Medical Immunology

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Lecture – 17 -

Ω Autoimmune Diseases:

- **Disease Association with certain HLA alleles (Relative Risk):**

- There are certain HLA molecules that if a person possesses them, then this person is more likely to develop a certain autoimmune disease than other people who don't have these molecules.

- This disease association is known as *Relative Risk*. So if you have a relative risk of 100 then you're at a high risk of developing an autoimmune disease, while if you have a relative risk of 4, then you're not at risk of developing an autoimmune disease.

- **Mechanism of disease association:**
  A. The HLA molecule itself may present self-antigens in an abnormal way (however, this might not be 100% true).
  B. Linkage disequilibrium (i.e. it's a gene that's inherited with the haplotype, and this is the gene that causes the disease).

  For example: Ankylosing Spondylitis is associated with HLA-B27, but not everyone who has HLA-B27 is going to actually develop the disease.
  Other examples :
  Rheumatoid arthritis is associated with DR4
  Insulin dependent diabetes mellitus is associated with DR3 and DR4 and having both of them Together increases the Risk of having DM-1

- **Examples on Autoimmune Diseases:**

- There's a spectrum of autoimmune diseases; ranging from organ-specific (where only one organ or one tissue is affected) to systemic (where many organs are affected).

Organ-Specific:
An example is *Pernicious Anemia*: megaloblastic anemia due to vitamin B12 deficiency, and it only affect the RBC's or the vertebral column.
It's caused by destruction of the parietal cells in the stomach.

Systemic:
An example is *Systemic Lupus Erythematosus*: many organs in the body are affected (kidneys, brain, eyes, skin, joints, etc).

Also, there are some diseases where only two or three tissues are affected .

- **Mechanism of Autoimmunity:**
    1. Antibody mediated: easy to detect.
    2. Cell mediated: hard to detect.

Some autoimmune diseases can be mediated by antibodies only, others by cells only, and others are mediated by both.

➢ **Antibody Mediated Autoimmune Diseases:** (auto- antibodies production)

1. Autoimmune Hemolytic Anemia:

- In this disease, *antibodies* against the membrane of the RBCs are produced, and this will cause hemolysis.

2. Autoimmune Thrombocytopenic Purpura:

- In this disease, *antibodies* against the membranes of platelets are produced, so the number of platelets will drop (thrombocytopenia) and you will get bleeding (purpura).

3. Pemphigus Vulgaris:

- This is a condition of the skin; where there's formation of bullae (swellings) full of water (serum) in the skin.
- In this disease, there will be production of *antibodies* against the intercellular junctions between the keratinocytes, so these junctions will be destroyed.

4. Vasculitis caused by ANCA:

- ANCA: Anti-neutrophil cytoplasmic antibodies.
- *Antibodies* against the neutrophilic granules proteins.
- During an inflammation particularly, ANCA will be produced, they will attack the neutrophilic granules, and this will lead to:
    1. Inflammation of blood vessels.
    2. Vasculitis.
    3. Involvement of the skin and kidneys.

5. Goodpasture's Syndrome:

- *Antibodies* against the basement membrane of the kidneys and lungs are produced.
- This disease will be associated with:
    1. Coughing blood (Hemoptysis).
    2. Passing blood in the urine (Hematuria).
    3. The inflammation can lead to renal failure.

6. Acute Rheumatic Fever:

- *Antibodies* against the M-protein of streptococcus pyogens are produced, and they will cross-react with antibodies in the endocardium causing inflammation of the heart and valves, leading to their stenosis and fibrosis.

7. **Myasthenia gravis:**

- *Antibodies* against the acetylcholine receptors of muscles are produced. If this happens, then the receptor will be blocked, Ach cannot transmit the nerve impulse to the muscles, so the muscles cannot contract leading to **weakness** of the muscles and paralysis.
- It's often associated with thymoma.
- The most distinctive feature of MG is: **ptosis** (weakness of the levator palpebrae superioris muscle).

8. **Grave's Disease (Hyperthyroidism):**

- *Antibodies* that stimulate the TSH receptor are produced (TSI – Thyroid Stimulating Immunoglobulin); so it's as if the antibodies work like TSH.
- The thyroid gland will be continuously stimulated, produces lots of the T3 and T4, so you will end up with **Thyrotoxicosis**.
- You can have other antibodies with graves disease: anti-microsomal antibodies, and antithyroid peroxidase antibodies.

9. **Insulin Resistant Diabetes:**

- *Antibodies* against insulin receptors are produced, so the insulin receptor will be blocked and it will not be able to interact with insulin properly, so the patient becomes resistant to exogenous and endogeous insulin.

10. **Pernicious Anemia:**

- *Antibodies* against the parietal cells of the stomach or against the intrinsic factor itself are produced.

11. **Systemic Lupus Erythematosus (SLE):**

- A ***variety*** of *Antibodies* are produced; many of them are directed against the nucleus (anti-nuclear factors), but there are other antibodies produced.
- It affects many tissues.

- **Cell Mediated and Antibody Mediated Autoimmune Diseases:**

1. Type I Diabetes:

- There's *cell-mediated* injury to the islets of Langerhans in the pancreas.
- There are *antibodies* directed towards insulin.

2. Rheumatoid Arthritis:

- *Cell-mediated* pathology; where cells infiltrate the joints and make them inflamed, thus causing pannus formation.

- There are *antibodies* produced:
  1. Rheumatoid factor (IgM against IgG):
     If you have rheumatoid arthritis with rheumatoid factor then you are sero-positive (about 70-80% of patients are seropositive).
     If you don't have rheumatoid factor, then you are sero-negative.

  2. IgA or IgG rheumatoid factors. (against IgG)

  3. Anti–citrullinated protein antibodies:
     During the breakdown and the inflammation in the body, the arginine in some proteins can be converted to citrulline (an Amino acid) under enzymatic effects, so this protein becomes foreign, and this foreign protein causes production of antibodies.
     It's an *excellent diagnostic indicator* for the diagnosis of Rheumatoid Arthritis.

3. Multiple Sclerosis (MS):

- *Antibodies* against the myelin sheath (MBP - Myelin Basic Protein) are produced.
- *Cell-mediated* injury by T_{H17} cells that produce IL-17 that promotes autoimmunity.
- Antibodies may be found in the CSF.

- The End of Part 1–

Done By: Sally Al-Khateeb.

Hypersensitivity

► It's defined as an immune response (normal when it comes to the nature of antibodies and immune cells// abnormal when it comes to its mechanism, because either it's produced by things that are not harmful -the immune response is weird in a way-, or because it –the immune response- goes on & on) which will lead to tissue damage.

●whatever the cause, it will end up with tissue damage which is unnecessary.

►There are four types of hypersensitivity:

Type I, Type II Type III and Type IV.

●Type I, II and III are antibody mediated.

●Type IV is cell mediated.

► Type I hypersensitivity

●It is also known as **immediate hypersensitivity** because once you have exposed to/ administered the antigen the symptoms appear very quickly within 15mins to 20 mins.

●It's mediated exclusively by IgE; actually IgE is a good antibody and very useful in parasitic infections.

● Main actions of IgE: IgE can produce ADCC against the parasite & causes its death through basic proteins; also when it adheres to mast cells and once it binds to the Antigen the mast cell will produce histamine and other inflammatory mediators; which will lead to increased secretions in the GIT (since many parasites live there) and increased peristaltic movement (increase the smooth muscle contractions), these movements and secretions lead to flush the parasite out (so first you kill them through ADCC then histamine will mediate the flushing out process as much as possible).

●**BUT** some people abnormally respond to some antigens by producing IgE.

- Those people who produce IgE against certain antigens instead of producing IgG are known as **Atopic people (Atopy).**
- These antigens that produce IgE response in atopic people are known as **allergens**
- Allergens can be pollens, food, fungi (molds), drugs and insects.

- **Normally,** when people are exposed to these allergens they produce **IgG** NOT IgE and get rid of them with no problem.

●in general 10-20% of people have hypersensitivity type I, this percent increases in developed countries to reach up to 30%, so 30%of people in developed countries are atopic.

●Some probable causes /risk factors for Type I:

1- **Genetic association**: some people say that there may be genetic disposition to being atopic, because when a member of a family is being atopic some other members also may have allergy, not necessary to the same allergen, but the risk increases; so it's possible to be determined by genetics, i.e. there is some sort of element of genetics concerned here.

2-**Developmental association**: some people say the developmental state and the hygiene of the society have something to do with type I hypersensitivity.

◊The developed countries have high percentage of atopy, on the other hand the developing countries have very low percentage of atopy.

◊The developed countries have low percent of parasitic diseases and developing countries have high percent of parasitic diseases.

***From the previous two points it's believed that in developing countries the production of IgE is directed to get rid of parasites (IgE is too busy to mess with allergens), but in developed they don't have parasites so IgE production is diverted against innocuous antigens →→ Summery: "قلة الشغل بتعلم التطريز"

●These molecules although they are harmless (allergens) they access to the body through mucus membranes mainly by Respiratory Tract and sometimes by GIT & in normal individuals that access won't lead to the production of IgE.

●But in case of atopic people, when the allergens enter the body they will produce an immune response; TH2 is diverted it will produce IL4 which will lead to iso-switching to IgE ;so IgE is directed against allergens now IgE will bind to 'Fc receptor for IgE' on mast cells.

-Indeed the Fc receptor for IgE has a special feature; the IgE can bind to it (without being attached to an Antigen), on the other hand the Fc receptor for IgG on neutrophils & macrophages doesn't bind to IgG until IgG binds to an antigen (i.e. forming an immune complex).

●The first time the atopic patient is exposed to the allergen, he will not produce symptoms but he will become sensitized because he produced IgE against that

allergen & that IgE is resting/ settling on his mast cells which are mainly present under the mucous membranes (of GIT& Respiratory tract for example) & under the skin.

●The second time when the patient exposes to the same antigen, the antigen will cross link the antigen binding sites of two adjacent molecules of IgE on mast cell, this will let them degranulate, so the mast cells are going to release their granules (mainly histamine).

●it's called immediate type of hypersensitivity because as soon as the IgE is exposed to the antigen, the signs and symptoms of hypersensitivity will appear immediately since histamine is already preformed in the granules and will be released immediately after the cross linking.

●In addition to histamine, the granules have long acting mediators which are synthesized de novo (leukotrienes and prostaglandins) & they are responsible for long term symptoms (prolonged hypersensitivity).

●Histamine, leukotrienes and prostaglandins will produce: swelling (due to increased vascular permeability & leakage of fluids and thus increased secretions), smooth muscle contractions & irritated nerve endings … so these are the effects & symptoms of hypersensitivity I, which appear on your skin, nose, throat, other parts of your respiratory tract and rarely appear in the GIT.

Diseases caused by type I hypersensitivity

A- *Allergic* Rhinitis / Hay fever ((Pollens – upper respiratory tract))

●The allergen here is pollen (common in spring) which is inhaled by the nose so all the symptoms will appear in the nasal cavity, sinuses & eyes too:

1- The nose will be blocked up due to swelling & there will be increased rhinorrhea (runny nose)

2-Runny eyes with tears due to increased permeability, thus there will be increased secretions

3-Congested (red) eyes due to dilatation of blood vessels

4- Itchy eyes due to Irritation

5- Sneezing

6- Breathing difficulties (since the nose is blocked)

B -Asthma ((House dust mites – bronchial tree & lungs))

● the allergen here is house dust mites (very small insects which you can't see by naked eyes & are present on dust, indeed they are present with their feces too) & actually, all the time in your house you are inhaling these mites with their feces.

●Normal people will react by producing IgG and they won't suffer, but atopic people will produce IgE (against the feces) which settle on mast cells in the bronchial tree and lungs.

●So every time atopic people inhale these mites the bronchi will constrict because of smooth muscle contractions and they will start wheezing at each inhale & exhale (they won't breathe properly).

●There will be increase in secretion; a lot of phlegm and Mucus will be produced.

● Obstruction of the air way passage due to activation of mucus secretion.

●Irritation will produce coughing.

**All these changes are physiological at the beginning, i.e.: these changes will be reversed or undone (the patient's status will be back to normal again).

●With recurrent attacks of asthma, the patient might have anatomical changes in lungs after initial physiological ones:

- Permanent narrowing of the airway passage and tissue damage due to infiltration by eosinophils, T-cells & other cells to the lungs and bronchi which leads to chronic inflammation & chronic obstruction of the airway passages.

●Asthma is a very serious disease and sometimes it can kill during its attack; sometimes the patient might go into ''status asthmaticus'' which produces prolonged mentioned symptoms and the patient dies with respiratory failure very quickly so it's fatal condition.

** One of the treatments of asthma is to reduce the dust as much as possible.