22

Immunology

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Sheet Slides

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Hypersensitivity reactions 2

At the beginning let's take a quick revision about the types of HSR :

- **Type 1** (immediate type) : it's IgE mediated.
- **Type 2** (Ab (antibody) mediated): usually it's related to autoimmune diseases and drug reactions. It can result from the binding of Ab to Ag (antigen) on cells and tissues.
- **Type 3** (immune complex (Ab-Ag) mediated) : circulating (soluble) immune complexes of Ab-Ag.
- **Type 4** (cell mediated) involving T cells and macrophages, it's a delayed one.
- **Type 5** subtype of type 2: the binding between Abs and receptors on the cells will stimulate or inhibt these receptors which will lead to change in the cell's function.

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We had already talked about allergic reactions and asthma which are examples of type 1 hypersensitivity reactions (HSR).
Today we are going to continue about the third example of type one hypersensitivity reaction which is **ANAPHYLAXIS**.

ANAPHYLAXIS

Anaphylaxis is **a systemic** type 1 (IgE-mediated, immediate) HSR. It happenes by the administration of allergens (the antigen that is responsible of type one hypersensitivity reaction) **directly into the blood** ,usually these allergens are drugs like(antibiotic; penicillin) or insects bite which are the most common cause of anaphylaxis.

what makes anaphylaxis reaction more dangerous than other types of allergy is its ability to develop rapid shock (anaphylactic shock) because the allergens go directly into the blood.

Other types of allergy are localized (the symptoms exist locally) and it could be managed

We have already said that anaphylaxis happens due to the direct administration of allergen to the blood but in some cases it happens by the administration of allergen through GI such as eating Peanuts.

Patients who have a history of anaphylactic reaction carry **EpiPen**(pen means injection and epi is related to epinephrine), they inject themselves by this drug because the epinephrine causes constriction for the vessels to retain the blood in it.

The word anaphylaxis is recognized and feared by most health care providers because of its association with potential death from cardiovascular collapse or asphyxiation caused by laryngeal edema.**So, How do they discover an anaphylaxis reaction??**

Scientists tried to make a vaccine (prophylaxis) to certain toxins, so they give a dog dose of certain vaccine ;nothing happened.Then after two weeks they injected it with another dose (supported dose), the dog showed swelling, skin reaction and it died after short period of time. Because the result was the opposite of expectation they named it anaphylaxis.

But, why we didn't recognize all these changes after the first injection ??

As with other exampls of type I HSR, the first exposure to an allergen in genetically predisposed individuals will lead to priming (sensitization), that's why the dog didn't die after the first injection.

REMEMBER :

Re-exposure to the same allergen systemically will cause the cross-linking of IgE that are bound to its high-affinity receptors on mast cells and subsequent release of inflammatory mediators including histamine.

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We are done with clinical conditions related to type 1 HSR , but as a doctor how can you know if the patient has an allergy ??
It will be done by **Allergy testing**

Allergy testing

The exam can be in the form of a **skin test,** checking for immediate **allergic** reactions to many different substances (allergens) at once.

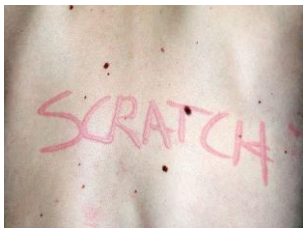
Divide the skin into parts as in the picture ⟶ Inject each part with specific allergen ⟶ If there is a swelling (raised lesions) that means this patient is allergic to this substance.

Regarding to the test :

- The substances differ from one region to another according to the environment and they may differ from one hospital to another.
- We can measure the swelling after short time because it's an immediate type HSR.
- Allergy testing- characteristic skin lesion wheal and flare , wheal means how much there is swelling, flare means redness on the skin.
- To ensure the validity of your skin testing results, it is important to include adequate controls to see if the patient is reacting appropriately to the procedure and the substances weren't prepared wrongly.

Prior to allergy skin tests, a **positive histamine control** test and a **negative saline control** test may be performed. **A positive control test** is used to determine if the patient reacts to histamine. If the patient does not immediately react to histamine, the results of allergy skin tests can be difficult to interpret. **A negative control test** involves applying a saline solution that does not include any allergens. Patients who react to this solution may have skin that is too sensitive to allow correct interpretation of allergy skin tests.

- patients with sensitive skin **(dermatographia sometimes called "skin writing,)**, can produce false positive results on a skin test, reducing the test's reliability.



dermatographia is another example of flare and wheal characteristic skin lesion.

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Management of Allergy

- **General measures include the identification of the culprit allergen and its avoidance.**
- **Drug treatment:** aims at blocking the effect of allergy inflammatory mediators (e.g. antihistamines, β2-adrenergic agonists as salbutamol which cause bronchodilation, epinephrine) these are examples of **symptomatic treatment**.
- **Topical steroid (anti-inflammatory):** it's important in delayed phase because of the recruitment of inflammatory cells including (eosinophils)and inflammatory mediator.
- **Sodium cromoglycate:** reduces mast cell degranulation that is responsible for symptoms.
- **Desensitization (immunotherapy):** It aims to improve allergy symptoms caused by a specific allergen. Allergen is injected subcutaneously in escalating doses (small dose that increase with time) to induce tolerance (possible mechanisms include induction of T_{H1} response or induction of T_{reg} response that inhibits the polarized T_{H2} response).
  The dose and the route of administration they determine if the allergy happens or not, so we try to change both of them to reach the desensitization.

We have covered type 1 HSR. So, let's start with type 2 HSR :

The doctor said that we should know the main concept, mechanism of injury and the manifestation and each disease from any type of HSR.

Ab mediated HSR (type 2)

Type II HSRs are initiated by the interaction of Abs **(IgG or IgM)** with cell membranes or extracellular matrix (ECM) components.The Ags can be self (cause an autoimmune disease) or exogenous molecules (nonself) that are adsorbed to membranes or ECM.

REMEMBER:
IgE related to Allergic reaction

- Abs against cells or tissues Ags tend to be **specific** (i.e. affecting the cells or tissues where the Ag present, causing **Organ-specific autoimmune disease** especially when it is autoantigen), not like type 3 HSR (circulation immune complexes) where the disease manifestations are systemic.

- Example of antigen adsorbed into certain cells is **penicillin**: it can bind to red blood cells, causing them to be recognized as foreign, B cell start to proliferate and antibodies(IgG and IgM) against the drug are produced. IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation to eliminate cells presenting foreign antigens (which are usually, but not in this case, pathogens).

  - **Penicillin can make ALL types of HSR (1/2/3/4).**

Tissue damage can occur through

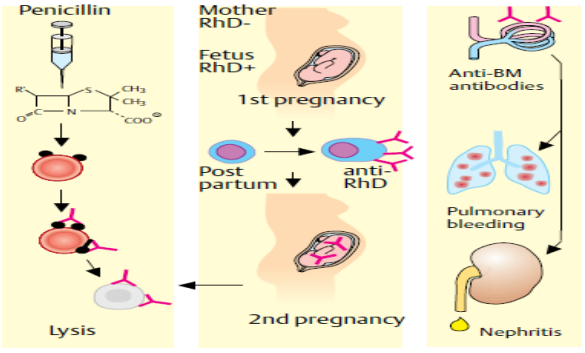
1- activation of the complement system :

IgM is a strong complement activator because of the high avidity (the collection of affinity).
IgG also has complement-fixing ability (activation) but less than IgM.
The subclass of IgG has different complement-fixing ability and the strongest one is IgG_3 followed by IgG_1 but also IgM is stronger than them.

When IgG binds, it can make cell injury by another mechanism like :

ADCC (antibody-dependent cellular cytotoxicity): by using natural killer cells which can destroy the cells that have IgG by ADCC.

2- phagocytosis with the Abs acting as opsonins.



Type II: Cytotoxic antibody reactions

The most common example related to type 2 HSR is :

Immune mediated hemolysis

Antigens of the ABO and Rh (C, D and E) systems are termed “alloantigens”, i.e. these Ags might differ from person to person and this variation caused by the variation of alleles. For example, there are more than one allel related to ABO system but in our body we have just 2 allels .
EXTRA INFORMATION: the alleles related to ABO system are (I^A ,I^B ,i) , If your blood is type A ,you may have (I^AI^A or I^Ai) in your body.

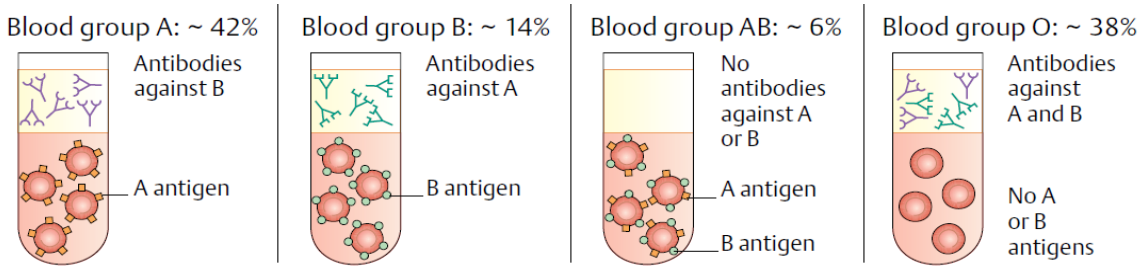
there are more than 20 types of antigens that exist on RBC and we can use them to categorize the blood. **In blood transfusion**, the most important system is ABO system, we have also Rh system.

ABO system: The people with type A blood have N-Acetylgalactosamine as a terminal sugar, type B people have galactose, type O don’t have an antigen on cell surface.
the person who has type A blood has anti B naturally (Their natural occurrence is likely due to the ubiquitous presence of identical epitopes in a variety of microbes), so when we give him type B blood, the IgM antibodies will bind to the antigens on RBCs of the donor causing extensive hemolysis and produce bilirubin (very toxic make shutdown for kidney and tubular necrosis within short period of time (hours)).

REMEMBER:
- If there is a carbohydrate antigen, B cells type1 will produce IgM.
- we have two types of B cells :

type 1 (independent T cell): which produces Natural antibodies and doesn’t need T cell because there are enough repetitive carbohydrate structures that can collect enough BCRs to activate the cell and produce antibodies.
type 2 (dependent T cell): they circulate in the blood all the time and they need T cell to give enough activation signal to produce antibodies.

Rh system: Anti-Rh Abs arise upon exposure to Rh Ags in individuals lacking these Ags, and are of the IgG type(because Rh antigen is protein) which coat the erythrocytes and recognized by Fc receptors on the splenic and hepatic resident macrophages.
Can do reaction but IgG weaker than IgM so it will not be as strong as in ABO.



A. The ABO blood group system

Alloimmunization against Rh antigens

Maternal alloimmunization occurs when a woman's immune system is sensitized to foreign erythrocyte surface antigens, stimulating the production of immunoglobulin G (IgG) antibodies.

If you are Rh-negative(d), your red blood cells do not have a marker called Rh factor on them. Rh-positive(D) blood does have this marker. If your blood mixes with Rh-positive blood, your immune system will react to the Rh factor by making antibodies to destroy it. **This immune system response is called Rh sensitization**.

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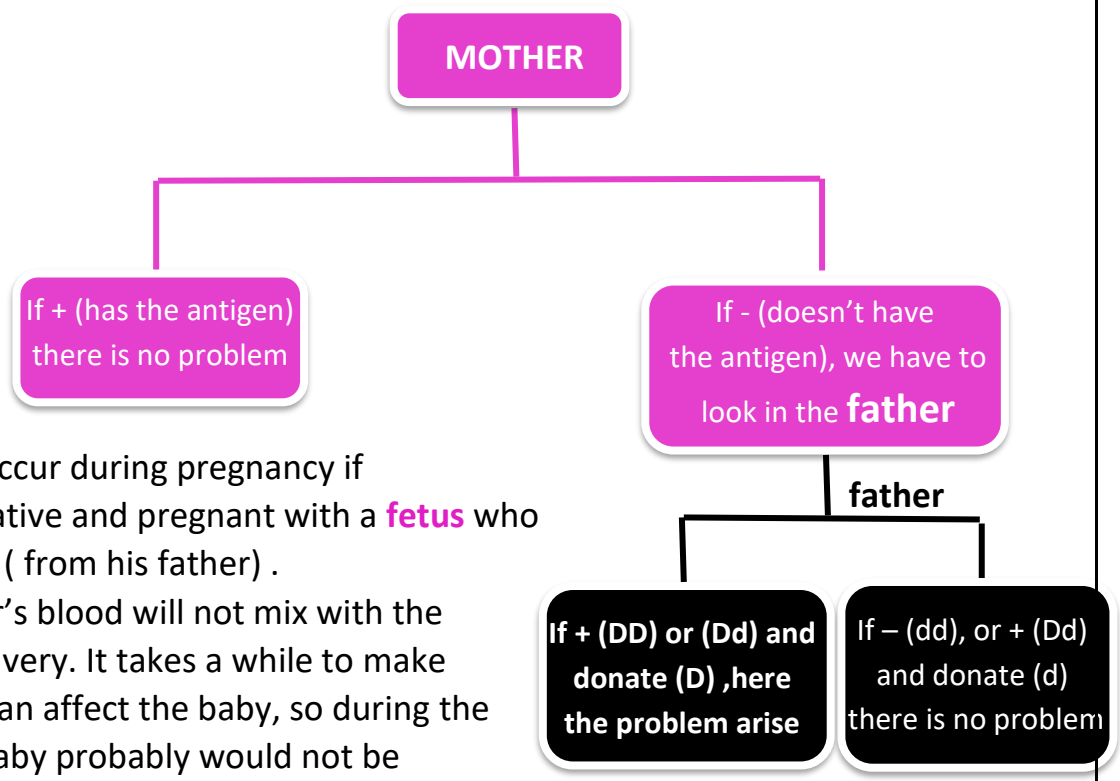
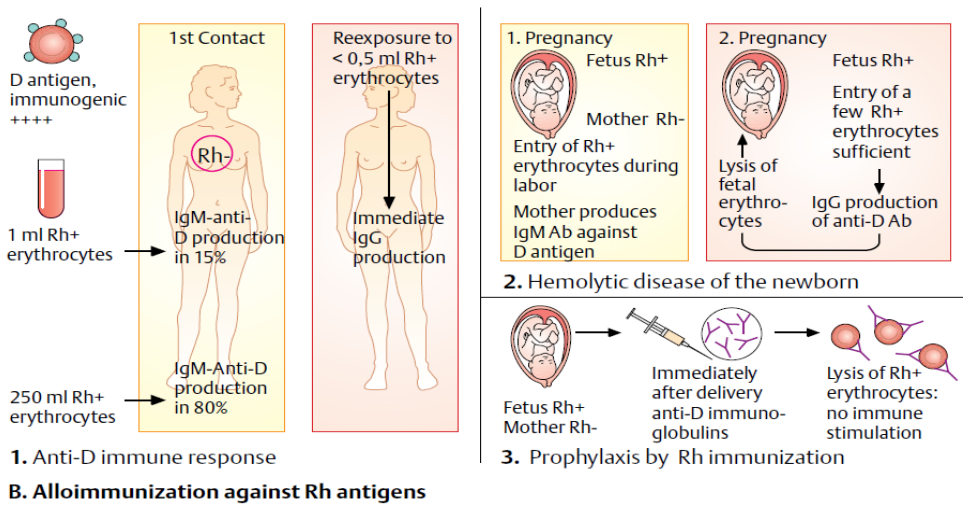
During pregnancy:



Rh sensitization can occur during pregnancy if the mother is Rh-negative and pregnant with a **fetus** who has Rh-positive blood (from his father) .

In most cases, mother's blood will not mix with the baby's blood until delivery. It takes a while to make antibodies(IgG) that can affect the baby, so during the first pregnancy, the baby probably would not be affected.

but if she gets pregnant again with a rh-positive baby, the antibodies already in her blood cross the placenta bind to the antigen that will attack the baby's red blood cells and cause hemolysis.



B. Alloimmunization against Rh antigens

Other diseases: (auto antigen)

Goodpasteur's syndrome (autoimmune disease): Auto-Abs are synthesized against **type IV collagen** present in the basement membranes of the kidneys and lungs.The tissue damage will be manifested clinically in hematuria , proteinuria and pulmonary hemorrhage. The diagnosis depends on detection of the Ab in the serum (indirect) or in tissue biopsy (direct immunofluorescence test).

Pemphigus vulgaris(common): A skin disease characterized by bullae(more than 1 cm). The auto-Abs are directed against **desmogleins** of the tight junctions in the skin. In epidermis between the cells give shape as a net. The diagnosis depends on detection of the Ab in the serum (indirect) or in tissue biopsy (direct immunofluorescence test).
There is another autoimmune disease called Bullous pemphigoid attacks the basement membrane so it will give basement membrane fluorescence.

Myasthenia gravis: An autoimmune disease that is characterised by muscle weakness and fatigue, mostly come with what we called ptosis (A drooping eyelid), it develops with time; start normall and then the muscle get fatigue. The name was derived from Greek language and means (myo: muscle, asthenia: weakness) and the Latin language (gravis: serious). Clinically, myasthenia gravis manifests with fluctuating fatigability and weakness affecting a variety of muscle groups (type V).

Graves disease: (type V HSR): Auto-Abs specific for TSH receptor mimicking the stimulating effect of the hormone can cause the disease without tissue damage. It causes hyperthyroidism (the condition that occurs due to excessive production of thyroid hormone by the thyroid gland).In type 5 we don't have a huge tissue damage, we have an effect on the function.

Wegener's granulomatosis(granulomatosiswith polyangiitis): Vasculitis caused by auto-Abs against **proteinase 3** that is present in PMNs (the Abs are termed cytoplasmic anti neutrophil cytoplasmic Abs [c-ANCA]). c-ANCAs activates PMNs and cause degranulation with subsequent damage of endothelial cells.

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Immune complexes HSR (Type III)

Immune complexes are lattices of Abs and with its cognate Ags. The physiologic function of immune complex formation is to facilitate the clearance of Ags by phagocytes. However, the presence of large numbers and networks of immune complexes can lead to tissue damage.
Failure of the immune mechanisms to clear immune complexes due to ongoing excessive production (e.g. chronic antigenemia), will end up in activating the complement system and recruiting leukocytes with ensuing inflammation and tissue damage.

Immune complex deposition is most likely where there is high blood pressure and turbulence (e.g. glomerular capillaries).
Deposited immune complexes can be visualized using immunofluorescence which aids in diagnosis.

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Some diseases related to type 3 HSR :

Systemic lupus erythematosus (SLE): The most common prototypic autoimmune disease characterized by the production of Abs to components of the cell nucleus in association with a diverse array of systemic clinical manifestations. The name comes from the malar rash also called butterfly rash which is a medical sign consisting of a characteristic form of facial rash. The autoantigen is nuclear antigens including DNA.

There are a set of 11 criteria if the patient has 4 of them, he is diagnosed as SLE patient. It's not necessary for the 4 to appear at one time, they may appear sequentially, so you can diagnose it based on 3 criteria but you have to wait for the fourth one to appear.
ANA (antinuclear antibody) is one of these citeria, nearly there is **no** patient with SLE will have negative ANA.
ANA test will be (+) in all SLE patients even if antiDNA antibody test is (+ or -). AntiDNA antibody test is (+) in 60% of the patients.
ANA is the first screening test for SLE and other systemic autoimmune disease, if it's positive we have to specify the antigen to know the specific disease.

Poststreptococcal glomerulonephritis:
Glomerulonephritis streptococcal Ags with biochemical affinity for glomerular basement membrane, will result in circulating immune complexes, and activation of complement. after the resolution of symptoms the infection ends , but the presence of autoimmune generation of Abs that react with similar Ags present in kidney will produce the disease, it won't stay for long time (self limited disease)prognosis by fever.

GOOD LUCK ❀

REMEMBER:
Group A strep pyogenes have supuritive and non supuritive complications .
from non suppurative complications we have :
- rheumatic fever associated with funingities
- skin infection associated with