Autoimmune Diseases

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The term autoimmune disease refers to a disorder in which there is evidence of an immune response against self, caused by the body producing an immune response against its own tissues (self-antigen), which mean the loss of tolerance to self-antigen.
It may be primarily due to either antibodies (autoantibodies) or immune cells, but a common characteristic is the presence of a lymphocytic infiltration in the target organ.
Normally, the immune system recognizes the tissues in the body are not "foreign" also called self antigen and does not attack them; this is what's called tolerance (the normal status of immunologic non responsiveness to self-antigen).

Autoantibodies

In some autoimmune diseases, B cells mistakenly make antibodies against tissues of the body (self antigens) instead of foreign antigens.
These autoantibodies either interfere with the normal function of the tissues or initiate destruction of the tissues. (e.g.) People with myasthenia gravis experience muscle weakness because autoantibodies attack a part of the nerve that stimulates muscle movement.

Typical features of autoimmune disease:-

- Significantly more common in women.
- Onset often in middle age.
- Family history frequently positive.
- Levels of immunoglobins (autoantibodies) usually raised.
- Circulating autoantibodies frequently also detectable in un affected family members.
- Often an increased risk of developing other autoimmune diseases.
- Immunoglobuline and/or complement often detectable at sites of tissue damage (e.g. pemphigus vulgaris).
- Immunosuppressive treatment frequently limits tissue damage.

Autoimmune diseases are more frequent in women than in men. It is felt that the estrogen of females may influence the immune system to predispose some women to autoimmune diseases.
It is also known that some women with SLE can experience worsening of their symptoms prior to their menstrual periods. This phenomenon, together with the female predominance of SLE, suggests that female hormones play an important role in the expression of SLE.

Autoimmune disorders fall into two general types:

1-Those that damage many organs (systemic autoimmune diseases)
2- Those where only a single organ or tissue is directly damaged by the autoimmune process (localized). However, the distinctions become blurred as the effect of localized autoimmune disorders frequently extends beyond the targeted tissues, indirectly affecting other body organs and systems.
Some of the most common types of autoimmune disorders include:

Systemic Autoimmune Diseases

- Rheumatoid arthritis (RA) and Juvenile RA (JRA) (joints; less commonly lung, skin)
- Lupus [Systemic Lupus Erythematosus] (skin, joints, kidneys, heart, brain, red blood cells, other)
- Scleroderma (skin, intestine, less commonly lung)
- Sjögren's syndrome (salivary glands, tear glands, joints)
- Goodpasture's syndrome (lungs, kidneys)
- Wegener's granulomatosis (blood vessels, sinuses, lungs, kidneys)
- Polymyalgia Rheumatica (large muscle groups)
- Guillain-Barre syndrome (nervous system)

Localized Autoimmune Diseases

- Type 1 Diabetes Mellitus (pancreas islets)
- Hashimoto's thyroiditis, Graves' disease (thyroid)
- Celiac disease, Crohn's disease, Ulcerative colitis (GI tract)
- Multiple sclerosis , Addison's disease (adrenal)
- Primary biliary cirrhosis, Autoimmune hepatitis (liver)
- Temporal Arteritis / Giant Cell Arteritis (arteries of the head and neck)

Multisystem autoimmune diseases
Systemic lupus erythematosus (SLE)

- An autoimmune inflammatory disorder of unknown etiology, primarily of young women, it can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain.
- In SLE, organ injury is secondary to either the direct binding of autoantibodies to self-antigens or the deposition of immunocomplex in vessels or tissues.
- SLE affects 9-10 times in female than male.
  An important feature is the formation of antibodies to DNA, which are associated with lupus nephritis

Lupus erythematosus either:-
1-systemic lupus erythematosus
2- Isolated cutaneous lupus (chronic discoid lupus)

3-drug-induced lupus is recognized.

Unlike SLE, drug-induced lupus rarely affects the kidney and is reversible on discontinuation of the offending agent (medication).

ETIOLOGY

Although the exact etiology of SLE is unknown, a complex interplay of genetic and environmental factors that leads to a progressive loss of peripheral tolerance and production of autoantibodies is believed to be crucial for SLE initiation.

1-Genetic Factors.(SLE in dizygotic twins is 3%, whereas it is up to 34% for monozygotic twins)
2- Environmental and Infectious Factors (viruses, vaccines, medications and ultraviolet). Environmental factors, including infections particularly with EBV and other viruses
3- Exposure to pollutants, hormonal factors, ultraviolet light and smoking
4- Diet has been linked to the development of SLE.
5- In addition, over 80 drugs, hydralazine, isoniazide, and procainamide are associated with drug-induced lupus.

Numerous immunologic abnormalities have been described in SLE. Processes thought to be central to the pathogenesis are:
1- Immune complex formation and deposition in target organs
2- Complement activation,
3- Attraction of effector cells,
4- Subsequent target tissue damage.

Common Symptoms of Lupus:-

Painful or swollen joints and muscle pain
Unexplained fever
Red rashes, most commonly on the face
Chest pain upon deep breathing
Unusual loss of hair
Pale or purple fingers or toes from cold or stress (Raynaud's phenomenon)
Sensitivity to the sun
Swelling (edema) in legs or around eyes
Mouth ulcers
Swollen glands
Extreme fatigue
Kidney problems

Clinical Manifestations

Skin lesions of lupus can be classified into
1- lupus-specific (having diagnostic clinical or histopathological features)
2- Non specific lesions.

Three subtypes of lupus-specific skin lesions
a- Acute ,b- subacute, and c- chronic.

Acute cutaneous lupus occurs in 30%–50% of patients and is classically represented by the butterfly rash—mask-shaped erythematous eruptions involving the malar areas and bridge of the nose but typically (as opposed to dermatomyositis) sparing nasolabial folds.
Bullous lupus and localized erythematous papules also belong to the acute lupus category.
Chronic cutaneous lupus occurs in 15%–20% of cases and affects the skin of the face or scalp in about 80% of cases.
The least common subtype, **subacute cutaneous lupus**, occurs in 10%–15% of patients and includes papulosquamous (psoriasiform) and annular-polycyclic eruptions usually on the trunk and arms.

Non specific but suggestive skin manifestations of lupus are common and include alopecia (both scarring, following discoid lesions and non scarring), photosensitivity, Raynaud's phenomenon, urticaria, erythema, telangiectases, and cutaneous vasculitis.

Renal

Clinically, renal disease in SLE can range anywhere from asymptomatic proteinuria to rapidly progressive glomerulonephritis with renal failure

Musculoskeletal

Non erosive symmetric arthritis most commonly affecting hands, wrists, and knees is typical of SLE. History of temporomandibular joint (TMJ)–related symptoms was reported in two thirds of SLE patients in one study. Myalgias and myositis are also common.

Central Nervous System

CNS manifestations include psychosis, stroke, seizures and transverse myelitis and are associated with poor overall prognosis

Cardiovascular

Cardiovascular involvement in SLE is classically manifested by vasculitis and pericarditis. In addition, endocardial damage (and superimposed bacterial endocarditis), myocarditis, and conduction defects.
Abnormalities in fibrinolysis, decreases of anticoagulant proteins (protein S), and presence of antiphospholipid antibodies contribute to increased tendency to thrombosis in SLE.

CNS and deep venous thromboses with pulmonary emboli are major causes of morbidity in these patients requiring high level of anticoagulation for prevention.

Oral Manifestations

1- Oral ulcerations,2- erythematous lesions, and 3- discoid lesions. Estimates of prevalence vary from 9% to 45% in systemic disease and from 3% to 20% in localized cutaneous disease.

Oral ulcerations are listed among the criteria for SLE diagnosis .These ulcerations cannot be easily distinguished from other common oral conditions, such as aphthous ulcers,

They occur with increased frequency on the palate and in the oropharynx and are characteristically painless

Discoid oral lesions are similar to those occurring on the skin and appear as whitish striae frequently radiating from the central erythematous area, giving a so-called brush border.

Atrophy and telangiectases are also frequently present.

Buccal mucosa, gingiva, and labial mucosa are the most commonly affected intraoral sites.

Isolated erythematous areas are also common, especially on the palate. It may be difficult to differentiate these lesions from other common mucosal disorders such as oral candidiasis or lichen planus, especially if there are few lesions and there is no systemic or cutaneous involvement.

Laboratory Findings:

1- Complete blood count (CBC)
Anemia, leukopenia, and thrombocytopenia
2- Erythrocyte sedimentation rate (ESR) increased
3- Urinalysis (albumin,cast and crystals)
4- Blood chemistries (urea and serum creatinine)
5- Complement levels
C3 and c4 (decreased)
6- Antinuclear antibody test (ANA)
7- Other autoantibody tests (anti-dsDNA which is +ve in 95% of SLE patients)
and for sjogren syndrom anti-Ro [SSA], anti-La [SSB])
Anticardiolipin antibody test

Antiphospholipid antibodies (anticardiolipin and lupus anticoagulant) are causatively associated with many manifestations of SLE including thrombocytopenia, thrombotic complications and recurrent abortions (antiphospholipid syndrome), and endothelial damage with accelerated atherosclerosis.

Diagnosis

Diagnosis of SLE is based on the compatible symptoms and signs in the presence of suggestive laboratory abnormalities.

The proposed classification rule is as follows: classify a patient as having SLE if 4 of the clinical and immunologic criteria are satisfied, including at least one clinical and one immunologic criterion

OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANAs) or anti-double-stranded DNA (dsDNA) antibodies.

the diagnosis of SLE, 11 criteria were established by the American Rheumatism Association.

1. malar (over the cheeks of the face) "butterfly" rash
2. discoid skin rash (patchy redness with hyperpigmentation and hypopigmentation that can cause scarring),
3. photosensitivity (skin rash in reaction to sunlight [ultraviolet light] exposure),
4. mucous membrane ulcers (spontaneous ulcers of the lining of the mouth, nose, or throat),
5. arthritis (two or more swollen, tender joints of the extremities),
6. pleuritis or pericarditis (inflammation of the lining tissue around the heart or lungs, usually associated with chest pain upon breathing or changes of body position),
7. kidney abnormalities (abnormal amounts of urine protein or clumps of cellular elements called casts detectable with a urinalysis),
8. brain irritation (manifested by seizures [convulsions] and/or psychosis),
9. blood-count abnormalities (low counts of white or red blood cells, or platelets, on routine blood testing),
10. immunologic disorder (abnormal immune tests include anti-DNA or anti-Sm [Smith] antibodies, falsely positive blood test for syphilis, anticardiolipin antibodies, lupus anticoagulant)
11. and antinuclear antibody (positive ANA antibody testing)

A person has SLE if any 4 out of 11criteria are present simultaneously or serially on two separate occasions.

Discoid lupus erythematosus

- DLE is essentially a skin disease with mucocutaneous lesions indistinguishable clinically from those of systemic lupus.
- Significant autoantibody production is present.
- It occurs predominantly in females in the third or fourth decade of life.
- Typical cutaneous lesion appear as red patches in sun-exposed area, such as face, extremities, these lesions expand by peripheral extension and are usually disk-shaped.

Signs

Discoid lupus erythematosus well-defined red plaques with an adherent scale and follicular plugging which may result in scarring and post-inflammatory hyperpigmentation

Management of LE :-

Diagnosis:- of SLE should be by the pattern of antinuclear autoantibodies. The most specific is that to double-stranded DNA.(ANA, Anti dsDNA)

Hematological finding in active SLE (raised ESR, anemia and leukopenia or thrombocytopenia).

Treatment:- oral lesion of DLE may respond to topical corticosteroids. Oral lesions in acute SLE may not respond to dose of corticosteroids adequate to control systemic effect of the disease, palliative treatment is need until the disease activity is decrease.

Ttreatment of systemic lupus erythematosus

1- There is no permanent cure for SLE. The goal of treatment is to relieve symptoms and protect organs by decreasing inflammation and/or the level of autoimmune activity in the body.

2- The precise treatment is decided on an individual basis. Many people with mild symptoms may need no treatment or only intermittent courses of anti-inflammatory medications.

3- Those with more serious illness involving damage to internal organ(s) may require high doses of corticosteroids in combination with other medications that suppress the body's immune system.

Avoidance of sun exposure is very important

Nonsteroidal anti-inflammatory drugs (NSAIDs) are helpful in reducing inflammation and pain in muscles, joints, and other tissues.

Corticosteroids are more potent than NSAIDs in reducing inflammation and restoring function when the disease is active. Corticosteroids are particularly helpful when internal organs are affected.

Hydroxychloroquine (Plaquenil) is an antimalarial medication found to be particularly effective for SLE people with fatigue, skin involvement, and joint disease. Consistently taking Plaquenil can prevent flare-ups of lupus.

Medications that suppress immunity (immunosuppressive medications) are also called cytotoxic drugs used for treating people with more severe manifestations of SLE, such as damage to internal organ(s).

Examples of immunosuppressive medications include methotrexate azathioprine (Imuran), cyclophosphamide (Cytoxan)

Dental Management

1- Risk of Infection

Daily treatment with higher doses of prednisone (over 7.5–10 mg/day) or other glucocorticoids, treatment with high doses of cyclophosphamide, and high disease activity are risk factors for infection in SLE patients.

If possible, elective oral surgical procedures with the potential for bacteremia should be delayed until the absolute neutrophil count is over 1000 cells/mm3, as neutropenia may be transient and respond to treatment with glucocorticoids.

If an oral procedure cannot be postponed, prophylactic antibiotics can be considered.

2- Risk of Bleeding

Traditionally, platelet transfusions have been recommended in surgical patients with platelet counts below 50,000 per mm3. For patients with lupus who are receiving anticoagulants, established guidelines should be followed.

In general, oral surgical procedures are safe in patients taking warfarin with therapeutic international normalized ratio (INR) ranges (2–3.5) and do not require discontinuation of anticoagulation.

3- Adrenal Suppression/Secondary Adrenal Insufficiency

There are very few reported cases of adrenal crisis occurring in association with a dental procedure.

Although, as a rule, a patient who has received a glucocorticoid in doses equivalent to at least 20 mg a day of prednisone for more than 5 days is at risk for hypothalamus–pituitary–adrenal (HPA) suppression, it is difficult to predict those patients with adrenal insufficiency.

Studies found weak correlations between total dose, duration of glucocorticoid treatment and tests of HPA function. Also, HPA suppression is more common in critically ill patients.

Scleroderma

Describes a group of clinical disorders characterized by thickening and fibrosis of the skin. Systemic sclerosis is a multisystem connective tissue disease in which the fibrosis extends to the internal organs, including the heart, lungs, kidney, and gastrointestinal tract.

It is autoimmune disease, a chronic, multisystem connective-tissue disease that involves:-

1- Hardening of the skin and mucosa (over production of normal collagen)

2- smooth-muscle atrophy

3- fibrosis of internal organs.

There are two main forms:

1- Systemic sclerosis (SSc)

SSc is further divided into:

a- limited cutaneous scleroderma

(previously called CREST syndrome for calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia)

b- Diffuse cutaneous scleroderma.(develop widespread skin thickening) progressing from the fingers to the trunk), internal organ involvement (including gastrointestinal and pulmonary fibrosis), and potentially life-threatening cardiac and renal failure. Overlap syndromes with SLE, is Sjogren's syndrome.

2- Localized sclerodema.

a- linear scleroderma

b- morphea.

Linear scleroderma is characterized by a band of sclerotic induration and hyperpigmentation occurring on one limb or side of the face.

This form of the disease develops as a thin band of sclerosis that may run the entire length of an extremity, involving underlying muscle, bones, and joints. When the disease crosses a joint, limitation of motion is possible, along with growth abnormalities. These lesions may result in hemi atrophy of the face.

Morphea is characterized by small violaceous skin patches or larger skin patches that indurate and lose hair and sweat gland function, later in the disease, the lesion burns out and appears as a hypo- or hyper pigmented area depressed below the level of the skin.

A small number of patients develop numerous larger lesions that coalesce, and these patients are said to have generalized morphea.

Etiology and Pathogenesis

The etiology of SSc is unclear, but the pathogenesis is characterized by vascular damage and an accumulation of collagen and other extracellular matrix components at involved sites.

The inflammatory process precedes the deposition of collagen.

cytokines induce fibroblast production of transforming growth factor (TGF)-β1, which is the main profibrotic cytokine in SSc.

Clinical Manifestation:

Raynaud's Phenomenon

Cutaneous Manifestations

Musculoskeletal Manifestations

Gastrointestinal Manifestations
Cardiac Manifestations
Pulmonary Manifestations
Renal Manifestations

Signs and Symptoms

1- Localized scleroderma characterized by skin thickening that is similar to that of systemic scleroderma, but without the disease features in the multiple internal organs & blood vessels

2- Raynaud's phenomenon (RP) which is the result of spasm of the blood vessels of the fingers &toes & can be triggered by cold temperature or stress.
Symptoms of RP include paleness, coldness, pain & numbness of fingers &toes. It is important to note that not all people with Raynaud's phenomenon have scleroderma.
3- Tethering and sclerosis of the skin (the skin feels hard, cannot be pinched and the skin creases disappear) and a shrunken mouth.
The skin becomes hard &thickened, movement become more difficult. Muscles become weak with joints stiffness
4- telangiectases on the face and fingers
5- calcinosis of the fingers
6- hirsutism
7- hyperpigmentation

Oral manifestations of scleroderma:
The clinical signs of SSc of the mouth and jaws are consistent with findings elsewhere in the body. 1- The lips become rigid, the oral aperture narrows considerably (microstomia).
2- Skin folds are lost around the mouth, giving a mask-like appearance to the face.
3- The tongue can also become hard and rigid, making speaking and swallowing difficult.4- Involvement of the esophagus may cause dysphagia.
5- Oral telangiectasia is equally prevalent in both limited and diffuse forms of SSc and is most commonly observed on the hard palate and the lips.
6- When fibrosis involves the muscles of mastication, mandibular resorption occur.
One study reported that about one-third of patients had resorption of either the angle of the mandible, the condylar heads, the coronoid process, or the digastric region.
7- Mandibular movement may be restricted by muscular fibrosis, and linear localized scleroderma may cause hemiatrophy of face.
8- Dental radiographic findings, Classic findings such as uniform thickening of the periodontal membrane, especially around the posterior teeth, are found in 10%–37% of patients .
Other characteristic radiographic findings include calcinosis of the soft tissues around the jaws.
The areas of calcinosis will be detected by dental radiography and may be misinterpreted as radiographic intra bony lesions. A thorough clinical examination will demonstrate that the calcifications are present in the soft tissue

9- Medications may reduce salivary flow rates, or patients with scleroderma may have secondary Sjogren's syndrome.
studies have estimated the prevalence of secondary Sjogren's syndrome in patients with scleroderma to be between 21% and 44%.
10- Significant fibrosis was seen in the minor salivary gland biopsies of patients.
Xerostomia results in an increased susceptibility to dental caries and *Candida* infections, Salivary Gland Diseases .
11- decreases their ability to maintain good oral hygiene. Oral hygiene can be complicated further if opening is limited

Laboratory evaluation

1- Antinuclear antibody.(ANA)
2- Anti- centromere antibodies(ACA) are found in the blood of 90 % of people with systemic scleroderma
3- Anti -topoisomerase-1 antibodies (Anti-SCL-70-AB)
4- anti–RNA polymerase I/ III
5- Rheumatoid factor may be seen in small percentage of patients
6- Anti-Ro & Anti-La seen in patients with sjogren syndrome.

Evaluation of organ systems as indicated: pulmonary function testing, Cheast-X Ray, barium swallow, etc.
Biopsy: Skin biopsy will show characteristic fibrotic changes

Treatment:

1-None specifically
2- Symptomatic treatment of complications (dysphagia, pulmonary hypertension, Raynaud's, etc.).
3- Use of immunomodulatory (prednisone, methotrexate, cyclosporine) or antifibrotic (penicillamine, colchicines) agents.
4- Follow-up: Routine monitoring of disease progression.
5- For Raynaud's phenomenon, avoidance of cold exposure is crucial. In addition, calcium channel blockers are prescribed for moderate to severe Raynaud's phenomenon.

If these are inadequate addition of another vasodilator, such as nitroglycerine, a phosphodiesterase inhibitor, or prostacyclin infusions(they open the blood vessels & also have anti-blood-clotting properties) may be considered.

6- Progressive or severe cutaneous involvement may be treated initially with methotrexate alone, or in combination with cyclophosphamide.

7- Severe disease may be treated with cyclophosphamide initially, Cyclophosphamide is used to treat early lung disease with alveolitis.

8- Other drugs reduce inflammation & block damage immune factors. These treatments, which include cyclophosphamides, pencillamine & bone marrow transplantation, may be helpful for improving skin thickness & reducing scarring, even in the lung.

Treatments that affect the immune system:

One major approach to scleroderma is to use treatments that suppress the immune system
1-Cyclophosphamide is the most important immunosuppressant

2-Other drugs used to suppress the immune system .They include: D-pencillamine, Methotrexate, corticosteroid, cyclosporine A. All these drugs have potentially severe sides' effects.

3- Biologic drugs such as rituximab (rituxan)

Other treatments:
Autologous stem cell transplantation

Rheumatoid Arthritis:-

It is multisystemic disease in which the immune system attacks the lining of the joint. This results in joint pain, stiffness, swelling and destruction.
In rheumatoid arthritis, the women are affected in the third and fourth decades. The smaller joints are mainly affected (especially those of the hand).
TMJ involvements ranges from 40-80 %.

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints.
Inflammation of the tissue around the joints and inflammatory arthritis are characteristic features of rheumatoid arthritis, the disease can also cause inflammation and injury in other organs in the body. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease

- Can cause chronic inflammation of the joints and other areas of the body.
- Rheumatoid arthritis can affect people of all ages.
- The cause of rheumatoid arthritis is not known.
- Rheumatoid arthritis is a chronic disease, characterized by periods of disease flares and remissions.
- In rheumatoid arthritis, multiple joints are usually, but not always, affected in a symmetrical pattern.
- Early treatment of rheumatoid arthritis results in better outcomes

- Chronic inflammation of rheumatoid arthritis can cause permanent joint destruction and deformity.
- Damage to joints can occur early and does not correlate with the severity of symptoms.
- The "rheumatoid factor (RF)" is an antibody that can be found in the blood of 80% of people with rheumatoid arthritis.
- There is no known cure for rheumatoid arthritis.
- The treatment of rheumatoid arthritis optimally involves a combination of patient education, rest and exercise, joint protection, medications, and occasionally surgery.

Laboratory Evaluation and Diagnosis

RF and anti-CCP (cyclic citrullinated peptide) antibodies are present in approximately 80% of adult patients with RA.
Other associated laboratory findings include an elevated erythrocyte sedimentation rate and normochromic normocytic anemia.
The classification system is aimed at classifying newly presenting patients and is applied to those with at least one joint with synovitis that is not better explained by another disease.

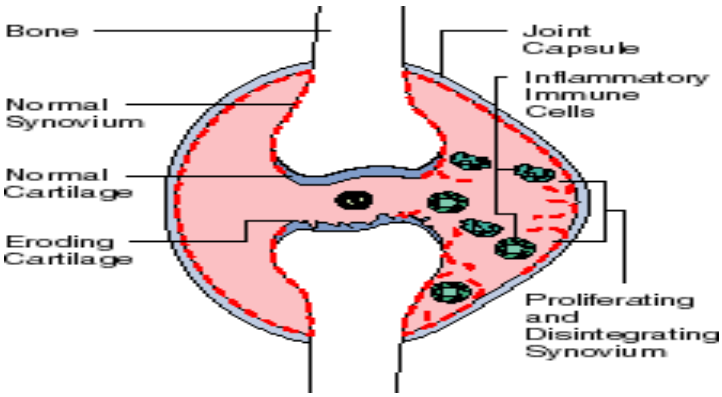
The criteria for the classification of Rheumatoid Arthritis (Arnett,1988)

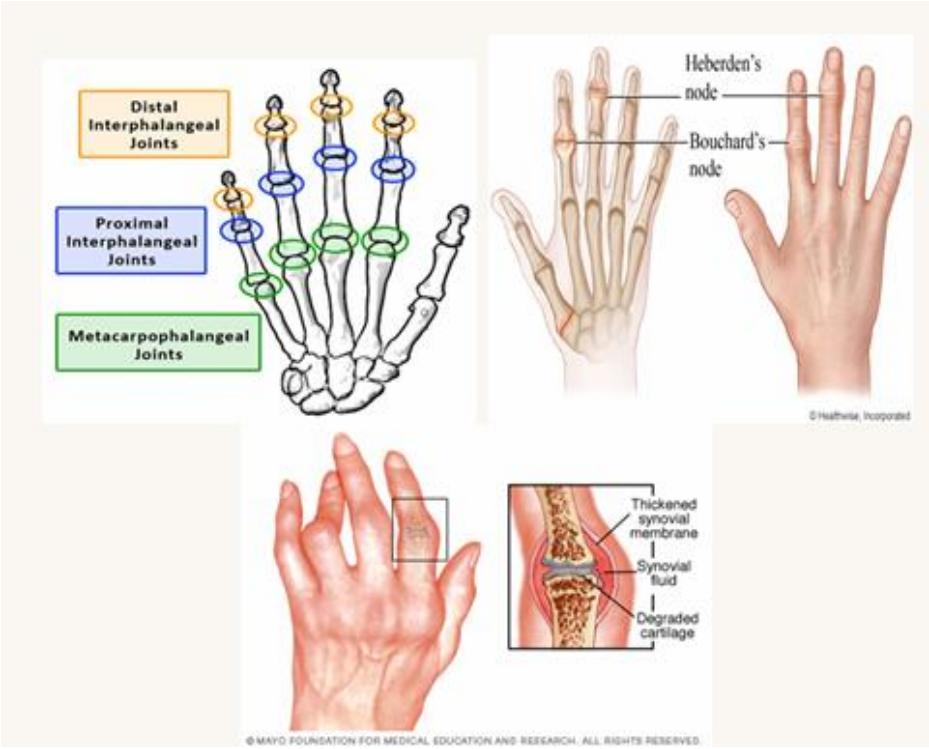
1. Morning stiffness of > 1hour most mornings for at least 6 weeks.
2. Arthritis and soft – tissue swelling of > 3 of 14 joints/joint groups, present for at least 6 weeks.
3. Arthritis of hand joints, present for at least 6 weeks.
4. Symmetric arthritis, present for at least 6 weeks.
5. Subcutaneous nodules in specific places.
6. Rheumatoid factor at a level above the 95th percentile.
7. Radiological changes suggestive of joint erosion.

At least four criteria have to be met for classification of rheumatoid arthritis.

In people with rheumatoid arthritis, the immune system predominantly targets the lining (synovium) that covers various joints. Inflammation of the synovium is usually symmetrical (occurring equally on both sides of the body) and causes pain, swelling, and stiffness of the joints. These features distinguish rheumatoid arthritis from osteoarthritis, which is a more common and degenerative "wear-and-tear" arthritis.

Heberden's node seen in pateints with osteoarthritis at the distal interphalengeal joints,while bouchard'sseen in proximal interphalengeal joints in rheumatoid arthritis patients.





An inflamed joint—the synovium—is attacked by cells and molecules of the immune system

Methotrexate is often used as initial therapy for symmetric polyarthritis involving three or more joints. This drug reduces disease activity, joint erosions and is associated with a significant long-term reduction in mortality.
Patients with severe disease are usually treated with combination therapy, and early aggressive therapy has been shown to be advantageous.

Many biological agents, typically antibodies that block receptors or mediators of inflammation, and used as treatments for RA. The most commonly prescribed are etanercept and infliximab, agents that block the actions of the cytokine TNF.

Anti-TNF antibody therapy is associated with an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with RA.

T.M.J involvement

R.A. is the important inflammatory disease of T.M.J (T.M.J involvement ranges from 40 to 80%).

The clinical features of T.M.J involvements are:

- Limitation in movement of mandible.
- T.M.Js bilaterally involved, tenderness, swelling over the joint area
- Morning stiffness
- Deviation of mandible on opening
- Ankylosis of the joint with facial asymmetry

Management :

- On diagnosis the clinical radiograph shows flatting of the condyle, loss of contour and irregularity of the articular surface.
- Joint space may be widened (acute phases) but later narrowed.
- Underlying bone may be osteoporotic.

  Treatment of TMJ disorders:
- By giving of non steroidal anti-inflammatory drugs.
- Any abnormalities in occlusion should be corrected.
- In sever symptoms (intra-articular steroids, PRP should be considered).
- Surgical treatment (placement of prosthetic joints) is indicated in sever functional impairment or pain).
- Use of a flat plane occlusal appliance may be helpful (if Para functional habits are increasing the symptoms).

Gland:

Sjogren's Syndrome:

A condition in which the immune system target's the salivary and lacrimal gland, leading to dryness of the eyes, mouth, and other body tissues.

There was a significant association between Sjogren's Syndrome with RA.

These combination of complaints are caused by two closely related but distinct diseases.

Sjogren Syndrome(SS)

This is a systemic autoimmune condition affecting salivary and lacrimal gland tissue that is seen primarily in middle-aged women.

Clinical manifestations of dry eyes and mouth are referred to as sicca syndrome, which may occur in conjunction with other autoimmune diseases such as rheumatoid arthritis and lupus which is secondary SS.

Diffuse non tender enlargement of the major salivary glands may be present.

The autoantibodies found in SS are commonly directed against:

● ribonucleoproteins, in SS-1 especially against SS-A (Ro), and in SS-2 against SS-B (La), ds DNA and other extractable nuclear antigens

● IgM [rheumatoid factor (RF)—
-Primary SS comprises dry mouth and dry eye not associated with any connective tissue disease.
-Secondary SS comprises dry mouth and dry eye associated with rheumatoid arthritis or other connective tissue disease.
SS primarily affects postmenopausal women (the female to male ratio is 9:1).
SS patients have peripheral neuropathies and rashes.

oral findings:

1- Persist oral dryness (xerostomia).
2- Difficult in chewing, swallowing and speaking without additional fluids.
3- Burning, cracking of the tongue and atrophy of the papillae.
4- Dry cracked lips and angular cheilitis.
5- Disturbed taste sensation and increase dental caries.
6- Saliva is thick and ropy.
7- Mucocutaneous candidal infections are common, (alter in oral flora).
8- Enlargement of parotid gland. A hot, tender parotid swelling with red overlying skin (supurative parotitis).
9- The tongue is red and the dorsum becomes lobulated with a cobble stone appearance.

Management:-

Diagnosis: by the presences of:-

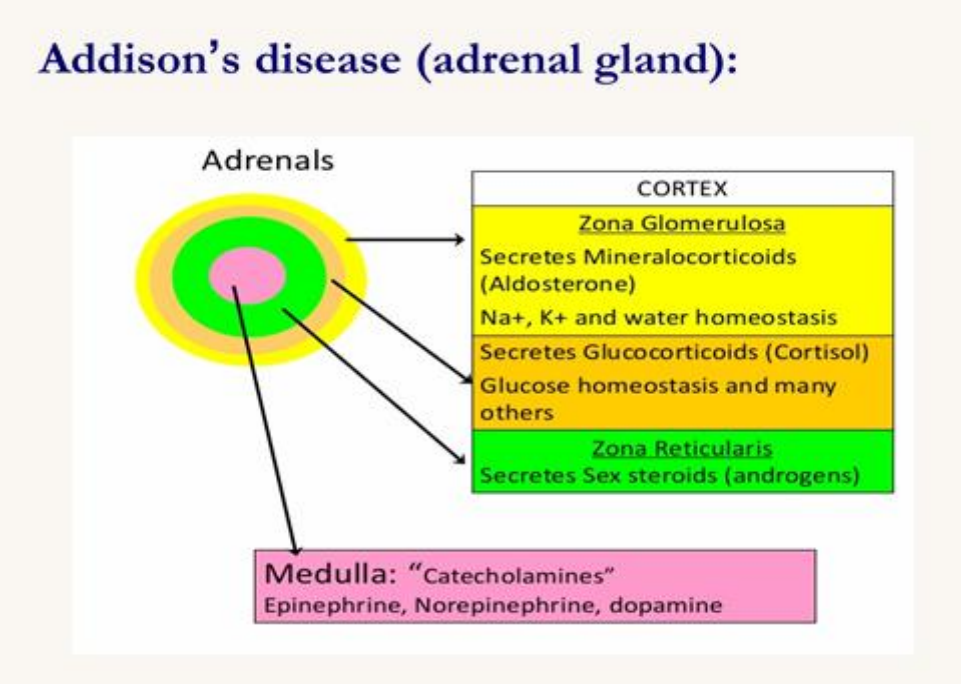
- Diminished total salivary flow rate. (Normal 1-2 ml / mint. reduce to 0.5ml/mint.).
- Labial salivary gland biopsy showing periductal lymphocytic infiltration.
- Antibody screen, especially positive ANA, Rheumatoid factor and anti-SS-A and anti- SS-B.
- Sialectasis on sialography (snow storm appearance).
- Diminished tear secretion (schirmer's test, apiece of filter paper is placed in the corner of the eye to measure the degree of wetting after 5 mints.).

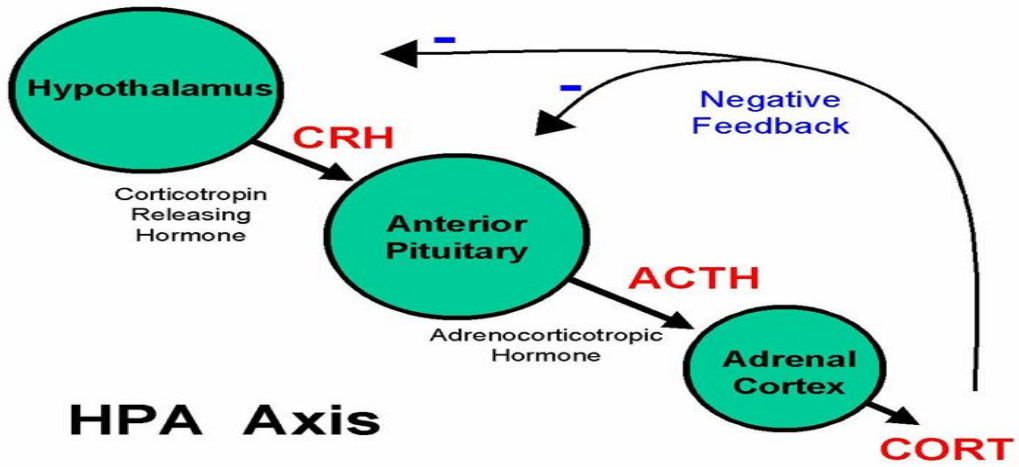
Treatment:-

1- Stimulation of salivary flow (remaining salivary function) by chewing sugar free gum.
2- Cholinesterase inhibitors (such as pilocarpine 5 mg) are stimulating salivary secretion.
3- A high standard of oral hygiene maintained and frequent dental checks are necessary.
4- Topical fluorides should be applied regularly and 0.2% chlor hexidine mouth rinses is used to reduce plaque formation.
5- Candida albicans, treated with Nystatin or amphotericin mixture.
6- Ophthalmologic investigation for keratoconjuctivitis sicca.

7- Observe regularly for possible development of ascending parotitis or lymphoma.

Addison's disease (adrenal gland):





Symptoms include severe weakness, weight loss, low pressure, digestive disturbances, hypoglycemia, lowered resistance to infection, and abnormal pigmentation (bronze color of the skin, with associated melanotic pigmentation of the oral mucous membranes, particularly of the gingival tissues).
Pigmentation (early sign) in the mouth (on the gingiva, buccal mucosa and lips).
It's pale brown to deep chocolate pigmentation (spreading over the buccal mucosa from the angle of the mouth).
This is due to a decrease of cortisol, then increase of ACTH, which affect melanocyte stimulating hormone, stimulate melanocyte ,lead to increase melanine pigmentation

Diagnosis:- by The clinical signs (hypotension, loss of weight, gastrointestinal disturbances, abnormal pigmentation of skin and oral mucosa).

By laboratory investigations , ACTH , serum cortisol,glucose and electrolytes(Na,K)

Management:-

- Because of fall in blood pressure, circulatory collapse (shock) and vomiting, which may be fatal (in case of surgery or anesthesia) so immediate treatment with intravenous hydrocortisone and fluid replacement may be life-saving.
- Patient with long term treatment of corticosteroids so the patient will be with complication of this treatment that includes.

-Depression of inflammatory and immune responses (Apportunistic infections).
-Impaired wound healing and moon face.
-Raised blood sugar, sodium and water retention.
-Mood changes.

Inflammatory bowel disease (IBD)

is a general classification of inflammatory processes that affect the large and small intestines.
1- Ulcerative colitis
2- Crohn's disease
Ulcerative colitis involves the mucosa and submucosa of the colon.
Crohn's disease or regional enteritis is an inflammatory condition involving all layers of the gut.
The precise etiology and pathogenesis of ulcerative colitis and Crohn's disease are unknown, and the two diseases share many features.
The diagnostic separation of these two disorders often depends on the results of the radiographic, endoscopic, and histologic examinations.
In people with IBD, the immune system mistakes food, bacteria, or other materials in the GI tract for foreign substances and responds by sending white blood cells into the lining of the bowels. The result of the immune system's attack is chronic inflammation.
IBD may affect any age. Most people with IBD are diagnosed before the age of 30, but can be diagnosed later in life.
There's currently no cure for IBD. This is a lifelong disease, with alternating periods of remission and flare-up, they tend to fluctuate between periods of inactivity (remission) and activity (relapse)
Modern treatments, however, allow people to live relatively normal and productive lives.

Ulcerative Colitis

The inflammation in ulcerative colitis may affect all or part of the large intestine.
Macroscopically, the mucosa may have a granular appearance if the disease is mild. When fulminant, the disease may include stripping of the mucosa, with areas of sloughing, ulceration, and bleeding.

Unlike Crohn's, ulcerative colitis is confined to the colon (large bowel) and only affects the top layers in an even distribution.

Symptoms of UC include:

- crampy abdominal pain
- loose stools
- bloody stool
- urgent bowel
- fatigue
- loss of appetite
- anemia due to blood loss (in severe cases only)

The hallmark of ulcerative colitis is rectal bleeding and diarrhea. The frequency of bowel movements and the amount of blood present reflect the activity of the disease.

Diarrhea is severe, possibly five to eight bowel movements in 24 hours.

Patients usually complain of pain that is in both abdominal quadrants and that is crampy in nature and exacerbated prior to bowel

Anemia is commonly associated with ulcerative colitis. It is most likely caused by blood loss and is typically a microcytic hypochromic anemia of iron deficiency.

Leukocytosis occurs in active disease and is usually associated with intra-abdominal abscess.

Electrolyte imbalances, hypoalbuminemia, and low serum magnesium and potassium levels may occur because of the severe diarrhea

Medical Management

Diagnosis of ulcerative colitis is made on the basis of careful history, physical examination, gastrointestinal radiography, and endoscopy, which involves direct visualization of the intestinal mucosa.

Most important is the sigmoidoscopic examination, which usually reveals the characteristic picture of multiple tiny mucosal ulcers covered by blood and pus.

The therapy for ulcerative colitis is aimed at reducing the inflammation and correcting the effects of the disease.

Sulfasalazine is used to initiate and maintain a remission in ulcerative colitis.

Corticosteroids and corticotropin

(adrenocorticotropic hormone [ACTH]) are used in patients who have not responded satisfactorily to sulfasalazine.

They are administered in high doses (e.g., 40–60 mg of oral prednisone daily initially and then maintenance doses of 10–20 mg of prednisone daily).

Immunosuppressive agents such as azathioprine, cyclosporine, and mercaptopurine are used.

Because of the risk of hematologic suppression and superinfection in patients taking these medications, they are reserved for patients who have not responded to traditional medical therapy.

Approximately 15%–20% of patients will receive surgery for intractable disease.

Proctocolectomy combined with ileostomy is a curative procedure for ulcerative colitis.

Remission periods tend to be longer with UC than with Crohn’s disease, and complications are far less frequent.
When complications do occur, they can be severe. Left untreated, UC may lead to:
holes in the colon
colon cancer
liver disease
osteoporosis
blood clots
Extra-abdominal and oral signs of UC, including:-
pyostomatitis vegetans, chronic stomatitis, aphthous ulcerations, lichenoid mucosal reactions oral manifestations of IBD may precede the onset of intestinal radiographic lesions by as much as one year or more.
Pyoderma gangrenosum is a condition that causes tissue to become necrotic, causing deep ulcers. When they occur, they can lead to chronic wounds that sometimes ulcerate through the tonsillar pillar.
Pyostomatitis vegetans, a purulent inflammation of the mouth, these oral lesions are characterized by deep tissue vegetating or proliferative lesions that undergo ulceration and then suppuration.

Crohn’s Disease

Crohn’s disease is an inflammatory disease of the small or large intestine. Inflammation occurs in all layers of the intestinal wall and patches of this inflammation can be scattered throughout the GI tract. In contrast, in ulcerative colitis, inflammation occurs in the innermost lining of the intestinal wall and is a continuous stretch within the colon.
Site of inflammation differs between Crohn's disease and ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract, including the mouth, esophagus, stomach, small and large intestines, rectum and anus. Ulcerative colitis is located in the colon, usually starting from the rectum.
Crohn’s disease affects all ages and both sexes and occurs most frequently in women aged 20–39 years.
The prevalence of Crohn’s disease among first-degree relatives is 21 times higher than that among non-relatives.
Evidence for familial association in Crohn’s disease includes increased incidence in Jewish populations, strong familial aggregation, and increased concordance among monozygotic twins or triplets.
The causes of Crohn’s disease are unknown.
The single strongest risk factor for Crohn’s disease, overpowering any influences of diet, smoking, stress, or hygiene, is having a relative with the disease (inherited).
The abnormal intestinal barrier could result in the increased uptake of injurious materials and/or enhanced immune reaction to intestinal antigens.
Other theories have included vascular disease, lymphatic obstruction, and emotional stress. Whatever the process, tiny erosions of the overlying normal mucosal lymphoid

tissues coalesce to form small aphthous-like ulcers or more diffuse ulceration of the mucosa.
With progression, there is marked hyperplasia of the lymphoid tissue extending through the wall, fibrosis, and muscular hypertrophy leading to constrictures, and inflammatory tracts.
Granulomas arepresent in about 50% of patients

The clinical presentation of Crohn's disease depends on the extent of inflammation and on the site of intestinal involvement.
The usual presentation is that of a young person in the late teens or twenties who has been ill for an indefinite period and whose disease suddenly worsens.

Symptoms of Crohn's disease include:
Abdominal pain
Diarrhea
Vomiting
Fever
Bloody diarrhea
Anal fistulae
Perirectal abscesses
Weight loss
Although bleeding is a prominent feature of ulcerative colitis, it is rare in cases of small bowel Crohn's disease. Inflammation of the small intestine may impair its absorption of vital nutrients. Calcium, iron, and folate which are absorbed in the duodenum, and their decreased absorption due to inflammation can lead to deficiencies.
Disease in the terminal ileum may interfere with the absorption of bile salts and vitamin B12.
Inflammation of the small or large intestines may impair the absorption of fat, fat-soluble vitamins, salt, water, protein, and iron.
Electrolyte abnormalities and low albumin levels commonly occur in cases of severe diarrhea.
Anemia, usually resulting from an iron or folate deficiency, may also be present.
Leukocytosis, cell counts of >15,000/cm3, is suggestive of abscess or perforation.

Oral Health Considerations
Oral lesions, both symptomatic and asymptomatic, affect 6%–20% of Crohn's disease patients. Most oral manifestations of Crohn's disease occur in patients with active intestinal disease, and their presence frequently correlates with disease activity.
1-Recurrent aphthous ulcers are the most common oral manifestation of Crohn's disease. It is not clear whether these oral manifestations are true expressions of Crohn's disease, direct results of medical treatment, or manifestations of an associated problem, such as anemia. Certainly,
2- pyostomatitis vegetans,

3- Minor salivary gland duct pathology represents granulomatous changes that constitute the hallmark of Crohn's disease.
4- Crohn's disease patients develop diffuse swelling of the lips and face,
5- Inflammatory hyperplasias of the oral mucosa with a cobblestone pattern,
6- Indurated polypoid tag-like lesions in the vestibule and retromolar pad area, and persistent deep linear ulcerations with hyperplastic margins.
Numerous medications, including anti-inflammatory and sulfa-containing preparations that are commonly used to manage IBD patients, have been reported to cause
7- oral lichenoid drug reactions.
8- Superinfection with *Candida albicans* is often associated with IBD and may represent a primary manifestation of the disorder, a reaction to the bacteriostatic effect of sulfasalazine, or an impaired ability of neutrophils to kill this granuloma-provoking organism

Depending on the results of the consultation with the patient's physician, the following laboratory studies may be indicated before surgical procedures are performed:
Complete blood count; (2) hematocrit level; (3) hemoglobin level; (4) platelet count;
(5) Coagulation studies (prothrombin time/INR, and partial thromboplastin time)
(6) Liver function test; and
(7) Blood glucose level.

Nerve and brain: Multiple Sclerosis:

A disease in which the immune system attacks the protective coating called myelin around the nerves.
The damage affects the brain and/or spinal cord and interferes with nerve pathway, causing muscular weakness, loss of coordination, and visual and speech problems between 2% and 3% patients with classical symptoms of trigeminal neuralgia may have multiple sclerosis.
In about 30%, pain, unlike trigeminal neuralgia, may be persist and lack trigger zone, or may be spread beyond the trigeminal area. The symptoms are bilateral, pain is sever but trigger zones may be absent, the pain becomes less severe but more continuous).
More in women in fourth decade of life
Facial and jaw weakness occur in some patients.
A staccato type of speech is described.
The lip may be affected (the range from paraesthesia to extreme hypersensitivity), the patient will laterally jump if the lip is touched.

Diagnosis:

- On the clinical features and the age of the patients.

By finding of neurological signs that can not be explained by a single lesion, progressive nature of the disease, and a history of exacerbation and remissions.

- The demyelinating changes can be seen on magnetic resonance imaging (MRI).
-By the increasing in immunoglobin (IgG) level in the cerebrospinal fluid without infection.

Dental Management:

- Treatment of trigeminal neuralgia-like pain by giving carbamazepine.
- Otherwise surgical treatment as for trigeminal neuralgia may be required.
- Those patients treated with corticosteroid.

Guillian-Barre Syndrome:

It is auto immune disease and an acute symmetrical ascending polyneuropathy.
Often occurring 1 to 4 weeks after an acute infection.
This syndrome follows a non-specific respiratory or gastrointestinal illness (but is can be occur after a few specific infection such as with cytomegalo virus, Epstein-barr virus, Entero virus or mycoplasma and after immunization).
Guillain-Barré syndrome (GBS) causes progressive muscle weakness and paralysis (the complete inability to use a particular muscle or muscle group), which develops over days or up to four weeks, and lasts several weeks or even months
The initial sensation of weakness or paralysis in the toes spreads upward within days to a few weeks to the arms and the central part of the body.
In medical terminology, this represents an ascending pattern of spread. The weakness and paralysis can also be accompanied by a tingling sensation, and a cramping or more constant pain in the feet, hands, thighs, shoulders and lower back.
Use of the hands and feet can become impaired. More serious development of paralysis can make breathing difficult, even to the point that mechanical ventilation becomes necessary.
*Impaired swallowing or Paresthesias of the mouth and face early signs of the disease.
*The seventh cranial nerve is involved.
*Bilateral facial weakness is common.
*Involvement of other cranial nerves may result in ptosis
*Dysarthria, dysphagia and diplopia may develop in sever cases.
Other, symptoms include blurred vision, clumsiness, difficulty in moving facial muscles, involuntary muscle contractions.
Symptoms that are indicative of an emergency include difficulty in swallowing, drooling, breathing difficulty, and fainting.

Treatment and prognosis:

- Prednisone is ineffective (prolong recovery time).
- Plasmapheresis is of value, its best performed within the first few days of illness (for clinically sever or rapidly progressive cases).