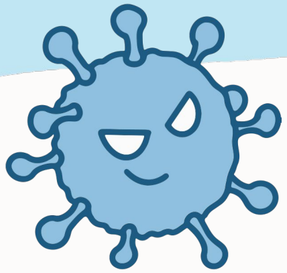
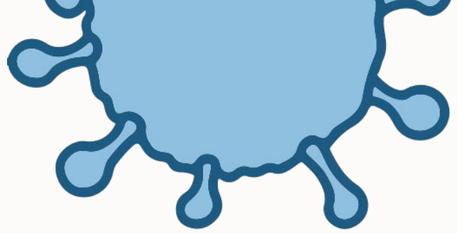
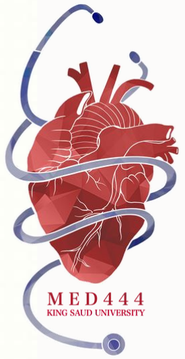
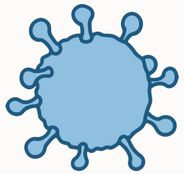
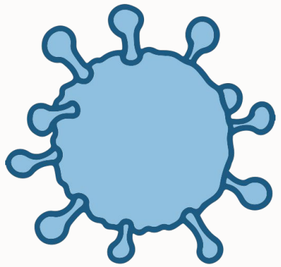





Autoimmune Diseases

MSK Block | Immunology

Color index:

Main text

Important

Girls slides

Boys slides

Doctor's notes

Extra

Objectives

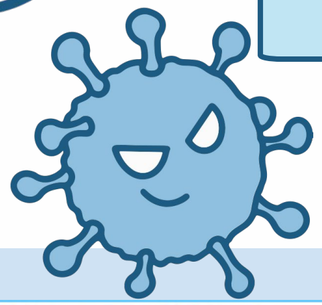
01 To know that the inflammatory processes in autoimmune diseases are mediated by hypersensitivity reactions (type II, III, IV).

02 To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues(systemic).

03 To understand that the manifestations of autoimmune diseases depend upon the organ and the degree of damage inflicted on the target tissues.

Reference: Kuby Immunology 7th Edition 2013
Chapter 16 Pages 525 - 531

Disease processes and tissue damage are due to Type II, Type III, and Type IV hypersensitivity reactions



SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
Organ-specific autoimmune diseases		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
Systemic autoimmune disease		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_{DTH} and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thryoid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes

Examples of Autoimmune Diseases Affecting Different Systems:

Nervous System:
Multiple sclerosis
Myasthenia gravis
Autoimmune neuropathies such as:
- Guillain-Barré Syndrome (GBS)

Autoimmune uveitis

Blood:
Autoimmune hemolytic anemia
Pernicious anemia
Autoimmune thrombocytopenia

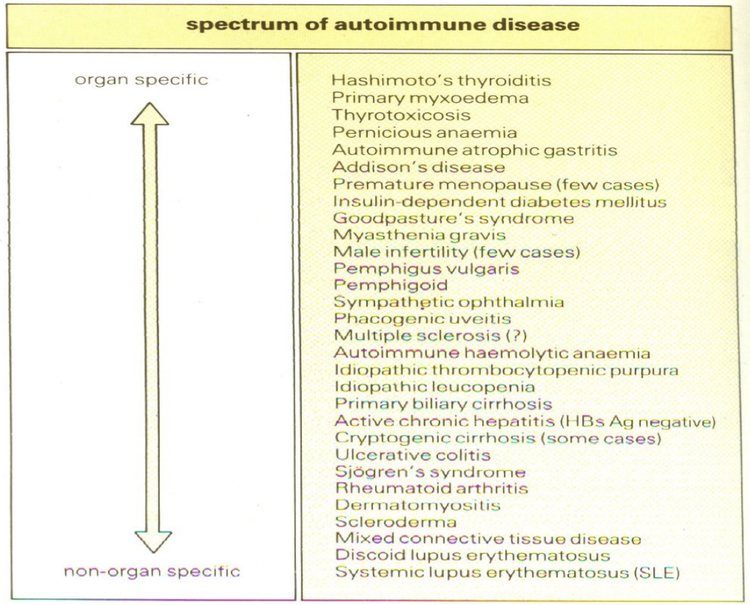
Blood Vessels:
Temporal arteritis
Anti-phospholipid syndrome
Vasculitides such as
Wegener's granulomatosis
Behcet's disease

Skin:
Psoriasis
Dermatitis herpetiformis
Pemphigus vulgaris
Vitiligo

Gastrointestinal System:
Crohn's Disease
Ulcerative colitis
Primary biliary cirrhosis
Autoimmune hepatitis

Endocrine Glands:
Type 1 or immune-mediated diabetes mellitus
Grave's Disease
Hashimoto's thyroiditis
Autoimmune oophoritis and orchitis
Autoimmune disease of the adrenal gland

Multiple Organs, Musculoskeletal System
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Polymyositis, dermatomyositis
Ankylosing spondylitis
Sjogren's syndrome



Autoimmune Diseases

Organ Specific Autoimmune Diseases

Mediated by:

- Stimulating autoantibodies.
  - Such as: (Grave's disease).
- Blocking auto-antibodies.
  - Such as :(Myasthenia gravis).

1- Graves Disease (Stimulate antibodies)

2- Myasthenia Gravis (Blocking antibodies)

Systemic Autoimmune diseases

"multiple organs"

441. Characterized by dysregulation of immune system which give rise to activation of immune cells to attack autoantigens and resulted in inflammation and tissue damages.

1- Systemic Lupus Erythematosus (SLE)

2- Rheumatoid Arthritis

Organ Specific Autoimmune Diseases

I. Graves' Disease (Thyrotoxicosis)

No negative feedback by the antibodies unlike tyrosine and triiodothironine hormones

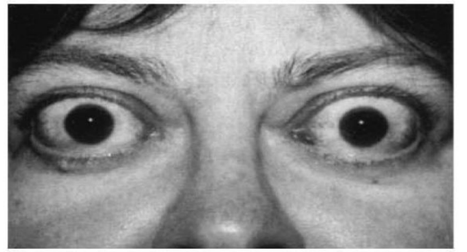


Fig. 1A

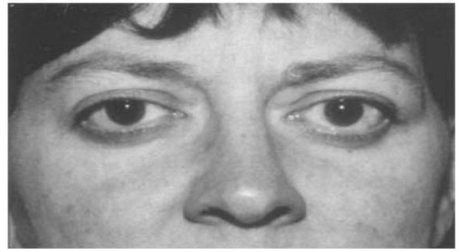


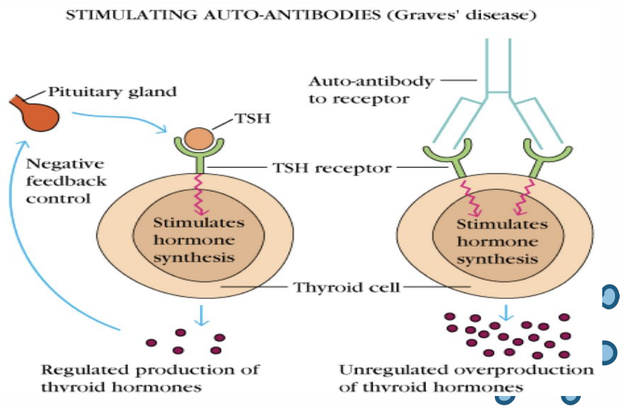
Fig. 1B

Normal State

The production of thyroid hormones is regulated by thyroid-stimulating hormones (TSH).
The binding of TSH to a receptor on thyroid cells stimulates the synthesis of two thyroid hormones: thyroxine and triiodothyronine

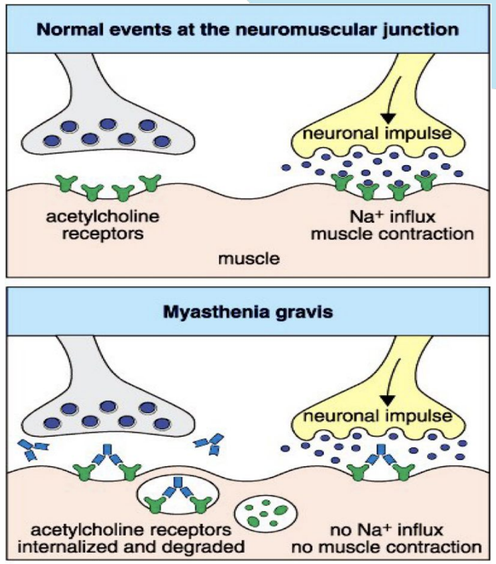
Abnormal State

A person with Graves' Disease makes auto-antibodies to the receptor for TSH.
Binding of these autoantibodies to the receptor mimics the normal action of TSH leading to over-stimulation of the thyroid gland



Organ Specific Autoimmune Diseases

II. Myasthenia Gravis (blocking antibodies)



Cause:

IgG antibody which is directed against (ACh) receptor, interacts with the postsynaptic acetylcholine receptor (AChR) at the nicotinic neuromuscular junction (NMJ).

Outcome:

It leads to a reduction in the number of functional AchR by increasing degradation (complement mediated) of receptors.

Clinical Characteristics :

Weakness and fatigability on sustained effort.

441:

It all starts when a foreign body binds to the Ach receptor instead of Ach itself, so the immune system will release antibodies against this receptor, and then these antibodies will bind to this receptor making it out of function. So now the Ach will no longer be able to attach to its receptor. With fewer receptor sites available, your muscles receive fewer nerve signals, resulting in weakness and inability to contract.

Systemic Autoimmune Diseases

I. Systemic Lupus Erythematosus (SLE)

Definition:

Is the prototype of systemic autoimmune disorder.
(Lupus: is a potentially fatal autoimmune disease)

Characteristics:

Butterfly rash (It becomes worse by exposure to sunlight).

Prevelance and incidence:

Women are 90% more prevalent to the disease.

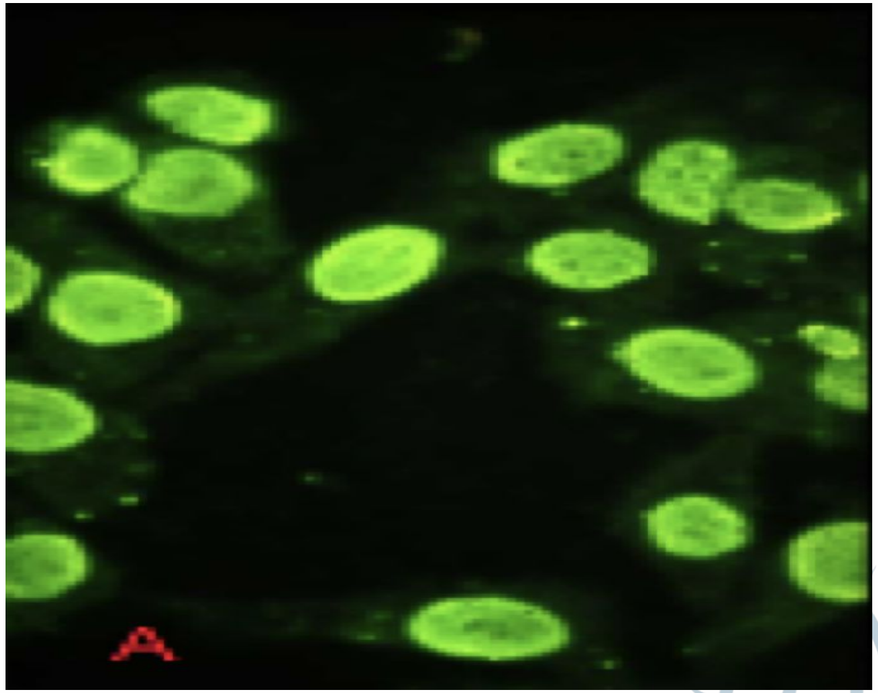
Treatment

- NSAIDs (Non-steroidal anti-inflammatory drugs)
- Antimalarials (Hydroxychloroquine)
- Immunosuppressive agents

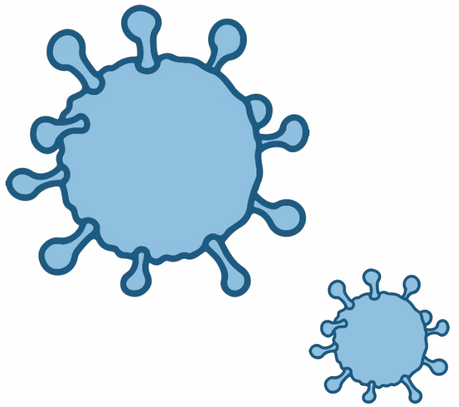
Auto antibodies

- The anti-nuclear antibody (ANA) test is the best screening test for SLE and is determined by immunofluorescence.

- The ANA is positive in significant titer (usually 1:160 or higher) in virtually all patients with SLE.



Other Investigations



01 Anti-double-stranded DNA titers

02 complement levels (CH50 , C3 , C4)

03 Complement Split products.

04 Decreased complement C1q

05 ESR

06 CRP

Significance of Autoantibodies in SLE

Antigen	SLE	Clinical Associations
ds DNA	70%	Nephritis (and flare)
Anti RNP	40%	Scleroderma, myositis
Histones	70%	Drug-Induced Lupus
SM Antigen	30%	Severe SLE
Anti ribosomal P	20%	Psychosis, Depression
Antiphospholipid	50%	Clotting, fetal loss
SSA/Ro	35%	SCLE, Sjogren's, NLS
SSB/La	15%	SCLE, Sjogren's, NLS
Anti neuronal	60%	Active CNS lupus

Genetic + Environment factors

Pathogenic Autoantibodies

-DNA/protein, RNA/protein complexes

Immune complexes

Complement activation

Chemotaxins

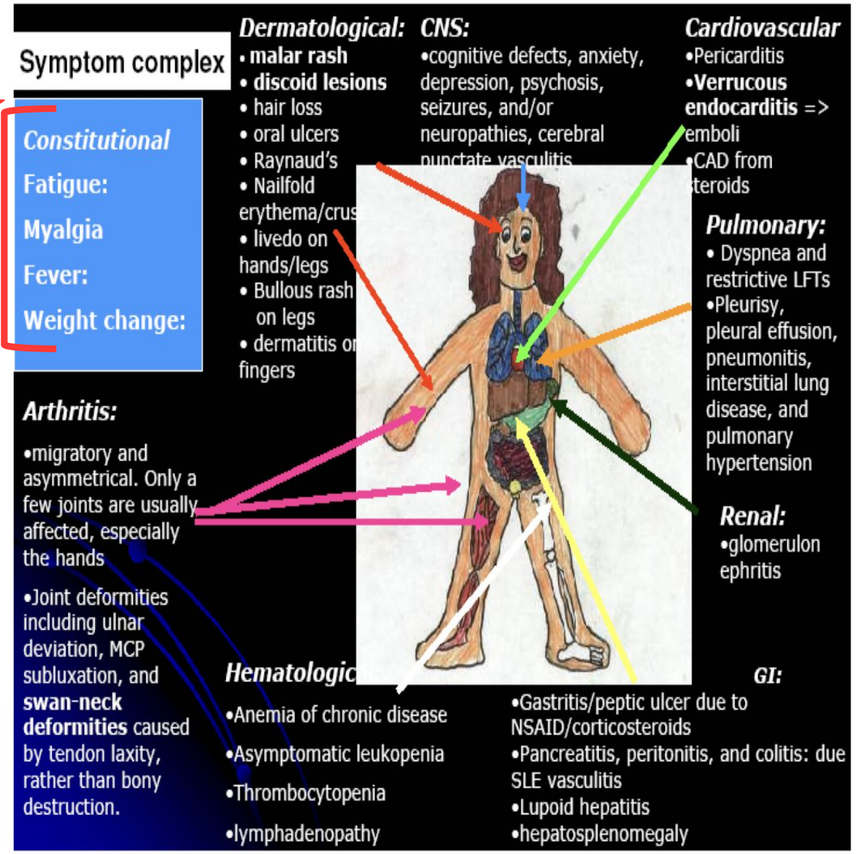
leukocytes

mononuclear cells

Inflammatory factors

IL-4, IL-6 IL-10

Destruction of cells



Systemic Autoimmune Diseases

II. Rheumatoid Arthritis

Definition:

Rheumatoid arthritis is a common autoimmune disease in which the normal immune response is directed against an individual's own tissue, including the Joints,Tendons and Bones.

Result in:

1.inflammation **2**.destruction of tissues **3**.progressive disability **4**.systemic complications (cardiovascular, pulmonary ..) **5**.early death

Prevalence & Incidence:

Both prevalence and incidence are 2-3 times greater in women than in men

Cause:

The cause of rheumatoid arthritis is not known but may be the cause related to :

1.complex interplay among genotype

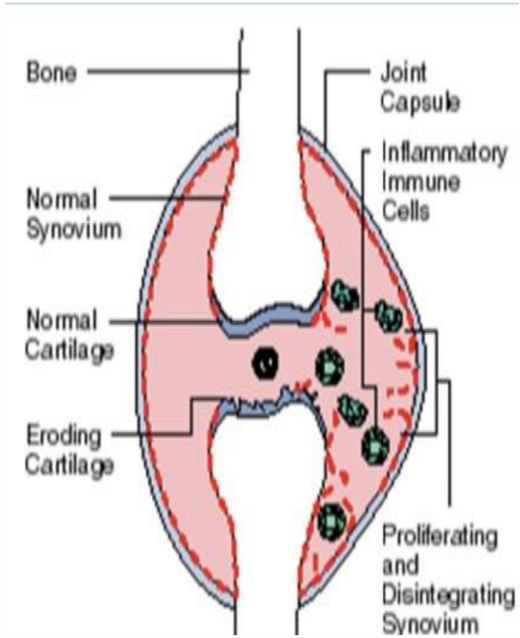
2.environmental triggers.

Genetic factors:

HLA-DR B1 locus alleles that contain a common amino acid motif (QKRAA) in the HLA-DRB1 region, termed the shared epitope, confer particular susceptibility.

Rheumatoid Arthritis cont.

Rheumatoid arthritis (RA) that affects peripheral joints, is characterized by inflammation of the Synovium (Synovitis) that may cause destruction of both cartilage and bone.



Pathogenesis

(Type III hypersensitivity reaction)

Inflammatory cells produce pro-inflammatory cytokines such as : TNF-a , IL-1, IL-6 that induce the secretion of metalloproteinases; Which are known to cause joint destruction.

T cell activation due to unknown antigens also contributes to the inflammation in RA (Rheumatoid arthritis).

There is a lack of tolerance to citrullinated proteins and the appearance of autoantibodies directed against citrullinated proteins.

439:

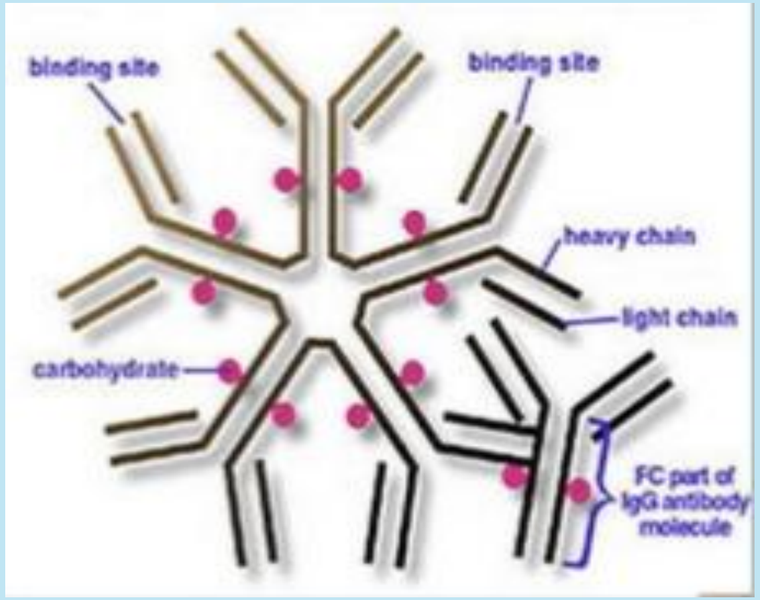
Citrullinated proteins: convert of the amino acid Arginine in a protein into the amino acid Citrulline Immune complex: integral binding of Ab with an antigen Metalloproteinases: cause joint destruction Anti-citrullinated proteins antibodies(ACP): Antibodies that attack the citrullinated proteins

Rheumatoid factor

In many individuals, they produce another group of auto-antibodies known as **rheumatoid factor** that react with determinants in the FC region of IgG.

Such auto-antibodies bind to normal circulating IgG, forming the igM-igG complexes. These complexes may be deposited in joints leading to activation of synovial macrophages (inflammatory cells).

The macrophages engulf the immune complexes and then release TNF and other pro-inflammatory cytokines e.g: IL-1.



The classic rheumatoid factor is an IgM antibody directed against Fc part of IgG.

Diagnosis:

1.Anti-citrullinated protein/peptides (ACP) antibodies / anti-CCP : specific markers.
2.Rheumatoid factor.

Medication:

1.Symptomatic: corticosteroids, NSAIDS (Non-steroidal anti-inflammatory drugs)

2.Disease-modifying antirheumatic drugs (DMARDs)

- Non biologic DMARDs: Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine…

- Biologic DMARDs: anti-TNF, anti-IL6R, anti-CD20..

3.Physical therapy

4.Surgery

Take home message

1. The spectrum of autoimmune disorders is wide ranging from single organ involvement to systemic disease.
2. The disease process is usually prolonged and is generally associated with significant morbidity and mortality.
3. The mainstay of the treatment is to maintain immunosuppression.

MCQs

1- A patient who is diagnosed with Graves (autoimmune disease), which of the following best describe his condition?

A) Under stimulation of thyroid gland (hypothyroidism)

B) IgG is directed against ACh receptor

C) Stimulation of antibodies

2- Which of the following is an indicator of Systemic Lupus Erythematosus?

A) C- reactive protein

B) Decreased complement C3

C) ECG

3- Antibodies directed against the Fc fragment of IgG are called?

A) Cytokines

B) Citrullinated protein

C) Rheumatoid Factor

4- Rheumatoid arthritis (RA) that affects peripheral joints is characterized by inflammation of?

A) Bursa

B) Synovium

C) Tendon

5-Rheumatoid factor forms a complex of which two antibodies?

A) IgM and IgG

B) IgA and IgD

C) IgE and IgM

Q1/ C, Q2/ B, Q3/ C, Q4/ B, Q5/ A

MEET THE TEAM

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