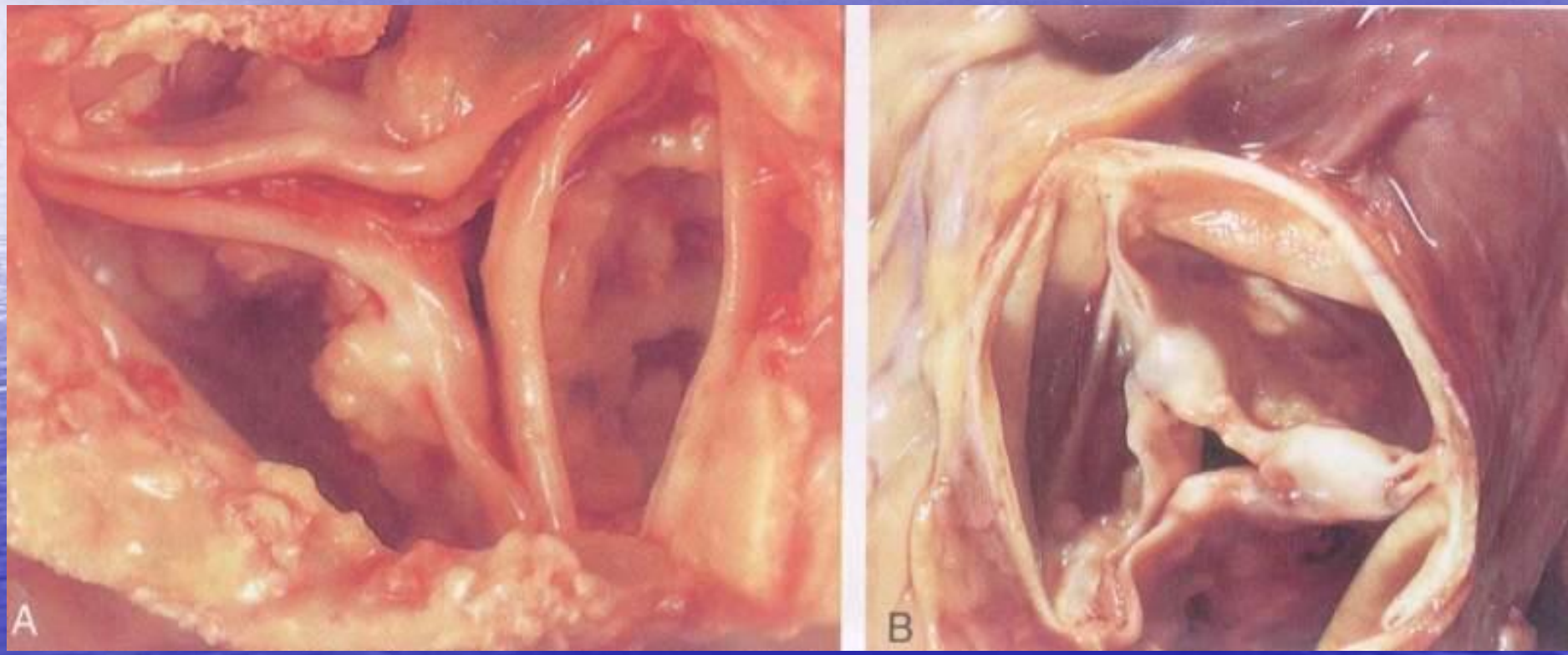




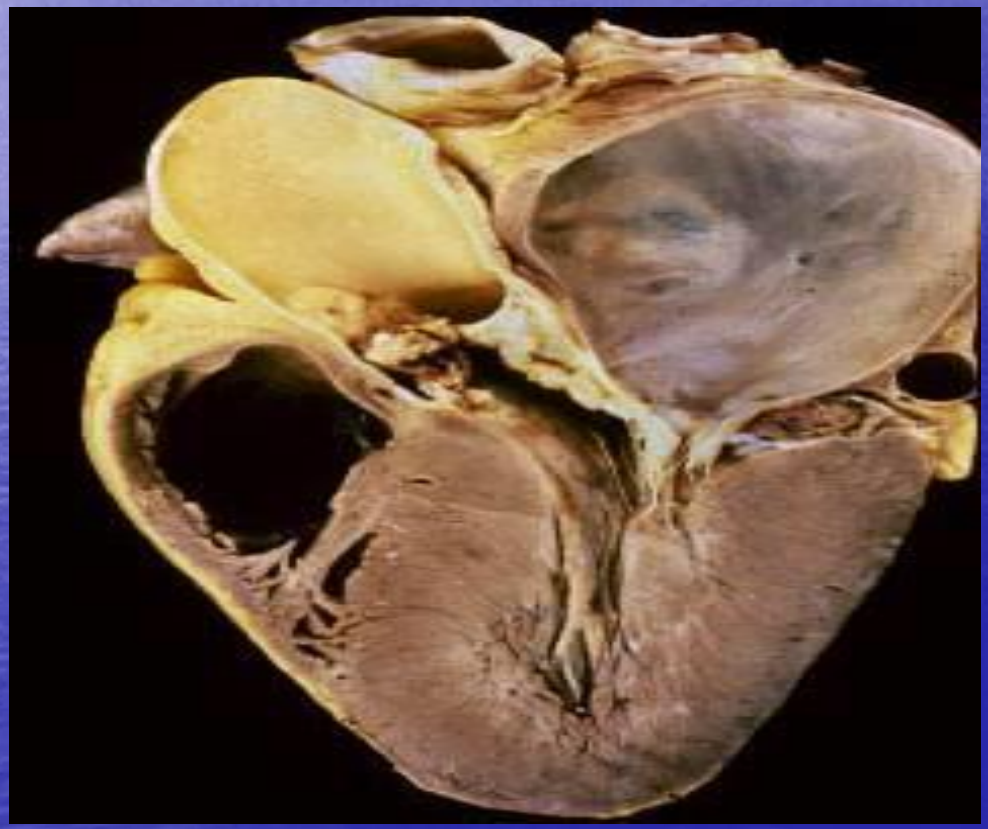
Plates McCallum in the left atrium

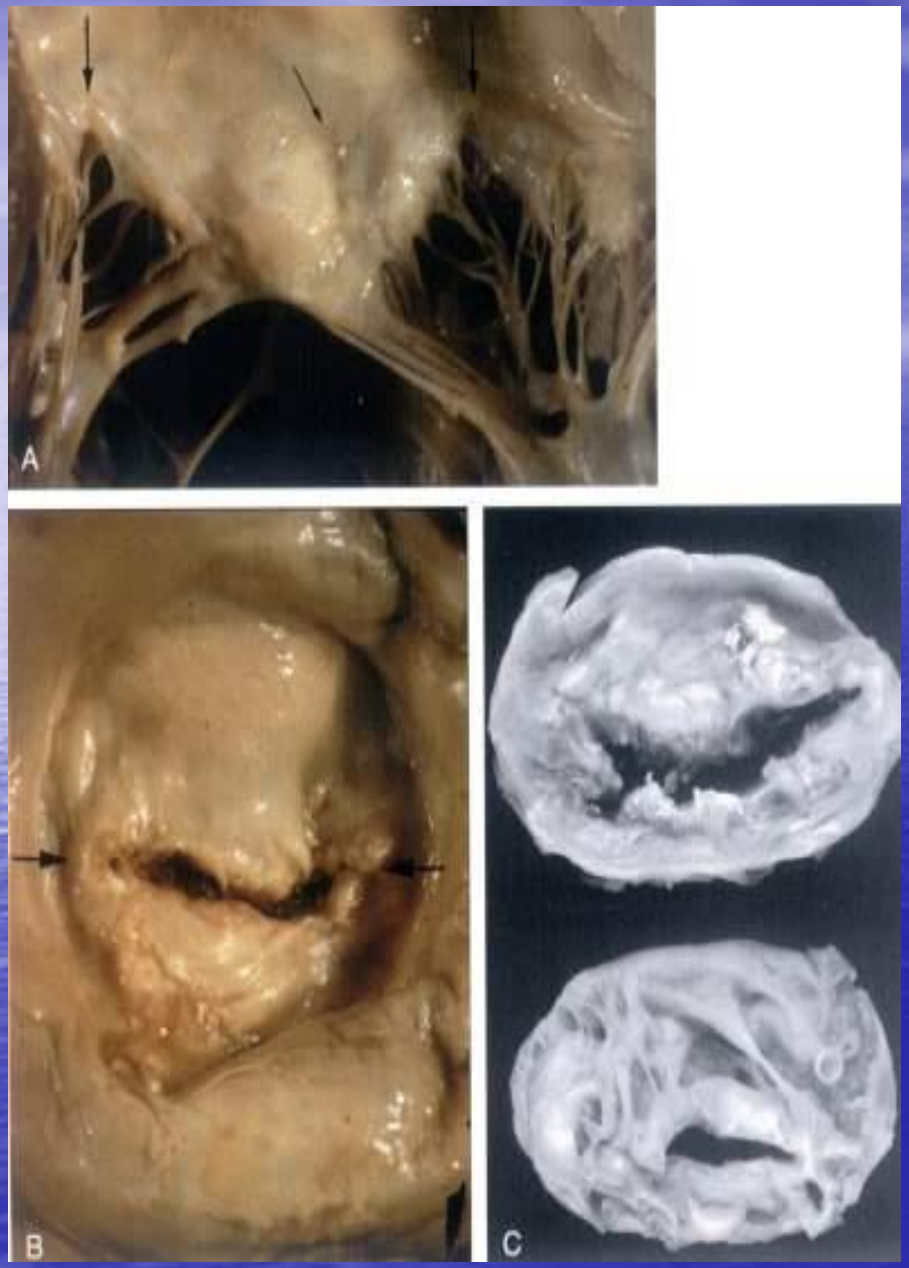


Calcinosis of aortic valves



Dilatation of left atrium and hypertrophy of left ventricul

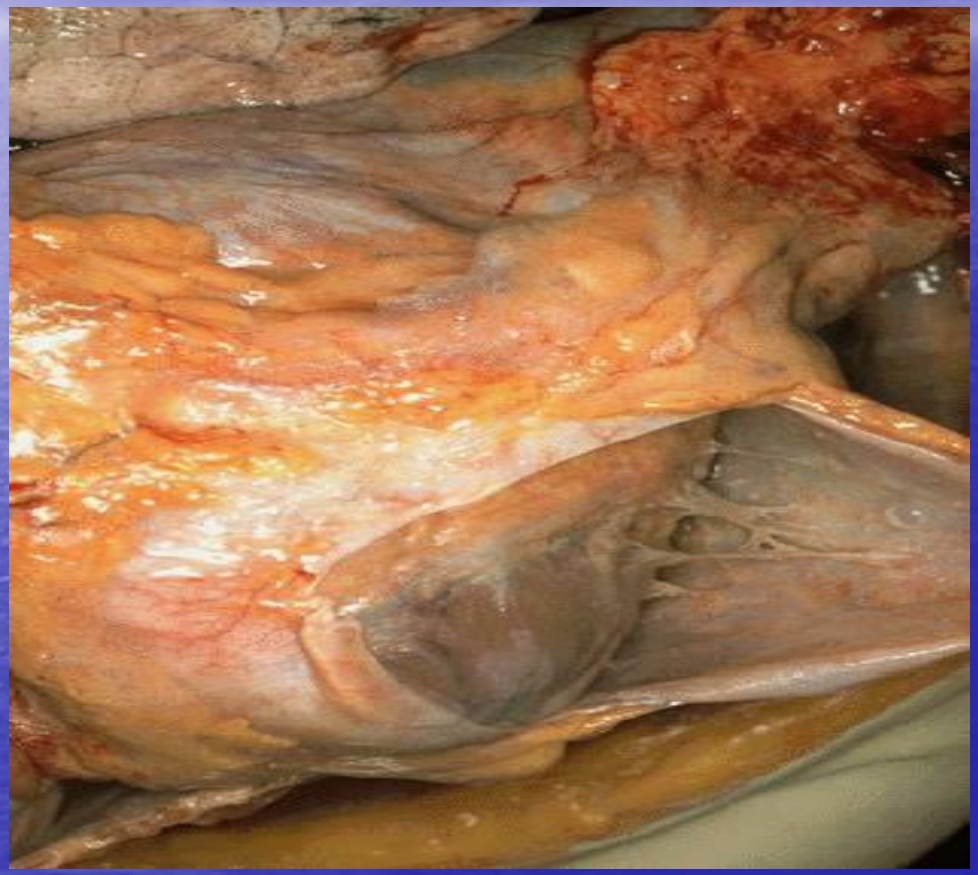




Narrow and short chordae

Stenosis of mitral valves like fish mouth

Fibrinous pericarditis
(villous heart)



Chorea

Sydenham chorea occurs in approximately 10–15% of patients with acute rheumatic fever and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing are characteristic, all exacerbated by stress and disappearing with sleep. The latent period from acute group A streptococcus infection to chorea is longer than for arthritis or carditis and can be months. Clinical maneuvers to elicit features of chorea include (1) demonstration of *milkmaid's grip (irregular contractions and relaxations of the muscles of the fingers while* squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue on protrusion, and (4) examination of handwriting to evaluate fine motor movements.

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute rheumatic fever) but characteristic rash. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic. It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute rheumatic fever) finding and consist of firm nodules approximately 0.5-1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more *nonspecific than major criteria*. The 1st of the 2 clinical minor criteria involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia and monoarthralgia. The 2nd clinical minor* manifestation is fever, *38.0°C - 38.5°C. The 2 laboratory minor criteria* are (1) elevated acute-phase reactants, defined as erythrocyte sedimentation rate 30 mm/hr - 60 mm/hr and/or C-reactive protein (CRP) at least 3.0 mg/dL, and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). A prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A Streptococcus Infection

Acute rheumatic fever typically develops 10-21 days after an acute episode of group A streptococcus pharyngitis. Evidence of an antecedent group A streptococcus infection is usually based on elevated or rising serum antistreptococcal antibody titers: anti–streptolysin O, anti–DNase B, antihyaluronidase.

Differential Diagnosis

ARTHRITIS: Juvenile idiopathic arthritis, Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia),* Serum sickness, Sickle cell disease, Malignancy, Systemic lupus erythematosus, Lyme disease *(Borrelia burgdorferi),* Pyogenic arthritis, Poststreptococcal reactive arthritis.

CARDITIS: Viral myocarditis, *Viral pericarditis,* Infective endocarditis, Kawasaki disease, Mitral valve prolapse, Congenital heart disease, *Innocent murmurs.*

CHOREA: Huntington chorea, *Wilson disease,* Systemic lupus erythematosus, Tic disorder, Hyperactivity, Encephalitis.

Treatment

Antibiotic Therapy: the patient should receive 10 days of orally administered penicillin or amoxicillin or a single intramuscular injection of benzathine penicillin to ensure eradication of group A streptococcus from the upper respiratory tract. If penicillin allergic, 10 days of erythromycin, 5 days of azithromycin, or 10 days of clindamycin is indicated.

Antiinflammatory Therapy: Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in 4 divided doses orally for 3-5 days, followed by 50 mg/kg/day in 4 divided doses for 2-3 wk and half that dose for another 2-4 wk.

Treatment

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive **corticosteroids. The usual dose of prednisone is 2** mg/kg/day in 4 divided doses for 2-3 wk, followed by half the dose for 2-3 wk and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in 4 divided doses for 6 wk to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen.

Treatment

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; **phenobarbital (16-32**mg every 6-8hr) is the drug of choice. If phenobarbital is ineffective, **haloperidol (0.01-0.03mg/kg/24hr divided twice daily) or chlorpromazine** (0.5mg/kg every 4-6hr) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

Complications

The arthritis and chorea of acute rheumatic fever resolve completely without sequelae. The long-term sequelae of rheumatic fever are essentially limited to the heart.

Primary Prevention

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute group A streptococcus pharyngitis is highly effective in preventing first attacks of acute rheumatic fever. Approximately 30% of patients with acute rheumatic fever do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute group A streptococcus pharyngitis in patients at substantial risk of recurrent acute rheumatic fever. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute rheumatic fever has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute rheumatic fever are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life.

Secondary Prophylaxis

Penicillin G benzathine - 600,000 IU for children weighing ≤30 kg and 1.2 million IU for children >30 kg, every 4 wk;
Sulfadiazine or sulfisoxazole - 0.5g, once daily for patients weighing ≤30 kg and 1.0g, once daily for patients weighing >30 kg
For People Who Are Allergic to Penicillin and Sulfonamide Drugs – Macrolide

Duration of Secondary Prophylaxis

Rheumatic fever without carditis - 5 yr or until 21 yr of age;
Rheumatic fever with carditis but without residual heart disease (no valvular disease) - 10 yr or until 21 yr of age;
Rheumatic fever with carditis and residual heart disease (persistent valvular disease) - 10 yr or until 40 yr of age, sometimes lifelong prophylaxis.

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