CONNECTIVE TISSUE DISEASES IN CHILDREN

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DEFINITIONS

- Connective tissue diseases (CTD) result from autoimmune processes that lead to inflammation of target organs- skin, musculoskeletal and cardiovascular systems, digestive tract, lungs, kidneys, SNS.

ETIOLOGY AND PATHOGENESIS

- The immune system normally responds to viruses, bacteria and others non-self molecules.
- The reactions are lost in CTD between similarity foreign and self molecules are recognized by immune cells, particularly T lymphocytes.
- T lymphocytes recognize viral, bacterial, vaccines antigens on the surfaces of antigen-presenting cells. Rubella, Epstein-Barr, influenza viruses, Chlamydia, Mycopl. Pneumoniae are identified in ARJ.
- Genetic factors- HLA alleles may influence susceptibility to developing disease.
- HLA-DR8,11, DRw2 in pauciarticular JRA, DR1,4 in systemic JRA; HLA-A1,B8, DR2,3 in SLE. Polymorphic markers on the chromosomes 1,6,19,20 specific in JRA.
- Activated macrophages produce inflammatory cytokines: TNF-a, interleukins IL-1, IL-6, IL12.
- Macrophages and T-cell invasion and cytokines cause tissue damage through direct effects or mediated by B lymphocytes, produce excessive antibody, including autoantibodies.
- Normal cells in target organs can be destroyed by complement-mediated cytolysis C3, C5, TNF-a, natural T-killer.

CLASSIFICATION

WHO proposed to include the follow diseases with involving the connective tissue inflammation:

1. Systemic idiopathic arthritis
2. Systemic Lupus Erythematosus
3. Scleroderma
4. Dermatomyositis
5. Undifferentiated connective tissue diseases

JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is a common rheumatic disease of early children.

Incidence is variable in different areas from 13.9/100,000=>70/100,000 children in different racial and ethnic groups (reports from USA, Sweden et al.), predominantly Caucasian.

JIA is classified as systemic, pauciarticular, or polyarticular disease according to onset within the first 6 months. Systemic-onset disease occurs with equal frequency in boys and girls.

Pathogenesis of JIA

- The synovitis with villous hypertrophy and hyperplasia, edema, increased of synovial fluid.
- Vascular endothelial hyperplasia with infiltration of mononuclear and plasma cells.
- Pannus formation and progressive erosion of cartilage and contiguous bone.
- All proinflammatory factors resulting in severe artthritis and systemic disease.
- As a result of increased B-cell activity, hyperglobulinemia, circulating immune complexes (CIC), antinuclear antibodies (ANA), and rheumatoid factor are commonly found in patients with JIA.

CRITERIA FOR THE CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS

1.Age of onset <16yr.

2.Arthritis (swelling or effusion, or the presence of 2 or more of the following signs, limitation of range, of motion, tenderness or pain on motion, increased heat in >1 joints.

3.Duration of disease >6wk.

4.Onset type defined by type of articular involvement in the 1st 6mo after onset:

- Polyarthritis >5 inflamed joints.
- Oligoarthritis (Pauciarthritis) 4 or< inflamed joints.
- Systemic disease arthritis with a characteristic high spiking intermittent fever, affections of visceral organs.

5.Exclusion of other forms of JIA.

Systemic clinical manifestation

Systemic onset of JIA (formerly called Still's disease) occur 10-20% of all cases of JRA.

- The intermittent fever >39o for >2wk in association with the macular nonpruritic rash is salmon-colored, may be linear or circular, often distributed on the trunk and extremities.
- Visceral involvement- hepatosplenomegaly, lymphadenopathy, pericarditis, pleural effusion with starting of disease. Some children with this disorder are initially thought to have leukemia because of the high white blood cell counts. Arthritis may not be evident for months following onset, making diagnosis difficult.

Pauciarticular onset of JIA

- Pauciarticular onset of JIA in patients with involvement less than four joints (50%of cases), during the first six months of disease. The peak incidence of it is in the second and third years, rarely begins after age 10, more often in girls.
- Pauciarticular JIA affects the large joints (knees, ancles, wrists, elbows), but virtually never begins in the hips.
- The complication is uveitis with photophobia, synechiae (irregular iris perimeter resulting from inflammatory adhesions of iris to lens).
- Monoarticular arthritis in a hip is highly unusual. Consider Legg-Calve-Perthes disease; toxic synovitis of the hip; septic arthritis.

Polyarticular JIA

- Is defined by the presence of more than 5 affected joints during the first 6 months of illness.
- Distribution of the age at onset: the first peak in incidence is between the ages of 2-5 years, and the second peak between 10-14 years. It is more common in females than males.
- Typically, larger joints (knees, ankles, wrists), cervical spine are affected with swollen and tenderness. Muscle atrophy often in extensor muscles(vastus lateralis, quadriceps), flexion contractures.
- Rheumatoid nodules on the extensor surfaces of the elbows, and over the Achilles tendons are associated with a more severe course.
- There are no characteristic laboratory findings, although an elevated ESR,≥40mm/hr, anemia Hb ≤11g/dL, and hypergammaglobulinemia may be present.

DIFFERENTIAL DIAGNOSIS

1. Psoriatic arthritis with limited joint involvement of the hand, ankle and skin manifestation.
2. Isolated hip pain with limited motion raises the possibility of suppurative arthritis.
3. Patients with acute lymphocytic leukemia and expansion of lymphoblasts in bone metaphyses, can present severe joint pain, even arthritis; neutropenia and lymphocytosis are present. Bone marrow aspiration confirms the diagnosis.
4. Children and adolescent with spondyloarthropathy, characterized by periods of inflammation of tendons and ligaments at the area of insertion into bone (enthuses)may present arthritis. Although enthesitis can be observed in pauciarticular JIA, eventual predominant of arthritis is more characteristic for JIA.

LABORATORY STUDIES

- ESR is always elevated in children with systemic and polyarticular JIA, but is often within reference range in pauciarticular disease.
- When elevated, ESR may be used to monitor success of medical treatment.
- CBC with differential and platelet count.
  - Lymphopenia is not uncommon because of migration of activated lymphocytes out of the circulation into synovium.
  - Neutropenia is uncommon and, particularly with lymphocytosis or thrombocytopenia, raises the possibility of acute lymphocytic leukemia.
  - Thrombocytopenia may also be observed in children with SLE presenting with arthritis.
  - Anemia may result from chronic active JIA; often microcytic, usually refractive to treatment with iron.
- Obtain ALT levels to exclude the possibility of hepatitis (viral or autoimmune) prior treatment with NSAIDs, which can cause hepatotoxicity.
- Perform a urinalysis to exclude the possibility of infection (as a trigger of JIA or transient arthritis) and nephritis (observed in patients with SLE).

Serum investigation

- Antinuclear antibody (ANA) observed in >25% of children with pauciarticular JIA.
- Titers of 1:80 or higher are positive; a 1:40 titer or lower is negative.
- When found in young girls a positive ANA is a marker of increased risk of uveitis.
- Very high titers may be in SLE.
- Rheumatoid factor defined as IgM 19S antiglobulin. Gel filtration at acid pH dissociated IgM from IgG and allows IgM RF. It is considered a marker for persistence of polyarticular JIA.
- Other laboratory tests:

- Total protein and albumin: levels are often decreased during active disease.
- Fibrinogen and D-dimer: levels are often elevated in patients with active disease.

IMAGING STUDIES

- X-ray of affected joints: is important to exclude other diseases, such as osteomyelitis or septic arthritis.
- Bone scanning as a means of identifying other abnormality.
- Perform MRI with gadolinium injection to enhance inflamed synovium.
- MRI is helpful when considering trauma in the differential diagnosis.
- Perform CT scanning when considering osteoid osteoma in a child with lower extremity pain, often at night.
- EcoCG in patients with possible systemic JRA and with fever.
- Perform EcoCG in patients with orthopnea in history to exclude pericarditis; in nonspecific rash, adenopathy to exclude coronary arterial dilation (possibly Kawasaki disease), to exclude valvular disease in other rheumatic diseases.

Functional classes according Steinbrocker

- I class - patient perform all activities
- II class- limitation of activities caused by pain and reduced joint mobility
- III class - limitation of home activities, difficulties in taking care of oneself.
- IV class - bed regimen of patient or sitting in carriage.

X-ray stages affections according Steinbrocker

- I stage - inflammation of soft tissue, mild enlargement of articular space
- II stage - anterior mention signs and diffuse periarticular osteopena, growth abnormalities
- III stage – narrowed of joint space, large boney erosions.
- IV stage- severe loss of cartilage, joint contractures, subluxation

OTHER PROCEDURES

- Arthrocentesis in a child with monoarticular swelling to exclude septic arthritis.
- Synovial biopsy may be helpful to exclude other diagnoses- villonodular synovitis, granulomatous arthritis; may demonstrate synovial infiltration with plasma cells, mature B lymphocytes, and T lymphocytes, with areas of thickening and fibrosis.
- Pericardiocentesis need to treat severe pericarditis.

TREATMENT OF JIA

NSAIDs are used to treat all subtypes of JRA, because of inhibition of prostaglandin synthesis.

Naproxen (7-20 mg/kg/d), Ibuprofen (30-50mg/kg/d not to exceed 2-4g/d), Diclofenac 2-3mg/kg/d, Tolmetin (20mg/kg/d), Indomethacin (1-2mg/kg/d). If NSAIDs are used , careful monitoring of hepatic and renal function is needed.

IMMUNOSUPPRESSIVE AGENTS

- Most children with polyarticular and some with aggressive pauciarticular JIA.
- Methotrexate (Rheumatrex): 7.5 mg/wk=> 2.5mg q12h for 3 doses.
- Sulfasalazine (Azulfidine, EN-tabs) in children>6yr 10mg/kg/d initially, increase by 10mg/kg/d qwk; typical dose is 30-50mg/kg/d; not exceed 2g/d.
- Cyclosporine has been effective in children with dactylitis who do not respond to Sulfasalazine.

CORTICOSTEROIDS

- Are used in systemic onset JIA to minimize toxicity, particularly in patients, who have not responded to a 6-12 week use of NSAIDs; in uveitis and intraarticular use in persistent limited joint disease.
- Prednisone dose 0.5-2mg/kg/d; taper over 2wk, as symptoms resolve.
- Methylprednisolone (Solu-Medrol) 15-30mg/kg/d ;IV administered over 30min for 2-3d, used temporarily for JRA until longer-term treatment provides effective relief.
- Intraarticular injections of corticosteroids are effective in polyarticular JRA, but more effective is systemic therapy.
- Uveitis is initially treated with topical corticosteroids, if the inflammatory process is not decreased systemic corticosteroids and/or methotrexate may be helpful. In severe disease , Cyclosporine, Adalimumab or Infliximab have been used.

TUMOR NECROSIS FACTOR (TNF) INHIBITORS

- TNF-a or cachecitin is produced predominantly by macrophages; TNF-beta or lymphotoxin is produced by lymphocytes. Both of them are involved in the inflammatory cascade in JRA.
- Etanercept (Enbrel) are used in children 4-17years: 0.4mg/kg twice/wk; should be used before Methotrexate, more effective, possibly less toxic.
- Adalimumab (Humira), has been effective in children who no responded to Etanercept.
- Infliximab (Remicade) have similar efficacy as seen with Etanarcept. Adverse effects such macrophage activation, alopecia and double increse of DNA antibodies was reported.

PROGNOSIS

- Children with pauciarticular JRA, particularly girls with onset at an age of <6yr, are at risk to develop chronic uveitis, cataracts, blindness.
- Functional risk in polyarticular disease with RF seropositivity, or rheumatoid nodules and early development of erosions or disease of the cervical spine or hips.
- Prognosis in the systemic-onset disease is dependent on the number of joints involved, duration of active inflammation, and the severity of the arthritis.
- The acute development of a severe anemia, thrombocytopenia or leucopenia with high, spiking fever, lymphadenopathy, and hepatosplenomegaly occurs with the macrophage activation syndrome, a rare and occasionally fatal complication of systemic JRA. Bone marrow biopsy demonstrate hemophagocytosis. Emergency treatment with high dose IV pulse Methylprednisolone, Cyclosporine or Etanercept, may be effective.
- Orthopedic complications, medical control of patients with contractures, psychosocial adaptation may be counseled by health professionals.

SYSTEMIC LUPUS ERYTHEMATOSUS

DEFINITION: A multiorgan rheumatologic disease characterized by widespread inflammation of the blood vessels and connective tissue with skin and visceral manifestations.

- Prevalence rates of 4-250/100,000, onset before 8yr of age, female predominance varies from 4:1before puberty to 8:1 afterward.

TRIGGERS:

- Chronic viral infections: myxovirus-like particles in endothelial cells. Increased serum titers of antiviral antibodies to rubella, EVB, paramyxovirus.

Criteria for the Classification of SLE

- Malar (butterfly) Rash
- Discoid-Lupus Rash
- Photosensitivity
- Oral or Nasal Mucocutaneous Ulcerations
- Nonerosive arthritis
- Pleuritis or Pericarditis

- Cytopenia
- Positive Antinuclear Antibody Test
- Nephritis**
- Proteinuria >0.5g/day
- Cellular Casts
- Encephalopathy**
- Seizures
- Psychosis

- Positive Immunoserology**
- Antibodies to nDNA
- Antibodies to Sm Nuclear Antigen
- Positive LE-Cell Preparation
- Biologic False-positive Test for Syphilis
- *** Four of 11 criteria provide a sensitivity of 96% and a specificity of 96%**

Skin Manifestations

- **Malar (Butterfly) Rash-** occurs in up to 33% of children at the onset of SLE, is not pathognomonic for SLE, a well demarcated, slightly elevated erythematous (red) rash. **D**istributed symmetrically in a butterfly fashion on both malar eminences and over the bridge of the nose, occasionally involves the forehead but spares the nasolabial folds, may be precipitated by exposure to sunlight , does not result in scarring

- **Discoid-Lupus Rash-** unusual in childhood SLE, occurs on the scalp or limbs. **D**istributed asymmetrically, heal with atrophy and scarring of the involved skin.
- **Oral and Nasal Ulcerations**
- **Hard Palate Lesions-**a shallow, erythematous, painless ulcer with an irregular border, can also get erythematous lesions without ulceration. **M**ucous membrane involvement almost always indicates active SLE . **Nasal Septum Lesions-** perforation of Little's area, are asymptomatic and uncommon. . **Aphthous Ulcers-**involve the mouth and pharynx, develop early in SLE and with exacerbations.

- **Photosensitivity**- **Maculopapular Rashs-**develop anywhere on the body but particularly on sun-exposed areas (face, upper chest), can be tender, heal without scarring or pigmentation changes, due to subcutaneous vasculitis .
- **Alopecia-**associated with active SLE, presents as excessive hair loss after brushing or shampooing or found on the pillow after sleeping. **F**rontal hair is usually affected initially and is noticed to be brittle and kinky. Alopecia usually represents diffuse thinning of the hair, patchy alopecia is uncommon and total alopecia is rare.
- **Nailbed Changes-**periungual erythema, nailfold infarcts, loss of nails in long-standing SLE .

Subacute Cutaneous Lupus

- Distribution is widespread involving the trunk, limbs, and face .**B**egins as papules which evolve into annular lesions with raised edges, may eventually become crusted, hyperpigmented, and atrophic.
- **Livedo Reticularis-** reflects active SLE, involves the lower extremities, associated with anticardiolipin auto-antibodies.
- **Others skin manifestations-** angiitic papules on soles and palms, bullae, chronic leg ulcerations. **E**rythema nodosum, rheumatoid nodules, gangrene, hypo/hyperpigmentation .**P**etechiae, purpura, telangiectases, urticarial or angioneurotic lesions.

Central Nervous System (CNS) Manifestations

- occur in 20-35% of children with SLE, tend to occur later in the course of the disease; a significant cause of morbidity and mortality; psychiatric manifestations are common in SLE

- **Headaches-**occur at disease onset in about 10% of children with SLE, are severe, may or may not indicate CNS disease in those with SLE, may recur during exacerbations and disappear with remissions
- **Seizures-**a common manifestation in SLE, may be focal or generalized, may or may not be recurrent ,not related to a poor prognosis.
- **Movement Disorders-** cerebellar ataxia is a rare CNS manifestation of SLE, chorea in children is associated with SLE but is an uncommon complication

Central Nervous System (CNS) Manifestations

- **Others SNS manifestations-** aseptic meningitis, cortical blindness, hypothalamic lesions, intracranial hemorrhage . **P**aralysis, pseudotumor cerebri, transverse myelitis.

Pulmonary Manifestations

- **P**atients may demonstrate moderate to marked functional impairment with normal chest x-ray.
- **Pleural Effusions and Pleuritis -**in 27% of children with SLE
- **Pulmonary Infiltrates/Atelectasis-**in 13% of children with SLE . **"Shrinking" Lung-** in 13% of children with SLE, secondary to diaphragmatic dysfunction; on chest x-ray is seen as a progressive elevation of the level of the diaphragm . **Pleuropulmonary Infections-** a common pulmonary complication of SLE . **Others-** pneumonitis - acute and chronic; pneumothorax; pulmonary hemorrhage.

Cardiovascular (CVS) Manifestations

- **Pericarditis-** occurs in up to 30% of children with acute SLE, may be asymptomatic.
- When symptomatic may be associated with precordial chest pain which worsens with lying down or deep breathing and relieved by sitting up and leaning forward..Complications include constrictive pericarditis and cardiac tamponade but are rare.

Cardiovascular (CVS) Manifestations

- **Myocarditis-** occurs in up to 25% of children with SLE. **A**ssociated with congestive heart failure, arrhythmias, cardiomegaly, and/or narrow pulse pressure, aortic insufficiency may be a complication .
- **Endocarditis-** Libman-Sacks verrucous endocarditis, may develop in acutely ill patients; may be associated with a clinically significant murmur or changing murmur. **A**ssociated with 1-4mm nodes of fibrinoid necrosis of the supporting connective tissue of the valves:
- mitral > aortic > pulmonic > tricuspid valve (in descending order of involvement), lesions are demonstrable on 2D echo

Investigation of SLE

- **1. Screening Tests**
- **1. Antinuclear Antibodies (ANA)-** a screening test to determine if autoantibodies to cell nuclei are present in patients with SLE. This test does not indicate which autoantibodies are present ,
- is a more sensitive test for SLE than the LE cell preparation test ,is the best screening test currently available for identifying SLE.
- is positive in almost all patients with SLE
- a positive test is not sufficient itself to diagnose SLE or to monitor the disease course.

Investigation of SLE

- **ANA Test-**is called the immunofluorescent anti-nuclear antibody test (ANA or FANA).
- The patient's blood is mixed with rat or mouse liver cells or HEp-2 cells, exposed to fluorescein-tagged anti-IgG antibodies, and then examined under a microscope , the preparations are assessed in two ways:
- **ANA Titre-** this tells how many times the patient's plasma had to be diluted to get a sample free of the fluorescein-tagged anti-IgG antibodies
- **ANA Pattern-** this looks at the distribution of fluorescein-tagged anti-IgG antibodies on the cells, there are 4 patterns .

Investigation of SLE

- **LE Cell Test-** the patient's blood is examined under the microscope for the presence of LE cells.
- The patient's tissues are examined under the microscope for the presence of hematoxylin bodies
- **Antinuclear Antibodies -**there are many different types of antinuclear antibodies which are directed towards varius antigenic epitopes found in 2 different nuclear structures: chromatin and snRNP's

Serum investigation of SLE

- **Acute Phase Indicies-** represent indicies of inflammation. **T**he following tend to be elevated in children with SLE: ESR, CRP, alpha-2-globulins, polyclonal hypergammaglobulinemia ,the degree of elevation is correlated with disease activity.
- **Complete Blood Count (CBC)- Anemia-** seen in 50% of children with SLE. **I**n SLE, there are several causes of anemia: anemia of chronic disease (normocytic, hypochromic), hemolytic anemia associated with auto-antibodies directed against erythrocytes (seen in 5% of cases), hypersplenism, microangiopathy.

Serum investigation of SLE

- **Thrombocytopenia-**PLT <150,000 in 30% of children with SLE; PLT <100,000 in 5% of children with SLE, may have normal platelet number despite increased production and destruction of platelets. **M**ay result in menorrhagia or gastrointestinal bleeding, may be severe enough to produce ITP or TTP.
- **Leukopenia-** WBC <4.5 in 40% of children with SLE, WBC <2.0 in 10% of children with SLE.
- Leukopenia (particularly lymphocytopenia) is a hallmark of acute SLE, children with leukopenia (WBC <2.0) may not respond to septicemia with leukocytosis.

Treatment of SLE

- NSAIDs have been used to treat the arthralgias and arthritis associated with SLE.
- Anti-malarial drugs used for constitutional, cutaneous, and articular manifestations.
- Cyclophosphamide (trade names Cytoxan and Neosar) is used in lupus nephritis.
- In more severe cases, medications that modulate the immune system (primarily corticosteroids and immunosuppresive drug) are used to control the disease and prevent recurrence of symptoms (known as flares).

Complications of SLE

- Patients who require steroids frequently may develop obesity, diabetes mellitus, and osteoporosis. Depending on the dosage, corticosteroids can cause other side effects such as puffy face, an unusually large appetite and difficulty sleeping.
- Long term use of even low doses can cause elevated blood pressure and cataracts. Due to these side effects, steroids are avoided if possible.
- Worse prognosis are seen in patients with severe lupus nephritis or cerebritis, with risk of chronic disability or progression to renal failure and need renal transplantation.
- Opportunistic infections in patients reseving immunosuppresive therapy. Osteonecrosis, especialy on the hips and knees.

Prognosis of SLE

- The mortality rate is currently about 1%.
- The period of active symptoms decreased from 3.5yr to <1.5yr.
- Monitoring inflammation and disease activity improved the prognosis.

Prevention of SLE

- Avoid ultraviolet light and sunlight exposure.
- Monitoring BP and serum lipids to prevent CAD of renal progression, myocardial infarction.
- ACE inhibitors and/or angiotensin receptor blockers in chronic renal disease.
- Calcium, vitamin D and prophilactic bisphosphonates may reduce the risk of glucocorticoid-induced osteoporosis.

JUVENILE DERMATOMYOSITIS

DEFINITION: Juvenile dermatomyositis (JDM) is an idiopathic inflammatory myopathy with characteristic skin signs. Incidence: 3.2 cases/million children/yr, 73% in whites. Girls are affected twice more than boys. Age of onset<4yr in 25% of children.

Etiology of JDM

- Genetic predisposition with antigen stimulation. Genetic markers on chromosome 6- DQA1● 0501 and DRB1● 0301, human leukocyte antigen (HLA) types DR3, DR5, DR7.
- Polymorphism of TNF-a have been linked to photosensitivity in patients with JDM.
- Infectious agents: Coxsackie virus, Parvovirus, ECHO-virus, Human T-cell lymphotrophic virus type 1 (HTLV-1; HIV). Streptococcus group A, Toxoplasma, Borrelia species et al.
- Drugs agents: Penicillamine, Statins, Quinidine, and Phenylbutazone.

Pathogenesis of JDM

- TNF-a, TNF-b abnormalities: up regulation of genes controlled.
- Complement-mediated vascular inflammation.
- Cytotoxic effect of CD8, CD56 lymphocytes on muscle.
- Damage of muscle fibers, fibrosis.
- Edema and vascular inflammation of skin.

CLINICAL MANIFESTATIONS

- Proximal muscle weakness when climbing stairs, walking, rising from sitting position.
- The heliotrope rash with edema in symmetrical periorbital skin.
- Gottron papules over bony prominences of metacarpophalangeal and proximal interphalangeal joints.
- Periungual teleangiectases, hypertrophy of the cuticle, small hemorrhagic infarcts in areas.
- Scalp involvement manifested by psoriasiform dermatitis.
- Dysphagia is an urgent prognostic sign for hospitalization and treatment to prevent aspiration.
- Pulmonary function tests for myosytis-specific documented decreased vital capacity.
- Gastrointestinal tract involvement associated with constipation, diarrhea, abdominal pain.
- Other signs: hepatosplenomegaly, retinitis, iritis, SNS involvement with seizures, depression.

JDM- DIAGNOSTIC CRTERIA

- Myopathic muscle weakness
- Elevated muscle enzymes.
- Electromyographic evidence of myopathy.
- Muskle biopsy: perifascicular atrophy, in addition to perimysial or perivascular infiltrates.
- Skin rash, calcinosis.

Four of the 5 criteria are related to muscle disease.

LABORATORY STUDIES

- Elevated serum levels of muscle-derived enzymes: CK, aldolase , AST, LDH.
- ANA, anti-Mi-2, anti-Jo-1 (antihistidyl transfer RNA), antisignal recognition protein (anti-SRP) antibodies.

IMAGING STUDIES

- MRI- may detect myopathy, differentiating, selecting a muscle biopsy site.
- Chest X-ray in pulmonary symptoms.
- A barium swallow in esophageal dysmotility.
- EMG for detecting muscle inflammation.
- CT scans in the evaluation of potential malignancy.

OTHER TESTS

- Pulmonary function studies
- Electrocardiography
- Esophagal manometry in select patients
- Muskle biopsy is useful in differentiating steroid myopathy from active inflammatory myopathy.

Treatment of JDM

- Bed rest in patients with severe muscle inflammation.
- In children with muscle weakness a program of physical therapy to prevent contractures.
- Corticosteroids, prednisone 1-2mg/kg/d; Methylprednisolone 30mg/kg/d for 3 days.
- Immunosuppresive- Cyclosporine 3mg/kg/d. In decreased levels of IgG <500mg/dl replacement with IV immunoglobulin 0.4g/kg/mo or 1-2mg/kg, 1-2days/mo to help prevent infections.
- Maximal protection against ultraviolet A and B. Vitamin D to prevent bone fracture.

Prognosis of JDM

- Depend greatly on the extent of muskle disease, onset time and initiation of therapy.
- JDM follows one of three clinical courses: an uniphasic course, in which patients are treated and improve without significant sequelae; a chronic recurrent course; and a chronic progressive course, marked by poor response to therapy and loss of function.

Scleroderma

Department of pediatrics

Definition

- The term systemic sclerosis (SS) is used to describe a systemic disease characterized by skin induration and thickening accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, humoral and cellular immune alterations.
- Robert H. Goetz described the concept of scleroderma as a systemic disease in 1945.

Causes of systemic sclerosis (SS)

- The exact etiology of SS is unclear, the following pathogenic mechanisms are always present: endothelial cell injury, fibroblast activation, immunologic derangement
- Trigger factors: exposure to silica, solvents, radiation or radiotherapy; human CMV, herpes virus 5 and drugs (Bleomycin, Pentazocine) may be involved in the development of SS

Classification of SS (ACR)

The American College of Rheumatology (ACR) criteria for the systemic sclerosis require one major criterion or two minor criteria, as follows:

- Major criterion: Proximal scleroderma - symmetric thickening, tightening, and induration of the skin of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joints. These changes may affect the entire extremity, face, neck, and trunk

Classification of SS (ARA)

- **Minor criteria**
  - Sclerodactyly includes the above major criterion characteristics but is limited to only the fingers.
  - Digital pitting scars or a loss of substance from the finger pad: As a result of ischemia, depressed areas of the fingertips or loss of digital pad tissue.
  - Bibasilar pulmonary fibrosis includes a bilateral reticular pattern of linear or lineonodular densities on standard chest X-ray.

Pathophysiology of SS

- Systemic sclerosis is a systemic disease that affects many organ and systems. It is most obvious in the skin; however, the GI tract; the respiratory, renal, cardiovascular, and genitourinary systems; and numerous vascular structures are frequently involved.
- The symptoms result from inflammation and progressive tissue fibrosis and occlusion of the microvasculature by excessive production and deposition of types I and III collagen. The levels of other macromolecules found in the connective tissue (eg, glycosaminoglycans, tenascin, fibronectin) are also increased.

Pathophysiology of SS

- The vascular alterations show a predilection for affecting the small arteries and arterioles. Vascular dysfunction is one of the earliest alterations of systemic sclerosis and may represent the initiating event in its pathogenesis.
- Severe alterations in small blood vessels of skin and internal organs, including fibrosis and perivascular cellular infiltration with activated T cells, are almost always present in systemic sclerosis.

Morbidity

Sex

- The risk of systemic sclerosis is 3-9 times higher in girls than boys.

Age

- May begin at any time during childhood.

Clinical manifestations

- Skin
  - Diffuse pruritus, pain or prickly sensation , edema reflect vascular changes or glycosaminoglycan deposits in the dermis. Skin tightness and induration. In the sclerotic phase tight shiny skin, loss ability to make a skin fold, loss of hair, decreased sweating
  - Raynaud phenomenon triggered by cold, smoking or emotional stress, occurs in 5-15% of the general population, the female-to-male ratio is 4:1
  - Skin pigmentary changes (hyperpigmentation or hypopigmentation -"salt and pepper" appearance, healed pitting ulcers in finger tips, calcinosis on the fingers or any area
  - Cutaneous and mucosal telangiectasias in the face, hands and anterior chest
  - Reduced oral aperture (microstomia), poor dentition, decreased salivary production- xerostomia

Musculoskeletal system

- Synovitis, tenosynovitis and nodules may mimic rheumatoid arthritis.
- Tendon friction rubs when moved actively or passively precede joint involvement.
- Arthralgia, myalgia, loss in joint range of motion, muscle weakness, morning stiffness.
- Acroosteolysis (resorption or dissolution of the distal end of the phalanx).
- Flexion contractures of any affected joint.

Systemic involvement in SS

- Gastrointestinal system
  - Gastroesophageal reflux caused by lower esophageal sphincter incompetence and decreased or absent peristalsis in the lower two thirds of the esophagus (may lead to hoarseness, aspiration pneumonia, and dysphagia).
  - Severe esophagitis, esophageal strictures, gastric vascular antral ectasia (watermelon stomach).
  - Dyspepsia, bloating, and early satiety; constipation, anal sphincter incompetence, colonic diverticula, malabsorption.
  - Liver dysfunction or associated primary biliary cirrhosis may progress slowly in SS.

Systemic involvement in SS

- Respiratory system -progressive dyspnea, dry persistent cough and dry rales suggest pulmonary involvement in SS
- Chest pain (precordial) and accentuated pulmonic secondary heart sound (P2) may indicate the presence of pulmonary artery hypertension (PAH)
- Pulmonary function tests: demonstrate a decreased vital capacity and total lung capacity, a systolic pulmonary artery pressure of >35mmHg represent PAH
- Right-sided heart catheterization provides the most accurate PAP
- CT scan may demonstrate a ground-glass appearance in areas of active alveolitis or septal fibrosis and honeycombing in areas of interstitial fibrosis

Systemic involvement in SS

- **Cardiovascular system**
- Dyspnea due to pericardial effusion, congestive heart failure, or myocardial fibrosis
- Pericardial effusion is usually asymptomatic, significant pericarditis is rare
- Replacement of cardiac muscle by fibrous tissue lead to cardiomyopathy and heart failure
- Palpitations, irregular heart beats, and syncope due to conduction abnormalities –complete A-V block, extrasystoles
- Cor pulmonale may develop secondary to long-standing pulmonary fibrosis or pulmonary artery hypertension

Systemic involvement in SS

- Renal system
  - Hypertension
  - Renal crisis- accelerated hypertension, oliguria, headache, dyspnea, edema, and rapidly rising serum creatinine levels. Renal crises more common in black than in whites, and males have a greater risk.
  - Chronic renal insufficiency

Other Problems to be Considered

Bleomycin-induced scleroderma
Toxic oil syndrome (adulterated rape seed oil)
Porphyria cutanea tarda
Digital sclerosis of diabetes mellitus
Morphea
Linear scleroderma
Vibration disease
Radiation exposure
Scleroderma sine scleroderma

Other Problems to be Considered

Intestinal obstruction
Infiltrative cardiomyopathy
Nephrogenic fibrosing dermopathy (nephrogenic systemic fibrosis); amyloidosis
Scleromyxedema (Hashimoto tyroiditis)
Scleredema adultorum of Buschke
Scleredema diabeticorum
Peripheral and sensory neuropathies

Complications

- Digital infarctions
- Pulmonary hypertension
- Myositis
- Renal failure
- Wound infections

Laboratory Studies

- The role of the immune system in the pathogenesis of systemic sclerosis remains unclear; patients have specific humoral and cell-mediated immunity abnormalities.
- Antinuclear antibodies are present in about 95% of the patients, usually with a speckled or homogenous pattern. A nucleolar pattern, although less common, is more specific for systemic sclerosis.
- Cell-mediated abnormalities involve lymphocytes, mononuclear phagocytes, and mast cells.
- Topoisomerase I antibodies (formerly Scl-70) are present in approximately 30% of patients with SS (absent in limited disease) and are associated with pulmonary fibrosis.
- Anticentromere antibodies are present in about 60-90% of patients with limited disease and are rare in patients with diffuse disease.

Laboratory Studies

- Fibrillarin antibodies and antibodies to U3 ribonucleoprotein (RNP) may be present. Anti-U3RNP is present mostly in patients with diffuse disease with overlap syndromes. These antibodies are more common in patients with skeletal muscle involvement and pulmonary disease.
- Anti-ThRNP is present mostly in limited disease and is associated with more extensive visceral disease.
- Anti-PM-Scl is present in limited and overlap states and is associated with myositis and renal involvement.
- A microangiopathic hematologic picture may precede renal crisis.
- Current studies report new autoantibodies in systemic sclerosis that may play a role in its pathogenesis; these autoantibodies include antiendothelial cell (AECA), anti-fibrillin (FBN1), anti–matrix metalloproteinase (MMP)–1 and anti–MMP-3, and anti–platelet-derived growth factor receptor (PDGFr).

Imaging Studies

- CT scan: HRCT scan may reveal a ground-glass appearance, possibly indicating active alveolitis, is the first abnormality during the development of lung fibrosis and replaced by honeycombing and traction bronchiectasis or bronchiolectasis. HRCT scanning should be performed every 6 months if active alveolitis or interstitial pulmonary fibrosis is present and every year if these abnormalities are not present.
- Radiography: Chest X-ray shows only late findings of pulmonary fibrosis, such as increased interstitial markings. Extremity radiography should be performed to reveal calcinosis and resorption of the distal tufts of the digits.

Imaging Studies

- Echocardiography: Conduct this test to evaluate the patient's pulmonary artery pressure and to assess septal fibrosis or pericardial effusions. Roughly 30% of patients have asymptomatic pericardial effusions.
- Right-heart catheterization for diagnosing pulmonary hypertension is performed after an elevated pulmonary artery pressure is found on echocardiographic screening.
- Esophagraphy: Perform this test to document esophageal dysmotility and incompetence of lower esophageal sphincter.

Other Tests

- Pulmonary function testing (every 6 months)
  - Conduct this test to evaluate the DLCO, forced vital capacity (FVC) and total lung capacity (TLC). A FVC/DLCO of greater than 1.6 increases the likelihood of pulmonary hypertension.
  - This is a very sensitive technique for detecting early fibrotic changes, alveolitis, and pulmonary hypertension.
  - An isolated reduction in the DLCO is the best predictor of pulmonary hypertension.

Other Tests

- Serum N-terminal pro-brain natriuretic peptide (NT-proBNP): Elevation of NT-proBNP levels may correlate with early pulmonary hypertension.
- Cardiac rhythm monitoring: Perform 24-hour a Holter monitoring to evaluate arrhythmias and serious conduction defects.
- Esophagogastroduodenoscopy, esophageal manometry, and pH monitoring studies.
- Bronchoscopy with bronchoalveolar lavage to assess active lung inflamation.

Histologic Findings

- Systemic sclerosis is characterized by excessive fibrosis in the skin and other affected organs. The skin and lungs also show prominent T-lymphocyte infiltration.
- A severe fibroproliferative vasculopathy that affects small arteries and arterioles is universally present in affected organs.
- Platelet microthrombi are often found in the lumen of the narrowed vessels.

Treatment of skin afections

- Moisturizers, histamine 1 (H1) and histamine 2 (H2) blockers, tricyclic antidepressants, and trazodone in pruritis
- Raynaud phenomenon can be treated with calcium channel blockers (to tolerance), prazosin, prostaglandin E1, dipyridamole, aspirin, and topical nitrates. In the event of thrombosis and vascular flow compromise, a tissue plasminogen activator, heparin, and urokinase may be necessary.
- In very severe cases, patients may benefit from pharmacologic cervical sympathectomy or from surgical digital sympathectomy.
- Bosentan, a dual endothelin receptor antagonist, is under investigation and may decrease new digital ulcer formation.
- Sildenafil has also been shown to be effective and tolerated in patients with primary Raynaud and is currently approved to treat pulmonary hypertension.

Treatment of digestive system

- Antacids, H2 blockers, reflux and aspiration precautions, proton pump inhibitors, prokinetic agents, octreotide, smaller meals, and laxatives.
- Diet- avoid large doses of vitamin C(>1000mg/d) because it stimulates collagen formation and its deposition. Avoid food, that decreased pressure of lower esophageal sphincter: citruses, coffee, tomato.

Treatment of respiratory system

- Pulmonary fibrosing alveolitis may be treated with cyclophosphamide, either orally or in intravenous pulses. Pulmonary hypertension may require supplemental oxygen. Bosentan is effective in treating primary (idiopathic) pulmonary hypertension associated with systemic sclerosis.
- In open and randomized controlled trials include other endothelin receptor antagonists such as sitaxsentan and ambrisentan; prostaglandin derivatives such as epoprostenol, treprostinil, beraprost and iloprost; and phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil. Preliminary nonrandomized studies have also shown benefit from mycophenolate mofetil.

Treatment of musculoskeletal system

- Myositis may be treated with steroids (first choice), methotrexate, and azathioprine. Doses of prednisone greater than 40 mg/d are associated with a higher incidence of sclerodermal renal crisis. Digital ulcers must be kept clean and dry.
- Arthralgias can be treated with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Instruct the patient to perform physical and occupational therapy to minimize or delay contractures.

Immunosuppressive agents

- **Methotrexate 5-15mg/M2/wk** + folic acid 1mg/day
- Azathioprine 2-3mg/kg
- Cyclosporine A 3-5mg/kg
- Anticytokines - Etanercept 0.4 mg/kg/wk
- Glucocorticosteroids - Prednisone 2.5-5mg/kg, gradually decrease to lowest possible dose

Chelating agents

- **Penicillamine (Cuprimine) 5mg/kg/day, may increase to 10 mg/kg/day- mechanisms responsible for the formation of collagen**

Treatment of vascular affections

- ***Endothelin Receptor Antagonist – Bosentan***, Ambrisentan for treatment of pulmonary arterial hypertension
- Phosphodiesterase Type 5 inhibitor – Sildenafil, peripheral vasodilator, promotes vasodilation in the pulmonary vascular bed.
- Calcium channel blockers – Nifedipin
- ACE inhibitors in renal crisis episodes

FOLLOW-UP

- Patients may need to be treated by other subspecialists depending on their symptoms (eg, cardiologist, pulmonologist, gastroenterologist, nephrologist, hand surgeon).
- The value of serology testing is for initial diagnosis and assessment of associated conditions, but it is of little use for monitoring disease activity.
- Instruct the patient to stop smoking, to avoid cold exposure, digital or skin trauma, to minimize the risk of Raynaud phenomenon.
- Renal and lung transplantation are performed in specialized centers for patients with end-stage renal or lung involvement.
- Current studies of autologous stem cell transplantation are ongoing and may lead to disease remission.

Prognosis

- For patients with limited involvement, 10-year survival rates are roughly 60-70%. For patients with diffuse disease, 10-year survival rates are 20%.
- Factors that imply a more severe prognosis are as follows:
  - Youth
  - African descent
  - Rapid progression of skin symptoms
  - Extent of skin involvement
  - Anemia
  - Elevated erythrocyte sedimentation rate (ESR)
  - Pulmonary and renal involvement

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