Immunology team - 437

2- Autoimmune Diseases

Objectives :

1. To know that the inflammatory processes in autoimmune diseases are mediated by hypersensitivity reactions (type II, III and IV)
2. To know that autoimmune diseases can be either organ specific or may be generalized involving many organs or tissues.
3. To understand that the manifestations of autoimmune diseases depend upon the organ and the degree of damage inflicted on the target tissues .

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

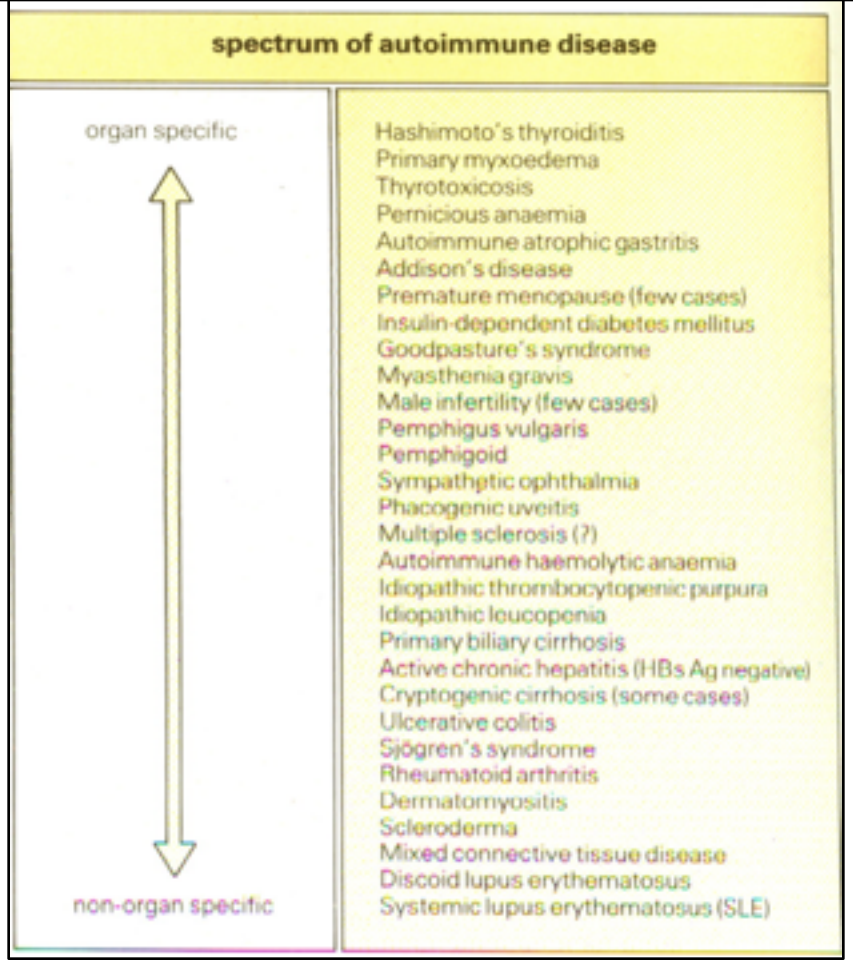
SOME AUTOIMMUNE DISEASES IN HUMANS

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

Causing

Attacks

- Gel and coombs classification of hypersensitivity: type I IgE Ab , type II IgG Ab to tissue, Type III IgG immune complex, type IV CMI.
- Absence of tolerance to self antigen causes autoimmunity.
- Autoimmunity could be targeted (local) or systemic or in between to affect only multiple systems.
- Tolerance central and peripheral : and relation to IL-10(???) .
- Addison`s disease causes loss of function of adrenal gland.
- For every autoimmune disease there`s self antigen and the immune system reacts to that by an immune response.
- The autoimmunity could either inhibit or activate (stimulate).
- Systemic diseases are important.



First disease and last disease the thing to note here is that terminal diseases are clearly either organ specific or non-organ specific

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

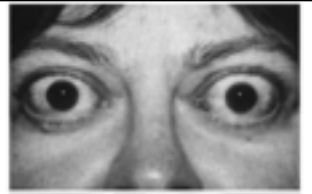
Multiple Organs, Musculoskeletal System
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Polymyositis, dermatomyositis
Ankylosing spondylitis
Sjogren's syndrome

It's important to know which systems are targeted by diseases

Organ Specific Autoimmune Diseases

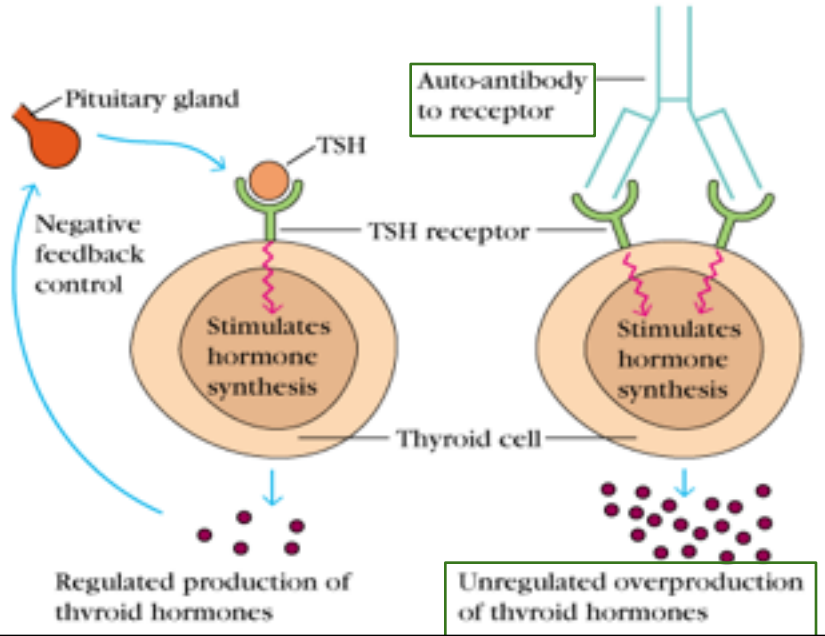
(Mediated by stimulating or blocking autoantibodies)

1. Graves' Disease (Thyrotoxicosis) [stimulating antibodies]



Exophthalmos (prominence of eyes)

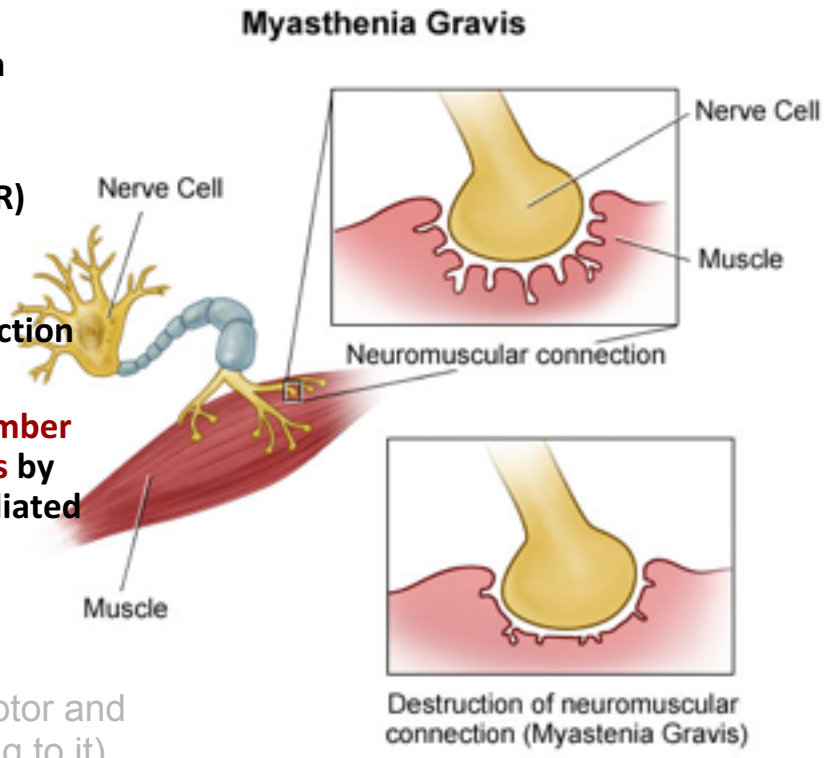
Normal State	Graves' Patient
• Production of thyroid hormones is regulated by thyroid-stimulating hormones (TSH) • The binding of TSH to a receptor on thyroid cells stimulates the synthesis of two thyroid hormones: 1. Thyroxine(T4) 2. Triiodothyronine(T3)	• A person with Graves' Disease makes auto-antibodies to the receptor for TSH. • Binding of these auto-antibodies to the receptor mimics the normal action of TSH leading to over-stimulation of the thyroid gland (يكون أجسام مضادة عملها شبيه بعمل الهرمون فتعمل عمله ويكون الانتاج مفرط)



Symptoms: Exophthalmos (prominence of eyes), tremors of hand, excessive weight loss, intolerance to heat.
Diagnosis of this disease is by testing serum: (decreased) TSH, (increased) T4.

2. Myasthenia Gravis [blocking antibodies]

- **Clinically characterised by weakness and fatigability on sustained effort**
- **Antibodies directed against acetylcholine receptor (AChR)**
- **IgG Ab interact with the postsynaptic AChR at the nicotinic neuromuscular junction (NMJ)**
- **There is reduction in the number of functional AChR receptors by increasing complement mediated degradation of receptors**



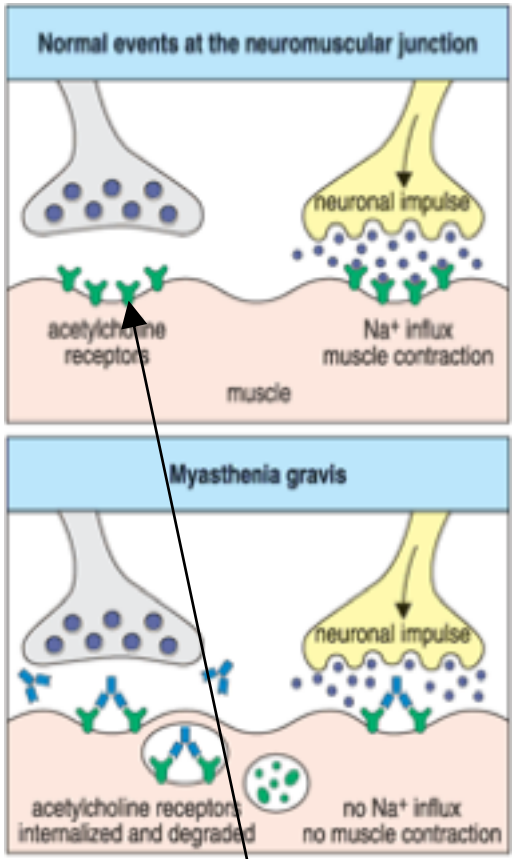


Fig 13.10 © 2001 Garland Science

(The antibodies block the receptor and prevent the agonist from binding to it)

Motor end-plates of muscles

Systemic Autoimmune diseases

I. Systemic lupus erythematosus (SLE)

- **Systemic lupus erythematosus is the prototype of systemic autoimmune disorder**
- **The characteristic "butterfly rash" is made worse by exposure to sunlight**
- **Lupus is a potentially fatal autoimmune disease**

- (Some of notes below are not related only to this slide)
- This autoimmune disease follows the III type of hypersensitivity,it is the classic picture of an autoimmune disease.
- Important butterfly rash.
- Predominant in females.
- All immune diseases are idiopathic.
- Normally all contents of cell are isolated from immune system
- Apoptosis leads sometimes to incomplete breakdown of self antigen(for example self DNA) and the immune system mistakenly makes auto-antibodies to it are thus (sensitized) the second time it comes into contact to that self antigen it starts the immune response.

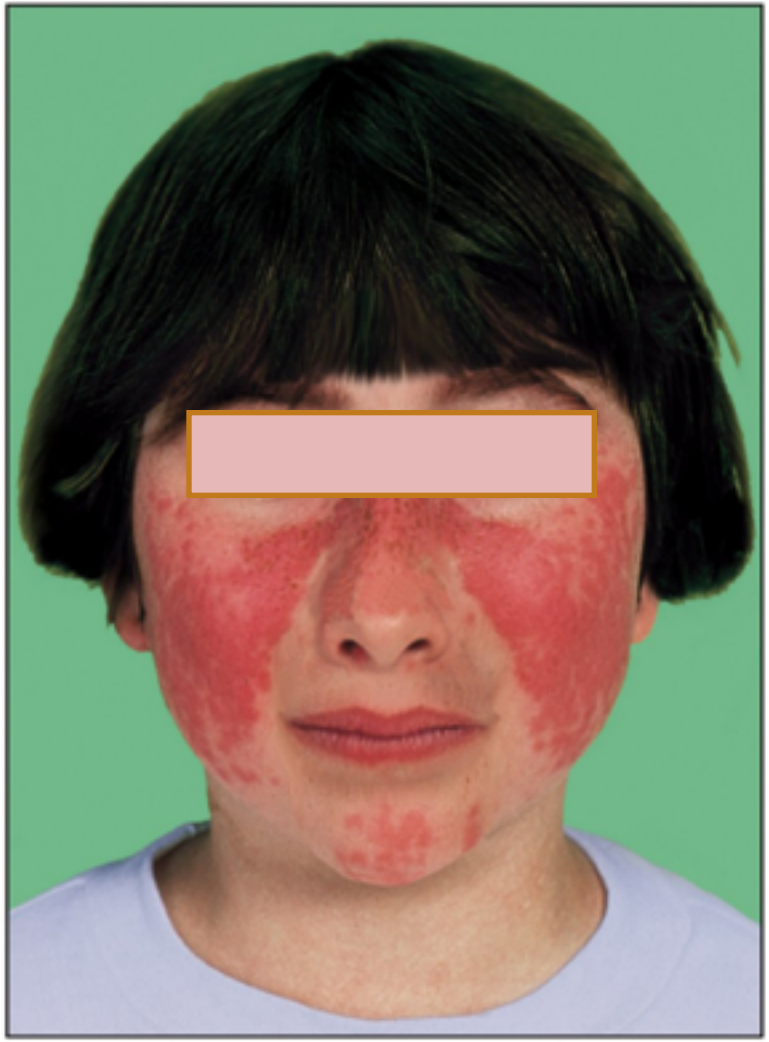
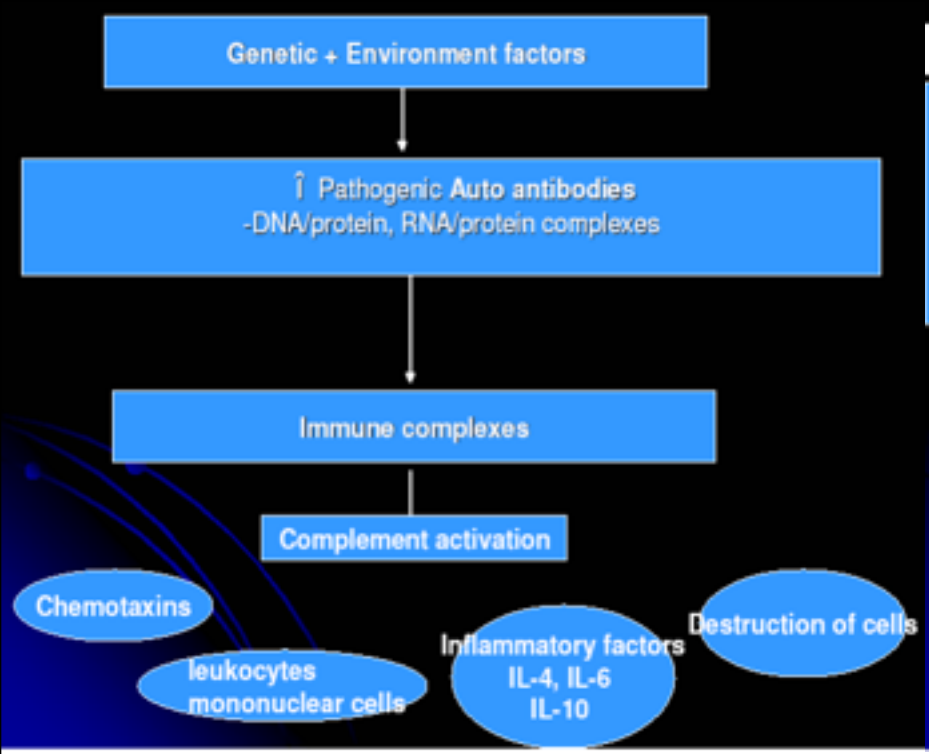
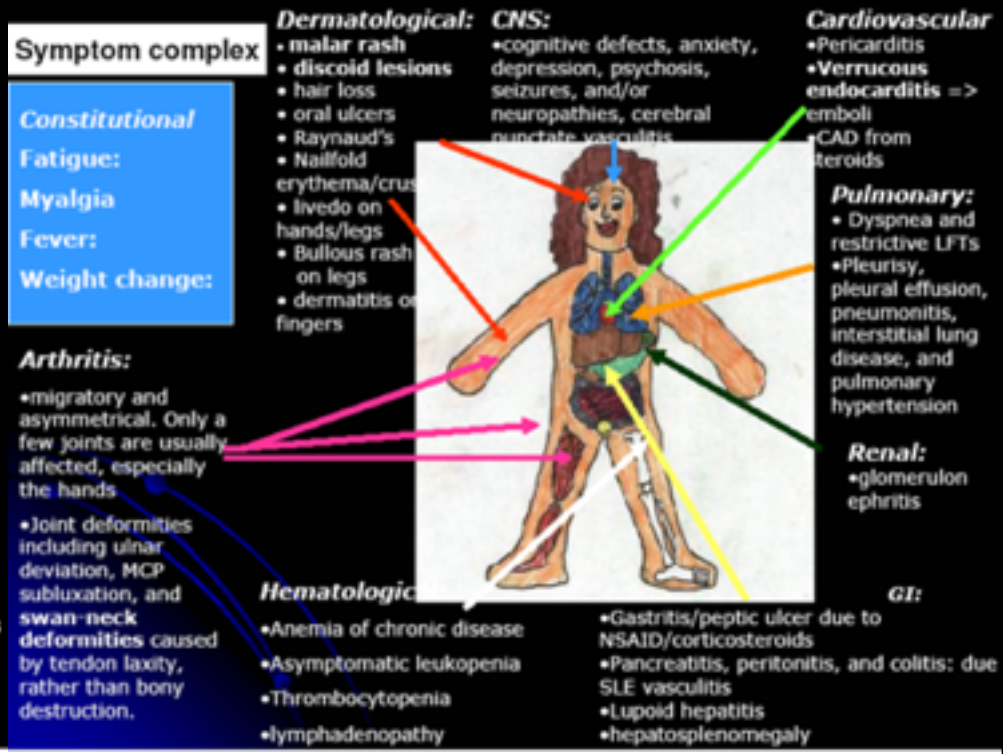


Figure 13.11 The Immune System, 3ed. (© Garland Science 2009)



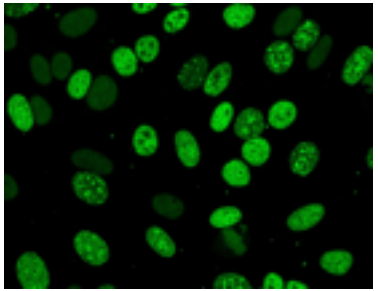


Autoantibodies

- **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**

- It's important to know which systems are affected.
- Immune diseases could have random symptoms.
- Sun or light hypersensitivity resulting from photosynthetic reactions.

Immunofluorescence



Other investigations

- Anti-double-stranded DNA titers
- Complement Levels (CH50, C3, C4)
- ESR
- CRP
- Complement Split products
- Decreased complement C1q

Treatment

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

- Those above in addition to clinical presentation will help confirm the diagnosis especially ds DNA)

The following are important:

- anti ribosomal.
- Histones (Drug induced SLE)
- ds DNA

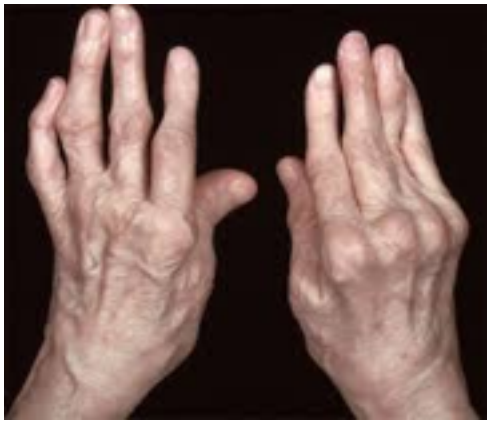
Significance of Autoantibodies in SLE

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	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

Red:important b\c high percentage
Blue: mentioned by doctor, histones are drug induced SLE

2. Rheumatoid Arthritis (RA)

- 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
- Bones



(Picture shows ulnar deviation)

Rheumatoid arthritis resulting in:

- **Inflammation**
- **Destruction of these tissues with progressive disability**
- **Systemic complication (cardiovascular, pulmonary)**
- **Early death**

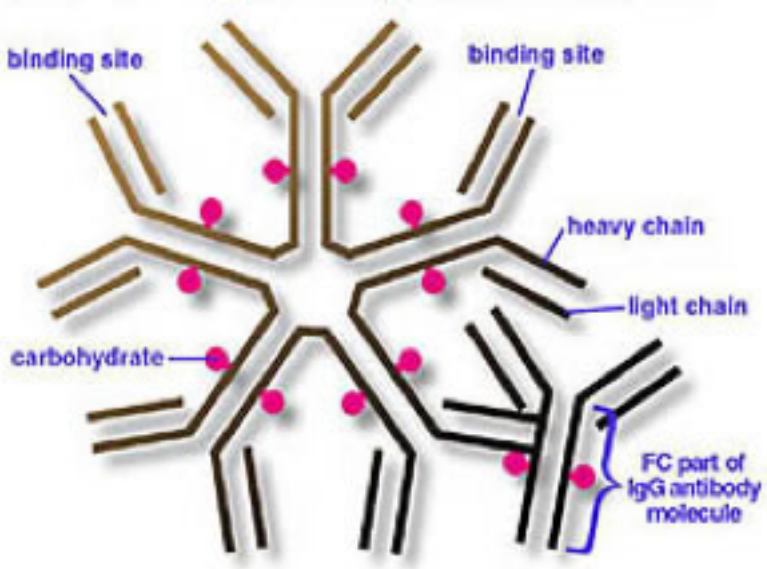
- The cause of rheumatoid arthritis is not known: complex interplay among genotype, environmental triggers.
- Genetic factors: HLA-DR B1 locus alleles that contain a common amino acid motif (QKRAA) in the HLA-DRB1 region, termed the shared epitope, confer particular susceptibility.
- Rheumatoid arthritis (RA) affects peripheral joints is characterized by an inflammation of the synovium(synovitis) that may cause destruction of both cartilage and bone.

- The prevalence and incidence are 2-3 times greater in women than in men.
- This disease resembles Type III hypersensitivity (SLE).
- Repeated attacks of rheumatoid arthritis results in total destruction of joints especially small joints in hands and they become fibrotic and thus cripple.

Pathogenesis

(Type III hypersensitivity reaction)

- **Inflammatory cells produce proinflammatory cytokines/ TNF-α, IL-1 that induce the secretion of metalloproteinases** (has a role in remodeling cytokines & chemokines & extracellular remodeling enzymes.)**; which are known to cause joint destruction.**
- **T cell activation due to unknown antigens also contributes to the inflammation in RA.**
- **There is a lack of tolerance to citrullinated proteins and the appearance of autoantibodies directed against citrullinated proteins.** (Anti-citrullinated protein antibodies (ACPAs) are autoantibodies to an individual's own proteins they are directed against peptides and proteins that are citrullinated. They are present in the majority of patients with rheumatoid arthritis.)
- **In rheumatoid arthritis, many individuals produce another group of autoantibodies known as rheumatoid factor.**
- **These antibodies react with determinants in the Fc region of IgG.**
- **Such auto-antibodies bind to normal circulating IgG, forming IgM-IgG complexes which may be deposited in joints.**
- **This leads to activation of synovial macrophages**
- **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

- **Anti–citrullinated protein/peptides(ACP) antibodies/ anti-CCP: specific markers**
- **Rheumatoid factor**

Medications

- **NSAIDS (Non-steroidal anti-inflammatory drugs)**
- **Disease-modifying drugs (eg, gold, hydroxychloroquine, sulfasalazine, penicillamine)**
- **Immunosuppressive therapy:**
  - **Corticosteroids**
  - **Methotrexate**
- **Surgery**
- **Physical therapy**
- ACP more specific for RA
- Disease modifying drugs (antimalaria) used to block antigen presentation?

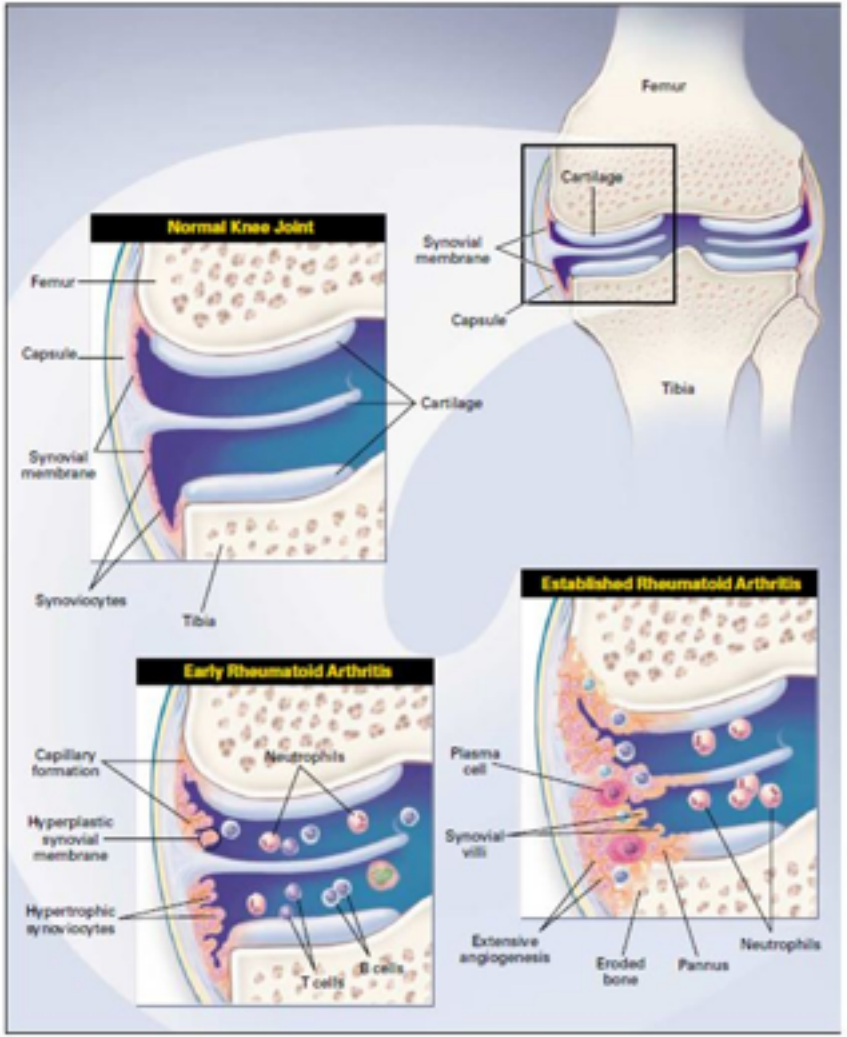


Figure 1: Pathogenesis of Rheumatoid Arthritis (Choy 2001)

Take home message

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

MCQ

1-Rheumatoid Arthritis Is more prevalence in ?
A-men B- women * C- elders D- innate
2-What is the main cause of Rheumatoid Arthritis ?
A- low level of Ca B- high level of Ca C-bacteria D- idiopathic *
3-What is the amino acid pattern found in the HLA-DR B1 locus alleles ?
A-QRKAA B-QKRAA* C-QAARK D-QARKA
4-What type of antibodies interacts with postsynaptic receptor ?
A- IgG B-IgM C-IgA D-IgD

1-B
2-D
3-B
4-A

SAQ

1-What's the main characteristics found in the Rheumatoid Arthritis in peripheral joint and what does it cause ?

2-what is the type of autoimmune diseases ?

3-give 4 example of autoimmune disease affecting system?

4-organ specific autoimmune disease mediated by two type of antibodies, what is them ?

5-The characteristic "butterfly rash" in Systemic lupus erythematosus is made worse by ?

6-mention 4 type of SLE investigation

Team members :

١- العنود المنصور
٢- غادة الحيدري
٣- شيرين حمادي
٤- العنود المعيثم
٥- غادة الحناكي

1. صالح المعيقل
2. عبدالله العمر
3. عبدالرحمن العوجان
4. فهد الفايز
5. محمد المعيوف

Team leaders :

رهف الشمري

عبدالعزيز الضرغام