Auto Immune Diseases

In depth comprehensive study of autoimmune diseases, their clinical and ocular manifestations.

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Autoimmune Diseases Introduction

Introduction:

- Autoimmune disease encompasses an array of 80 to 100 disorders affecting different body systems/organs. Studies have not focused on them as a single entity and also because many of them are rare.
- Autoimmune diseases affect approximately 50 million individuals in the United States, a number greater than that of cancer(12 million) and heart disease(27 million) combined.
- Autoimmune diseases are chronic illnesses, with most having no available cure.
- Half of all cases of autoimmune diseases remain undiagnosed because of challenges in diagnosis.

Introduction Continued

- Individuals average four physicians over a period of 4 years before a correct diagnosis was made.
- 45% of individuals reported that they had been labeled as a chronic complainer because no cause for their symptoms could be determined.

Overview of Autoimmune Diseases

- The autoimmune diseases with the highest reported prevalence rates are Graves' disease, rheumatoid arthritis, and Hashimoto's thyroiditis; prevalence rates are lower for such diseases as celiac disease and autoimmune hepatitis.
- Other commonly occurring autoimmune diseases are systemic lupus, Sjogren's syndrome, multiple sclerosis, myasthenia gravis, inflammatory bowel diseases(ulcerative colitis and Chron's disease), pernicious anemia, scleroderma, primary biliary cirrhosis.

Overview Continued

- Many autoimmune diseases follow a progressive course, even with appropriate management, and serious or life-threatening complications can develop.
- Most autoimmune diseases occur frequently in female individuals than in male individuals, many occur during the middle adult years.
- Autoimmune diseases ranked eighth as the leading causes of death among all female individuals younger than 65 years of age.

Pathogenesis

- The immune system is designed to work with a balance, responding to a wide variety of foreign threats, such as harmful bacteria, viruses, or cancer cells, while maintaining self-tolerance.
- In a small proportion of individuals, this balance is disrupted, and there is unregulated activation of the immune system and loss of self-tolerance.
- Virtually every body system can be affected, and the target of the immune system can be a specific organ such as in thyroiditis, or multiple organs such as in systemic lupus.

Pathogenesis Continued

- In organ-specific diseases, such as thyroiditis, type 1 diabetes, inflammatory bowel disease, or multiple sclerosis, a normal immune response is misdirected against a self-antigen or organ, and inflammation and production of autoantibodies are usually confined to antigens specific to the target organ.
- When multiple organs are targets in autoimmune diseases, autoantibodies are directed to different autoantigens, typically resulting in chronic activation of innate and adaptive immune cells and an array of clinical manifestations.
- Some autoimmune diseases are characterized by an organ-specific immune process but are systemic because they also involve autoantibodies to autoantigens outside of a specific organ.

Differential: T-Cell vs. B-Cell

- **T-cells:**
  - Lymphocyte stem cell from the liver (spleen) Fetus→central Lymphoid tissue (thymus)→peripheral lymphoid organ→ immunocompetent T-cell→
  - Memory cells
  - Cytotoxic (Killer)cells
  - Lymphokine producing cells
  - Helper cells
  - Suppressor cells
- **B-Cells:**
  - Lymphocyte stem cell from the Bone marrow in adult→stem cell→Bursal equivalent tissue (peripheral lymph tissue)→Immunocompetent B Cell
  - Memory cells
  - IgG, IgM, IgA, & IgE-producing cells

Pathogenesis Continued

- Rheumatoid arthritis is primarily a joint-selective disease, but other autoantibodies can cause extra-articular manifestations.
- Organ-specific autoimmune diseases differ according to whether disease is mediated primarily though autoantibodies, autoreactive T cells, or a combination of the two.
- Systemic autoimmune diseases can be categorized as being associated with either cell-mediated immunity or autoantibodies, or immune complexes.
- T-cell or B-cell activation can cause tissue damage directly, by binding to cell-surface autoantigens, or indirectly by forming antibody-antigen complexes that become deposited in tissues.

Pathogenesis Continued

- The autoimmunity process is cyclic, as tissue damage leads to the release of cytokines, activated T cells, and additional self-antigens, further stimulating the immune response.
- The detection of an autoantibody does not necessarily indicate the presence of an autoimmune disease, as some autoantibodies, such as rheumatoid factor and antinuclear antibodies, are found in individuals without evidence of an autoimmune disease.
- In addition autoantibodies can be detected years before related autoimmune disease develops.

Genetic Factors

- Genetics play a major role in rendering a person susceptible to an autoimmune disease.
- The mode of inheritance of an autoimmune disease is complex, and research indicates that the genes involved in autoimmune disorders are pleiotropic (they affect more than one trait) rather than disease-specific.
- Common alleles may have the potential for alternate clinical phenotypes under different sets of genetic and environmental factors, and data support the premise that clinically distinct autoimmune diseases may have common susceptibility genes.
- At least 68 genetic risk variants have been associated with various autoimmune diseases, and several loci have been identified as being associated with more than one autoimmune disease.

Genetic Factors Continued

- Studies with monozygotic twins have been done to determine the genetic basis for many autoimmune diseases.
- Reported concordance rates include 12% to 30% for rheumatoid arthritis, 25% to 57% for systemic lupus, 30% for multiple sclerosis, 30% to 50% for type 1 diabetes, 70% to 75% for celiac disease, and up to 80% for Graves' disease.
- The concordance rate does not reach 100% for any autoimmune disease, which means that factors other than genetics must have a role in the pathogenesis.

Environmental Factors

- Environmental factors that have been found to have influence are infectious agents, stress, sex hormones (estrogens and androgens), and cigarette smoking.

Infectious Agents

- The immune response is triggered by antigens of a micro-organism that closely resembles self-antigens, a mechanism that has been termed molecular mimicry.
- Another theory is that autoimmunity is induced by a mechanism known as the bystander effect: the invading micro-organism directly damages tissue during active infection, thereby exposing self-antigens to the immune system.
- The most often associated with infection as an etiological factor are multiple sclerosis, type 1 diabetes, rheumatoid arthritis, systemic lupus, fibromyalgia, myasthenia gravis, and Guillain-Barre syndrome.
- The micro-organisms most often implicated are viral, including Epstein-Barr virus, hepatitis C virus, parvovirus, and cytomegalovirus.

Stress

- Physical and psychological stress affects the immune system, most probably the result of downstream neuroendocrine alterations that modulate immune function.
- Inflammatory autoimmune diseases, such as rheumatoid arthritis and systemic lupus, are the most likely diseases to be influenced by stress.
- ⇧stress ⇨ ⇧inflammation.

Sex Hormones

- Estrogen/Progesterone (Testosterone)-chemically all are steroids from cholesterol.
- Systemic lupus offers the strongest evidence for sex hormones as a development factor because of its incidence trend (i.e., high after puberty and low after menopause) and the fluctuations in disease severity according to menstrual cycles and pregnancy.

Cigarette Smoking

- Cigarette smoking had also been found to be a potential trigger for autoimmune diseases, most notably rheumatic diseases (rheumatoid arthritis and systemic lupus) and, to a lesser degree, thyroiditis.

General Characteristics

- Each immune disease is a distinct entity with its own constellation of signs, symptoms, and clinical manifestations.
- Many autoimmune diseases share some common characteristics, including female preponderance, similar symptom profiles, difficulty in diagnosis, importance of history and physical examination in diagnosis, and similarity in the approach to disease management.

Female Preponderance

- Autoimmune diseases have a definite gender bias, with women accounting for nearly 80% of cases overall.
- The female-to-male ratio varies according to disease, from Hashimoto's thyroiditis, which has a female preponderance of 52%.
- Fibromyalgia is also more prevalent in women (3.4% vs. 0.5%).

Male Predominance

- A few diseases have been reported to occur more often in men than women, including Type 1 diabetes, ulcerative colitis, Guillian-Barre syndrome, and psoriasis.

Difficulty in Diagnosis

- The surveys have shown that individuals consult an average of four (and as many as 13) healthcare providers, typically over 2 to 4 years, before a diagnosis is made.
- There are several reasons for the challenge.
  - −The initial symptoms are often subtle, nonspecific, and intermittent until the disease enters the acute stage.
  - −Symptoms can also affect many body organs, making it difficult for specialists in one area to recognize a disease within another specialty area.
  - −Most individual autoimmune diseases are rare, a primary care clinician may be unfamiliar with the clinical manifestations of each disease.

Difficulty Continued

- The diseases lack a single distinguishing feature. Clinicians need to rely on varying combinations of information gathered for the history, physical examination, and laboratory and imaging studies.
- History and comprehensive physical examination are particularly vital for the diagnosis of autoimmune diseases and fibromyalgia.

Difficulty Continued

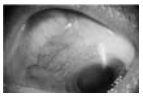
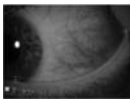
- Autoimmune diseases within families have shown significantly higher frequencies of autoimmune disease in general and of specific autoimmune diseases among first-degree relatives compared with controls.
- An individual with a diagnosed autoimmune disease is often at increased risk for the co-occurrence of another autoimmune disease.

Approach to Disease Management

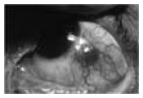
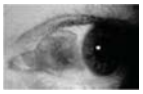
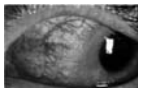
- Goals: relieve symptoms, preserve organ function, and control the autoimmune process; treatment often involves use of immunomodulatory/immunosuppressant drugs.
- Long-term management of individuals with autoimmune diseases requires a multidisciplinary approach with potential referral to specialists such as: rheumatologists, endocrinologists, gastroenterologists, neurologists, nutritionists, physical/occupational therapists, counselors, and optometrists.
- The management of autoimmune diseases is often complicated by patients' response to the diagnosis and their coping with the disease.

Ocular Manifestations of Autoimmune Diseases

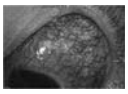
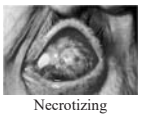
Episcleritis


Nodular Episcleritis

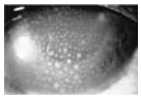




Scleritis

Necrotizing

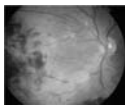
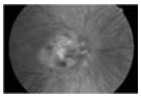
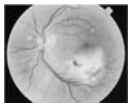
Uveitis



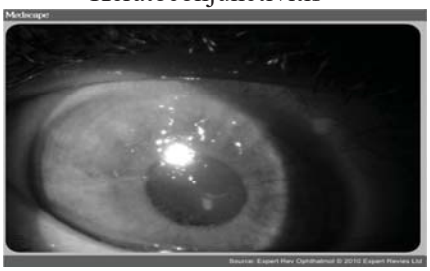
Granulomatous

Non Granulomatous

Retinitis

Keratoconjunctivitis



▪All can result in punctate epithelid erosions and limbic superior keratoconjunctivitis.

Diagnosing Autoimmune Diseases

Blood Work Associated with these Ocular Manifestations

- CBC – complete blood count
- Sed. Rate - sedimentation rate
- ANA - Antinuclear Antibody
- Lupus Anticoagulant Antibody
- HLA-B27 (AS)- Human Leukocyte Antigen
- Rheumatoid Factor
- ACE- serum angiotensin Converting Enzyme

ANA – Antinuclear Antibody -Types of Antibodies (test for Lupus)

- Antibodies are proteins produced by white blood cells.
- Autoantibodies, instead of acting against antibodies, attack body's own cells.
- Antinuclear antibodies have the ability to attack the nucleus of cells. The nucleus of a cell contains genetic material referred to as DNA.
- ANA blood test can be performed on a patient's blood sample.

ANA Titer

- A titer is determined by repeating the positive test with serial dilutions until the test yields a negative result.
- Fluorescence is the titer which gets reported.
- Positive ANA$\rightarrow$ follow up test ENA (Extractable Nuclear antigen antibodies) & scleroderma antibodies.

ANA Pattern

- Patterns can vary between laboratory testing sites, perhaps because of variation in methodology.
  - Homogeneous
  - Peripheral
  - Speckled
  - Nucleolar
- ANAs are found in autoimmune diseases.
- Can be found also in patients with lung diseases.
- ANAs are actually found in about 5% of the normal population.
- With a positive ANA and a high titer rate, an additional blood test called lupus anticoagulant antibody test and is helpful in diagnosis.

HLA-B27

- Surface antigen
- Strongly associated with ankylosing spondylitis.
- Chronic inflammatory arthritis disease affects mainly spine and sacroiliac joint in the pelvis.

Rheumatoid Factor

- RF is the autoantibody(antibody directed against an organism's own tissues) that is most relevant in rheumatoid arthritis.
- It is defined as an antibody against the Fc portion of IgG.
- RF is often evaluated in patients suspected of having any form of arthritis even though positive results can be due to other causes, and negative results do not rule out disease.
- High levels of rheumatoid factor(in general, above 20IU/mL, 1:40, or over the 95th percentile) occur in rheumatoid arthritis(present in 80%) and Sjögren's syndrome(present in 70%).
- The higher the level of RF the greater the probability of destructive articular disease.

ACE

- is primarily ordered to help diagnose and monitor sarcoidosis.
- ACE will be elevated in 50% to 80% of those with active sarcoidosis.
- This test is ordered when someone has signs or symptoms such as granulomas, a chronic cough or shortness of breath, red watery eyes, and/or joint pain that may be due to sarcoidosis or to another disorder.
- This is especially true if the person is between 20 and 40 years of age.
- Sarcoidosis can be present without elevated ACE levels, however, se a normal ACE level cannot be used to rule out sarcoidosis.

Celiac Disease

- Celiac Disease- It is an immune-mediated small intestine enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.
- 12% of Downs Syndrome patients are gluten intolerant
- 14% of Autoimmune Thyroid Disease

Signs and Symptoms

- Diarrhea
- Weight Loss
- Abnormal Distention
- Fatigue
- Abnormal Pain
- Flatulence

*38% or more may be asymptomatic

Celiac Disease/Thyroid Disease

- Molecule structure of gliadin (protein portion of gluten) closely resembles that of thyroid gland.
- When gliadin breaches the protection of the gut →enters the blood stream → immune system tags it for destruction
- These antibodies to gliadin also causes the body to attach the thyroid glad
- Immune response to gluten can last up to 6 months
- If you are gluten intolerant, you have to be 100% gluten-free to prevent destruction of your thyroid

Major Complications of Celiac Disease

- Short Stature
- Dermatitis herpetiformis
- Dental Enamel hypopslasia
- Recurrent stomatitis
- Fertility Problems
- Cancer...Not breast?

- Osteoporosis
- Gluten ataxia and other neurological disturbances

Treatment

- Lifelong avoidance of gluten-STRICT
- Oats are tolerated by most.. Controversy
- Daily multiple vitamin and calcium
- Folic Acid for women of child-bearing age
- No initial role for bisphosphonates (class of drugs that prevent loss of bone mass)

Rheumatoid Arthritis

Rheumatoid Arthritis

- Rheumatoid arthritis is a chronic disease characterized by inflammation of synovial tissue that can lead to long-term damage of the joint, resulting in chronic pain, loss of function, and disability.
- A cytokine network, which includes tumor-necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, has an integral role in the development of the inflammatory response.
- The course and severity of the illness vary considerably. The disease tends to progress over time along with the occurrence of intermittent disease flares.

Rheumatoid Arthritis Continued

- Rheumatoid arthritis ranks among the most chronic diseases with the greatest effect on health-related quality of life and the most substantial socioeconomic impact.
- The mortality rate associated with rheumatoid arthritis is also high, representing the second highest death count among autoimmune diseases for women older than 65 years of age.

Epidemiology of Rheumatoid Arthritis

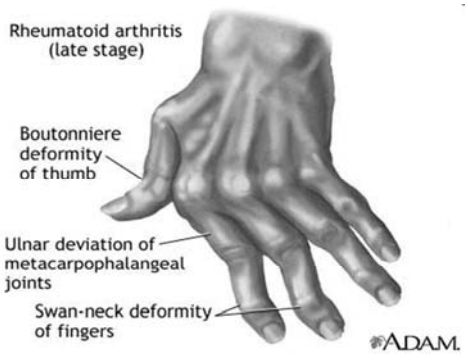
- The prevalence of arthritis (all types) increases with age.
- According to data from the 2003-2005 NHIS, the prevalence is approximately 8% for individuals 18 to 44 years of age, compared with 29% for individuals 45 to 64 years of age and 50% for individuals 65 years of age and older.

Potential Environmental Risk Factors

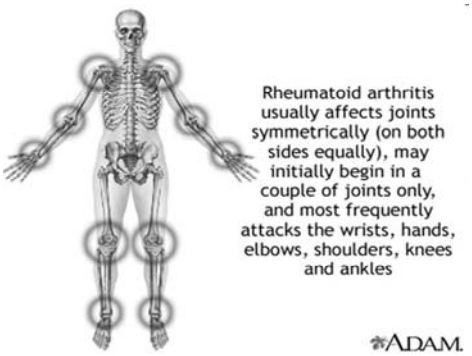
- Environmental factors that have been linked to rheumatoid arthritis include infection, smoking, and stress.
- Among the infectious micro-organisms thought to be associated with rheumatoid arthritis are Epstein-Barr virus, Mycobacterium tuberculosis, Escherichia coli, Proteus mirabilis, retroviruses, parvovirus B19, and hepatitis C virus.
- Smoking has also been identified as a significant risk factor for the development of rheumatoid arthritis. Greater smoking intensity (number of cigarettes per day) and longer smoking history further increase the risk.

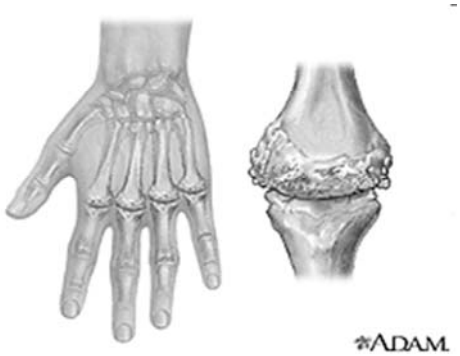
Clinical Manifestations

- Pain and stiffness in multiple joints are the primary characteristics of rheumatoid arthritis; approximately one-third of individuals with the disease initially have pain in only one joint.
- Other symptoms of rheumatoid arthritis include fatigue, weakness, general muscular aches, and anorexia.
- Approximately 46% of individuals with rheumatoid arthritis have extra-articular manifestations; the most common of which is rheumatoid nodules, followed by pulmonary fibrosis, dry eye syndrome.
- Rheumatoid nodules are soft, poorly delineated subcutaneous nodules, and they also occasionally affect internal organs such as the pleura, sclera, vocal cords, and vertebral bodies.



Rheumatoid Vs. Osteo





Diagnostic Evaluation

- The most commonly involved joints are the wrist joint and the proximal interphalangeal and metacarpophalangeal joints; the distal interphalangeal joints and sacroiliac joints are typically not affected.
- Morning joint stiffness with rheumatoid arthritis usually lasts more than 1 hour, in contrast to osteoarthritis, in which morning stiffness usually resolves within 30 minutes after waking.
- For most individuals, symptoms develop over a long period of time (weeks to months).

Diagnostic Evaluation Continued

- Affected joints have limitations on the range of motion, and the strength of muscles near the affected joints is usually decreased.
- The patient may keep an affected joint in flexion to avoid pain related to extension.
- Rheumatoid nodules are often found in pressure areas (e.g., the elbows and finger joints) and the extensor surface of the forearm.

Differential Diagnosis

- A wide range of medical conditions should be considered in the differential diagnosis of rheumatoid arthritis, including:

- Connective tissue diseases (e.g., systemic lupus, systemic sclerosis)
- Psoriatic arthritis, gout, and other forms of arthritis
- Fibromyalgia
- Polymyalgia rheumatica
- Thyroid disease
- Sarcoidosis (discussed in later slide)
- Hemochromatosis (Too much iron build-up being absorbed from the gastrointestinal tract.)
- Still's disease (Disorder featuring inflammation, fever spike, and rash that comes and goes.)

Differential Diagnosis Continued

- Overlapping signs and symptoms can make it challenging to distinguish rheumatoid arthritis from many of these conditions, especially connective tissue diseases and other forms of arthritis.
- A positive ANA titer may help distinguish systemic lupus from rheumatoid arthritis.

Treatment Options

- Treatment goals are to preserve the structural integrity of the joint, enhance function and quality of life, minimize pain and inflammation, and control systemic complications.
- These goals are achieved through a combination of disease-modifying drugs, anti-inflammatory agents, and nonpharmacologic measures.

Disease-Modifying Antirheumatic Drugs

Disease-modifying antirheumatic drugs, or DMARDs, are antimetabolite/cytotoxic agents.

- Several nonbiologic and biologic disease-modifying drugs are now available, allowing clinicians and patients to select a specific drug after considering several factors.
- These are among the recommended nonbiologic agents:
  -Methotrexate is generally considered to be the standard first-line treatment.
  -Tetracycline minocycline
  -The antimalarial drug plaquenil (mode of action PH of the lysosome results in inhibition of release of lysome acidic protease: inflammatory response)
- The biologic agents include three anti-TNF-α agents (Humira, Enbrel, and Remicade).

Disease-Modifying Antirheumatic Drugs Continued

- A combination of nonbiologic drugs, methotrexate, and a biologic drug have led to better clinical response rates and functional outcomes than either methotrexate or a biologic agent alone, especially in early active disease.

Methotrexate

- Methotrexate is used in treatment of cancer and autoimmune diseases. It acts by inhibiting the metabolism of folic acid.
- Methotrexate is a highly teratogenic drug and categorized in pregnancy category X.
  - Pregnant women must not take the drug.
- Penicillins may decrease the elimination of methotrexate and thus increase risk of toxicity.
- For the treatment of rheumatoid arthritis, the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine, or the inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells.
  - In these cases, patients should supplement their diets with folate.

Disease-Modifying Antirheumatic Drugs

- There are several contraindications to starting or resuming treatment with a nonbiologic or biologic agent for rheumatoid arthritis.
- Acute hepatitis B or C infection is a contraindication for all nonbiologic or biologic disease-modifying drugs; chronic hepatitis B or C infection may also be a contraindication.
- Plaquenil is contraindicated only in individuals who have chronic hepatitis B or C viral infection (Child-Pugh class C) and are not receiving therapy for the infection.

Anti-Inflammatory Medications

- Anti-inflammatory medications are used to reduce joint pain and swelling associated with rheumatoid arthritis.
- Because these drugs do not change the course of disease, they must be used in conjunction with a disease-modifying drug
- Treatment typically begins with a nonselective nonsteroidal anti-inflammatory drug (NSAID); a cyclooxygenase-2 (COX-2)-selective inhibitor and/or glucocorticoids may also be used.
- A gastroprotective agent (proton-pump inhibitor) should be prescribed with an NSAID for individuals at high risk for gastrointestinal complications.
- There is good evidence that nonselective NSAIDs and COX-2 inhibitors have comparable efficacy and that COX-2 inhibitors are comparable to each other.

Anti-Inflammatory Medications Continued

- Although COX-2 inhibitors have better tolerability in general compared with NSAIDs, there is considerable variability across individual drugs in terms of protection against serious gastrointestinal events.
- The adverse event profiles of both nonselective NSAIDs and COX-2 inhibitors should be considered when selecting a specific drug for an individual patient.
- In addition to their anti-inflammatory properties, glucocorticoids may substantially reduce the rate of further joint erosion and should be considered as a temporary adjunct to treatment with disease-modifying drugs.
- Because of the substantial risk of adverse effects, glucocorticoids should be given for the shortest time and at the smallest dose possible, and treatment should be discontinued gradually.

Prognosis: What is the greatest associated risk for increased mortality among individuals with rheumatoid arthritis?

- Of all the autoimmune diseases, rheumatoid arthritis is a leading cause of mortality especially among women older than 65 years of age.
- Studies have shown higher rates of mortality for individuals with rheumatoid arthritis than for the general population.
- The increased mortality has been linked to several factors including: extra-articular manifestations, markers of disease severity, and diminished function within the first year.
- Cardiovascular disease has been thought to confer the greatest risk for increased mortality.
- Only methotrexate has been shown to be associated with a reduced risk of cardiovascular disease among individuals with rheumatoid arthritis.

Lupus and the Autoimmune Process

4 Types of Lupus

- Systemic
- Discoid
- Drug Induced
- Neonatal

Systemic Lupus Erythematosus (SLE)

What is SLE?

- Autoimmune disorder of the connective tissue
- Affecting the skin, joints, blood, and kidneys
- Other body systems/organs can also be affected.
- Complex, often unpredictable.
- Prognosis varies from mild to threatening.
- As with other autoimmune diseases characterized by recurring remissions and flares.

Systemic Lupus Erythematosus (SLE): Epidemiology

- Most women affected by SLE are of childbearing age.
- Average age of diagnosis of adult-onset systemic lupus is 36.5 years.
- 10% - 20% cases are individuals 50 -65 years of age.
- Risk of the disease is approximately 20 times more likely for the sibling of a person who has systemic lupus.

Epidemiology Cont.

- In the 1960's, five year mortality was 50%.
- Today in the United States, Europe, and Canada the survival rate has risen:
  - 95% at five years
  - 90% at 10 years
  - 78% at 20 years
- Incidence of SLE although has nearly tripled since the 1950's.

Background Immunology

- Inborn mechanisms of self-tolerance usually protects an individual from potential self reactive lymphocytes.
- Scientists thought that all self-reactive lymphocytes were eliminated during the maturation process.
  - By 1970's it became known that not all lymphocytes are deleted.
  - The presence of the self-reactive lymphocytes does not inevitably result in disease.
- The activity of these cells is highly regulated in normal individuals by some sort of effective suppression.
  - Failure of the suppression leads to clones of T and B cells that can target self-antigens.
  - Deregulation amplifies resulting in significant damage to target cells which in return creates autoimmune diseases.

SLE Continued

- SLE is a chronic disease characterized by widespread immunologic abnormalities.
- It has potential for multiorgan damage.
- Immune complexes form from union of autoantibody with antigen.
  - Result is dramatic cascade of complement and its membrane-attack complexes.
  - damages blood vessel walls and can lead to vasculitis and nephritis.

Effects of Systemic Lupus Erythematosus

The effects of SLE include: fatigue, pain, and neurocognitive dysfunction.

- The neurological deficits caused by SLE often cause systemic lupus individuals to stop working.
  - Systemic review showed individuals stopped working 3 – 15 years after diagnoses.
- Improved options have led to longer survival for people with systemic lupus especially cardiovascular disease.

Systemic Lupus Erythematosus Patients

- Lupus Patients
  - Group 1: low grade, limited disease
  - Group 2: life threatening organ failure
- This is the function of the interplay among receptiveness genes and environment triggers.
- Lupus autoantibodies
  - Known to be present in the serum of lupus patients as long as 5 years preceding to the development of clinical disease.
- Behavioral Changes to help with the treatment of SLE:
  - Stop smoking
  - Use sun protection
- Frequency of SLE varies significantly by ethnicity and race.
  - Higher rates are reported among Hispanics and African Americans; especially in African American women where the rate is 3-4 times higher than white.
  - Twice as common among African American men compared to white men.

Potential Environmental Risk Factors with SLE

- Environmental contributors to the development of systemic lupus:
  - Evidence has been found for infection, smoking, and hormones.
  - Strong association has been identified between SLE and Epstein-Barr infection (mono)
    - Immune response to the Epstein-Barr virus- important role to the development of systemic lupus in at least some individuals with SLE.
- Tobacco smoking has been linked o the inflammatory response in rheumatic disease.
  - Smoking can trigger immune response to anti-double stranded DNA, antibodies that are relatively specific.

Primary Vision Care with SLE

- Plaquenil:
  - An antimalarial drug used in many patients with lupus.
  - It modifies cell signaling , reduces the activation of dendritic cells that mitigate the inflammatory process.
- Two distinct areas of the eye may be affected:
  - -Cornea
  - -Macula
- Patients are on the medication indefinitely and should be monitored indefinitely.

Self-Care and Triggers

- Sun protection is essential for SLE patients.
  - UV radiation causes flares in approximately 70% of patients.
- Smoking increases hypertension and interferes with the benefit of plaquenil.
- Exercise helps prevent fatigue and joint stiffness.
- SLE increase can be associated with both postmenopausal hormone replacement therapy and estrogen oral conceptive (OC) therapy.

Biologic Therapies

- Benlysta (FDA approved):
  - The first drug to have been developed specifically for lupus
  - Novel biologic agent that targets B-cell maturation and survival.
- The human monoclonal antibody, Benlysta, is infused monthly.
  - Binds to B-cell surface molecules called “BLyS (bliss).
  - Drivers of intercellular signaling.
  - Inhibitor blunts the survival o f B-cells, including autoreactive B-cells .
  - Reduces the differentiation of B-cells into antibody-producing plasma cells.

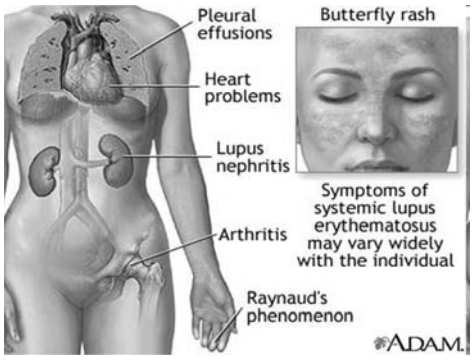
Clinical Feature/Types of Lupus

- Age: onset after puberty
- Most common ethnic population affected: African American and Hispanic women in their 20’s and 30’s.
- Core Features: photosensitive rashes, polyarthritis, and nephritis.
- Core Labs: persistent, large amount of protein in urine.
- Autoantibody formation quantified by positive ANA determination.
  - Population felt to be >1:640

Clinical Manifestations

-Systemic lupus varies widely and symptoms may develop abruptly.

- **Butterfly shaped rash**
  - Malar area of the face
  - Present in up to 90% of cases
- **Discoid rash may also occur somewhere else on the body.**
- **40% of individuals have photosensitivity.**
- **90% of individuals have joint pain**
  - Often symmetrical and typically
  - Proximal joints of the fingers
- **80% have Low-grade fever.**
- **50% have unintentional weight loss.**



Association with other Autoimmune Diseases

- Other autoimmune diseases occur frequently in systemic lupus individuals.
- Study: 41% of subjects with lupus have at least one other autoimmune disease.
- Thyroiditis, rheumatoid arthritis, Sjogren’s syndrome, fibromyalgia, and antiphospholipid antibody syndrome(autoimmune hyper coagulate that is caused by antibodies against cell-membrane phospholipids – blood clots in arteries and veins; tx: anticoagulants).
  - Researchers believe that there is a common genetic receptiveness to both systemic lupus and rheumatoid arthritis.
  - Genetic studies have shown an increased risk for both diseases.
  - Antibody syndrome found in about 14% of individuals.
- Systemic Lupus has also been found to be risk factor for Fibromyalgia (occuring in 22%-65% of individuals with SLE).

Diagnostic Evaluation

  - Waning symptoms over time and variation of disease severity and in the organ system.
- Malar rash (symmetrical, dull to bright erythema over the cheeks and the bridge of the nose) is associated with systemic lupus.
  - Can be misdiagnosed as rosacea or seborrheic dermatitis.
  - Usually asymptomatic, lacking symptoms such as:
    - Burning, itching, and tingling, that accompany other facial rashers.

Diagnostic Criteria

- A physical examination can identify nearly half of criteria, including malar and discoid rash, arthritis, and pleuritis or pericarditis.
- Absensce of these symptoms may not necessarily exclude the presence of SLE.

Criteria Continued

- Laboratory testing can help to recognize the remaining clinical criteria: hematologic, renal, and neurologic disorders.
- The work-up should include a CBC with differential platelet count, chemistry profile, and urinalysis.

Antibody Testing for Systemic Lupus

Diagnostic Test	Prevalence (among people with systemic lupus)	Comments
Antinuclear antibody titer	93%-100%	Positive titer also found in systemic sclerosis (up to 80%) and Sjogren’s syndrome (up to 97%), as well as many healthy individuals
Anti-double-stranded DNA	70%-80%	Positive test highly specific for systemic lupus. Associated with greater risk of skin disease and lupus nephritis.
Anti-Ro/Anti-Nuclear Antibodies	30%-40%	Also associated with Sjogrens syndrome (up to 70%). Associated with greater risk of skin disease, lupus nephritis, and fetal heart problems.
Antiphospholipid antibodies	20%-30%	Associated with greater risk of thrombosis and pregnancy loss.
Anti-Sm : a family of RNA protein binders	10%-30%	Positive test highly specific for system lupus. Associated with greater risk of lupus nephritis.
Anti-La: a family of RNA protein binders	15%-20%	Associated with Sjogren’s syndrome (up to 50%). Associated with fetal heart problems.

Drug Induced Lupus

Drug-Induced Lupus

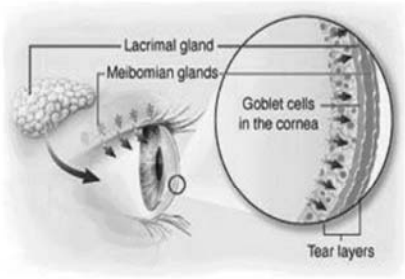
- Reactive form of the disease:
  - Develops in response to specific drugs.
  - Consists primarily of arthritis and serositis (pleuritis or pericarditis).
  - Patients test positive for ANAs.
  - Resolves with cessation of the culprit drug.

Drugs Associated with Lupus

- Hydralazine (Apresoline)
- Isoniazid (Tubizid)
- Phenytoin (Di-Phen , Dilantin, Phenytek)
- Procainamide (Procanbid)
- Quinidine
- Development of drug-induced lupus
  - Anti-tumor necrosis factor medications
    - Etenercept (Enbrel)
- Early signs are often fatigue, hair loss (especially around face), sun-sensitive facial rash, and arthralgias.
- Not unusual to present with nephritis or a pleural/pericardial effusion in significantly positive ANA titer.
- In March 2011, the FDA approved belimumab (a monoclonal antibody against B-lymphocycte) for lupus in more than 50 years.

Systemic Lupus: Other

- Systemic Lupus often affects the eyes, with patients having dry eye syndrome.
- Routine exercise may reduce the fatigue exacerbated by SLE.
- As SLE progresses from moderate to severe it can affect any major organ system.
  - Kidneys are most commonly involved.
- Lupus nephritis occurs in 50%-70% of individuals with SLE.



Follow-Up/Prognosis

- Follow-up care is essential for individuals. Not only to evaluate the response, but to also monitor for drug-related adverse events.
- Because of the risk of lupus nephritis, patients need to be followed up closely for signs of progression of disease to the kidneys.
- Develops within the first 5 years after symptoms
- Usually age 20-40
- Test includes creatinine/BUN, protein in urine, RBC, or WBC
- Creatinine and BUN (urea nitrogen).

Drug Induced Ocular Pathology

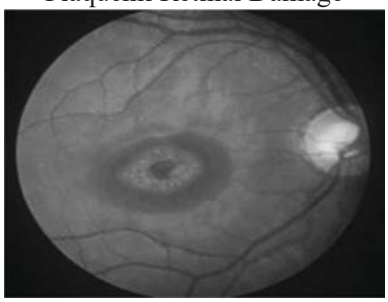
Retinal Pathology

- Plaquenil increases the risk for retinopathy.
  - This toxicity is rare.
  - Less than 6.5 mg/kg/day for fewer than 5 years.
  - Ophthalmologic follow-up is important for early detection.
  - ⇧ over age 60
  - High doses for years
  - Kidney disease
- Risk of cancer is slightly increased for individuals for systemic lupus specifically.
  - Especially non-Hodgkin's Lymphoma

Retinal Toxicity from Plaquenil

- After cessation of the drug there is little if any visual recovery.
- Visual loss over several years after the drug has been stopped.
- Therapy has not been proven effective Plaquenil toxicity other than cessation of the drug.
- Functional loss where cessation allows reversal.
- Significant clinical recovery does not occur after bull's eye maculopathy becomes evident.
- Appears to be minimal risk of toxicity for individuals using less than 6.5mg
- 200 mg daily dose will be relatively safe for all but extremely small individuals.
- A daily dosage of 400mg puts anyone under 135 lbs in the high risk category.

Plaquenil Retinal Damage



silverspringeye.com

Monitoring/Treatment of Drug Side Effects

- Infection, osteopenia/osteoporosis, and bone marrow suppression are the major side effects of treatment with systemic lupus.
- Gastrointestinal, hepatic, renal/genitourinary, cardiovascular, and neurologic effects may also occur.

Prevention of Infection

- Infection has been estimated to be responsible for 30-50% of morbidity and mortality in patients with systemic lupus.
- A leading cause of mortality.
- 80% infections are caused by:
  - Bacterial micro-organisms, with the skin, respiratory tract, and urinary tract infection
  - Accounting for more than two-thirds of affected sites
- Viral Infections occur less commonly
  - Most common viral organisms are the Parvovirus B19 and cytomegalovirus.
  - Symptoms often mimic disease flares.
  - Women are at increased risk for infection with the human papillomavirus (HPV)-16 and therefore, are at risk for premalignant cervical lesions.

Prognosis

- Of the autoimmune diseases SLE is one of the leading causes of death.
  - Associated mortality is higher than that expected for the general population.
- 10 year and 15 year survival rates have been reported to be approximately 90% and 80% respectively.
- Survival is the result of earlier diagnosis and use of ANA testing.
- Death rates are associated with:
  - Age at time of diagnosis.
  - Mortality higher in the African American population.

Discoid Lupus

Discoid Lupus Erythematosus

A chronic skin condition that can cause scarring in the face, ears, and scalp.

- A condition where the immune system of the body incorrectly attacks normal skin.
- The condition has a scaly crusty appearance.
- A small percentage of patients with discoid lupus can develop disease of the internal organs as with SLE.
- Females outnumber males with this condition 3 to 1.
- Cortisone ointment applied to the skin in involved areas and Plaquenil will often improve the condition.

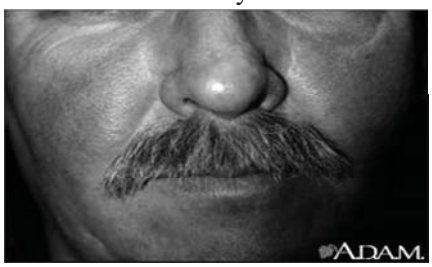
Discoid Lupus

- Generally ANA negative
- Fewer than 5% of cases progress to SLE.
- Malar Rash can exist in discoid and systemic.

UV light triggers lupus: Rash

- Skin has complement of immunocytes including:
  - B-Cells
  - T-Cells of classic types (effector memory cells [Tem], regulatory cells [Treg]
  - Helper cells [Th17]
  - Dendrite cells
  - Monocytes/macrophages
- Cells participate in local immune responses.
  - loop mechanism for the process has been established
- UV radiation (UVR) produces DNA damage
  - Linked to local immunosuppression in skin by Tregs
  - Stimulates autoimmunity
- UVR damage to keratinocytes
  - Leads to recruitment and activation of macrophages
  - Then releases other cytokine activators
  - Causes keratinocyte death
  - Leads to enhanced amplification of inflammation

Facial Butterfly Rash



Subacute Cutaneous Lupus Erythematosus (SCLE)

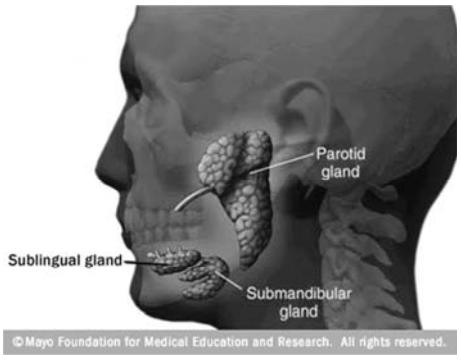
- SCLE is often mistaken for a severe fungal rash.
  - This condition appears scaly.
  - 15% of SCLE patients test positive for ANA.
  - 50% of patients with SCLE will have SLE.

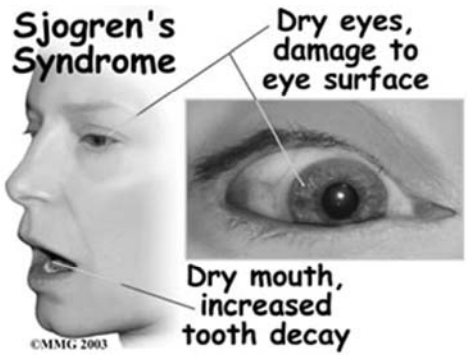
Sjogren's Syndrome

Sjogren's Syndrome

Sjogren's Syndrome is a systemic chronic inflammatory condition.

- **Characterized primarily by:**
  - Decreased function of lacrimal glands
  - Decreased function of salivary glands.
  - Enlargement of parotid gland
  - Often extraglandular manifestations
- **Classifications:**
  - Primary when develops in a previously healthy individual.
  - Secondary when associated with underlying rheumatic disease.





Sjogren's Syndrome continued

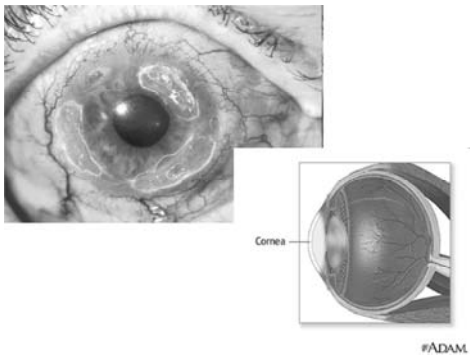
- **Pathogenesis of Sjogren's syndrome:**
  - primarily organ specific autoantibodies
    - Antibbodies to cellular antigens of salivary ducts (lacrimal glands)
    - Thyroid gland
    - Gastric mucosa
    - Erythrocytes
    - Pancreas
    - Prostate nerve and cells
  - Predominant in women
    - Ratio of more than 9:1
    - Mean age reported to be 53 years.

Diagnostic Evaluation

- Diagnosing primary Sjogrens's syndrome is challenged by its:
  - Insidious onset
  - Variable course
  - Wide range of clinical features
  - Nonspecific and not always concurrent symptoms
- No single diagnostic characteristic of Sjogren's syndrome.
- Xerophthamlmia and xerostomia is found in nearly all individuals with the syndrome.
  - May be symptoms of other conditions.

Diagnostic Evaluation Continued

- Physical examination should focus on evaluation of:
  - Eye
  - Mouth
  - Parotid glands
- Clinician should look for signs of corneal ulceration, superficial erosions of the corneal epithelium, conjunctival injection, and clouding or irregularity of the cornea.
- Mucus membranes of the mouth may appear to have a decreased saliva pool.



Diagnostic Criteria for Sjogren's Syndrome

- At least one of the following eye-related symptoms:
  - Daily, persistent, troublesome dry eyes for more than 3 months
  - Recurrent sensation of sand or gravel in the eyes
  - Use of tear substitutes more than three times per day
- At least one of the following mouth-related symptoms:
  - Daily feeling of dry mouth for more than three months
  - Recurrent of persistently swollen salivary glands.
  - Patient feels the need to drink liquids frequently to aid in swallowing dry food.
- Positive results from the Schirmer test and/or the Rose Bengal test or other ocular dye test.

Treatment Options for Sjogren's Syndrome

- Focuses on alleviating symptoms and preventing complications
  - No cure is available.
- Treatment of dry eyes involves artificial tears
- A topical anti-inflammatory agent for moderate to severe symptoms.
- Trials have shown that topical ocular cyclosporine (0.5%) significantly improves objective measures of dry eye, blurred vision, and use of artificial tears in patients with moderate, severe dry eye.

Follow-Up and Prognosis

- Prognosis for patients with established syndrome is good.
- Studies have shown no increase in rate of all-cause mortality.
- Among the complications reported to be associated with Sjogren's syndrome are oral infections and lymphoproliferative diseases.

Other Autoimmune Associated Disorders

Sarcoidosis

Sarcoid Diagnostic Testing

- ACE level-angiotensin converting enzyme
- Chest X-Ray

Sarcoidosis

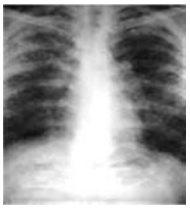
- Disease which abnormal collections of chronic inflammatory cells (granulomas) form as nodules in multiple organs.
- Cause of sarcoidosis is unknown.
- Often appear in the lungs or the lymph nodes.
- Any organ can be affected.

Signs and Symptoms

- Symptoms are vague, such as fatigue, lack of energy, weight loss, aches and pains, swelling of the knees, blurry vision, shortness of breath, and dry hacking cough or skin lesions.

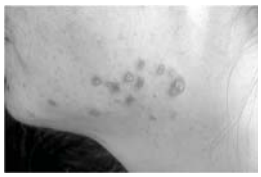
Lungs

- Of individuals with sarcoidosis, 90% have an abnormal chest x-ray at some time during their course.



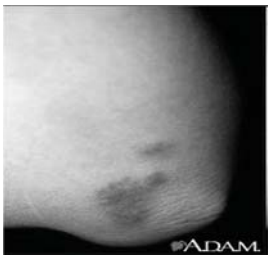
Skin

- Sarcoidosis involves the skin in about 25% of patients.

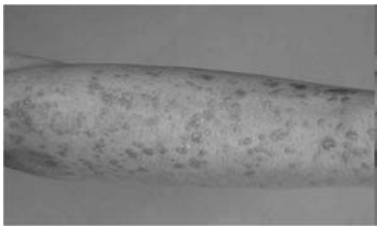


Sarcoidosis on the Face

Sarcoidosis On Elbow



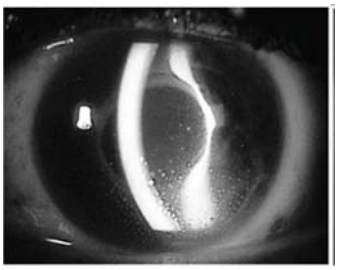
Sarcoidosis on the arm

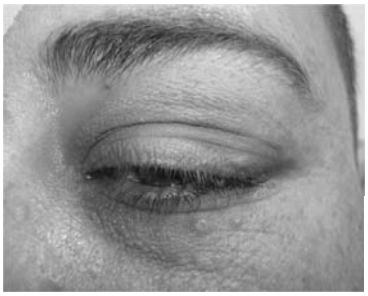


Clinical Manifestations of the Eye

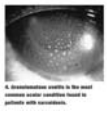
- Manifestations in the eye include uveitis, uveoparotitis, and retinal inflammation.
- Loss of visual acuity or blindness.
- Combination of anterior uveitis, VII cranial nerve, paralysis, and fever is called uveoparotid fever.

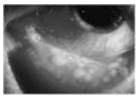
Granulomatous Uveitis

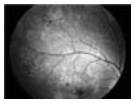




Sarcoidosis of the Eye







Causes

- Current working hypothesis is that susceptible individuals sarcoidosis is caused through alteration in immune response after exposure to:
  - Environmental, occupational, or infectious agent

Pathophysiology and Diagnosis

- Granulomatous inflammation
- Primarily by accumulation of moncytes, macrophages, and activated T-lymphocytes.
- Diagnosis of Sarcoidosis is often a matter of exclusion.

Diabetes

Latent Autoimmune Diabetes

- Type 1
- Type 1.5
- Type 2

Latent Autoimmune Diabetes of Adults (LADA)

- Definition of Type 1 autoimmune diabetes
- Type 1 diabetes, cellular-mediated autoimmune destruction of the beta-cells of the pancreas.
- In Type 1 diabetes beta cell destruction is quite variable, being rapid in some individuals, mainly infants.
- Slow in others, mainly adults.
- LADA is a genetically-linked hereditary autoimmune disorder in the body, mistaking the pancreas, by attacking and destroying insulin producing beta cells of the pancreas.
- Autoimmune disorders, including LADA, are an "allergy to self."
- Adults with LADA are initially misdiagnosed as having Type 2 diabetes, based on age, not etiology.

Is Type 2 Diabetes an Autoimmune – inflammatory disorder of the innate immune system?

- Type 2 diabetes is an autoimmune-inflammatory disease.
- It results from pathological expression of the innate immune system in nonimmune hypothalamic cells, visceral adipocytes, B-cells of the pancreas, and vascular endothelium. (Innate immunity the self defense response of our body to an environmental molecule that is perceived as an injuring agent or something foreign, hyperlipidemia.)

Type 2 Diabetes Continued

- Response is mediated by Toll-like receptors (Class of proteins that play role in innate immune system. Single receptors that recognize structure molecules derived from microbes, once breached activate immune receptor), and the result is a cellular gene response that can cause a nonimmune, as well as immune, cell to a cascade of immunologic proteins, e.g. cytokines.

Type 2 Diabetes Continued

- TLR's in nonimmune cells are now implicated in multiple autoimmune-inflammatory diseases including, for example, Hashimoto's, colitis, and type 1 diabetes.
- TLR's contribute to crosstalk between immune cells and inflammatory mediators. Many of the functions traditionally attribute to immune cells and also performed by non immune cells.
- TLR in the nonimmune cells is associated with expression of autoimmune inflammatory.

Type 2 Diabetes Continued

- Acquisition of visceral obesity is now recognized as a resistance and DMII.
- Associated with obesity
- Development of visceral obesity, insulin resistance, and DMII.
- Large visceral fats depots produce excessive amounts of free fatty acids, adipokines, and cytokines including TNF, which can induce insulin resistance.

Type 2 Diabetes Continued

- High lipid diet leads to leptin resistance.
- Leptin resistance occurs via a similar mechanism as that of insulin resistance.
- Leptin: protein hormone that plays key role in regulating energy expenditure acts on receptors in hypothalamus where it inhibits appetite. Absence of receptor leads to uncontrolled food intake and obesity.
- Has potential, but far-reaching implications, by possibly relating DMII to inflammatory diseases associated with over expression of TLRs and TLR signaling.

Type 2 Diabetes Continued

- Proinflammatory cytokines released from nonimmune
- Possibly via TLRs tie in with the receptors for leptin and insulin.
- Receptors for leptin share a common pathway.
- Receptors bind
- SOCS-3 works to block the binding of insulin receptor, causing resistance.

Fibromyalgia

Fibromyalgia

- Most elusive 'WhoDunnits' is medicine for anyone over 40 years of age
- Unexplained muscle pain, fatigue, and cognitive symptoms
- Great majority of patients were women, who were thought to be attention seeking Hypochondriacs

New theory of the 'Howdunnit' of Fibromyalgia

- Leptin
  - Satiety hormone made by adipose cells
  - Regulates energy balance in opposed Ghrelin (hunger hormone)
  - Primary target is Hypothalamus, tells the brain we have 'enough stored'
  - Leptin resistance is now believed to be the leading driver of fat gain in humans

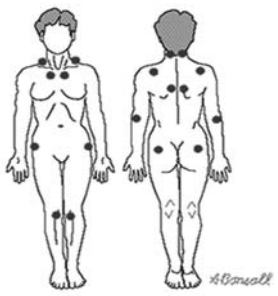
Elevated Leptin

- Implicated in chronic pain and fatigue, especially in women who have higher levels of leptin than men
- Microglia cells, 10% of cells in CNS which is the main form of active immune defense in the brain. Separated from the body by series of endothelial cells (Blood/Brain Barrier)

- Microalgae cells are exposed to high levels of leptin for long periods of time, causing the microglial cells to go into a high state of activity looking for a reason to 'fight'
- Stress, injury, and illness will trigger microalgae cells to start pumping cytokines and proinflammatory substances into CNS
- The pain is often described to be similar to the flu

Treatment

- Searching for anti-inflammatory drugs that can reach the blood/ brain barrier



Tender Points of Fibromyalgia

Dual Problem: Fibromyalgia and Chronic Fatigue Syndrome

- T cells send signals to activate the immune response memory cells (watchdogs)
- T lymphocytes CD4 (helper cells) and CD8 (suppressor cells) are called
- these T cell numbers are reduced in patients with CFS and FM
- It's an immune system dysfunction
- normal levels are between 500-1600 cells
- Therefore there in an overall decrease to response information

Special Thanks to:

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Coordinator