Today's topic is immunodeficiency. Immunodeficiency is a disturbance in the immune system and has two types; **Acquired** and **Congenital** (inherited).

1. **<u>Acquired immunodeficiency</u>**

It is much more likely you will come across this type, as congenital immunodeficiency occurs very rarely, ex. 1 in 20,000 or even 1 in 1,000,000. It can appear at any age depending on when you are exposed to the stress. As soon as you remove the stress, the immunodeficiency disappears.

Various causes include:

- **Malnutrition**
  This is one of the most common causes. When you are malnourished your immune system doesn't work quite well and you may develop immune diseases.
- **Various types of stresses** such as environmental stresses and strenuous exercising (exercising is very beneficial but excessive exercise may temporarily depress your immune system).
- **Infection** is a causative agent whether it is viral or bacterial, it can depress the immune system, ex. HIV (attacks immune system)
- **Tumors**
- **Drugs**
  Ex. immunosuppressants, steroids, chemotherapy or addictive drugs, such as heroin.

2. **<u>Congenital Immunodeficiency</u>**

- As mentioned previously, congenital immunodeficiency occurs very **rarely**.

- Mainly recessive, since it is inherited it could be either autosomal or sex-linked. When it is x-linked males are more affected than females.

- Disease appears early on in **childhood**

- People with congenital immunodeficiency are more likely to exhibit other abnormalities of the immune system such as **autoimmune diseases**. This is because regulatory cells of the immune system are found in lower numbers and so brake on autoimmunity is removed; this leads to the development of autoimmune disease.

- Related to **increased incidence of tumors**. The immune system normally suppresses tumors and prevents their growth, but when the immune system is depressed, tumors will grow.

- People with Congenital Immunodeficiency are **more liable to developing allergies**. This may be explained by the lower levels of IgA. When we have lower levels of IgA in the gastrointestinal tract, a lower number of antigens will be eliminated by IgA, and these antigens may go on to produce allergies. (This concept is not yet fully understood).

- Almost all factors of the immune system can be affected, including the complement system, T-cells, phagocytic cells and B-cells. We will discuss the deficiencies of each of these one by one.

Complement System deficiencies:

Classical pathway deficiencies

C1, c2 and c4 are the main participants in the classical pathway. The most common of these deficiencies is the **c2 deficiency**, occurring 1 in every 20,000 people. If there is a deficiency in c1, c2 or c4, the classical pathway will not be activated. You may think that this would cause recurring infections, but this is not the case as the alternative pathway can take over and deal with any bacterial infection. So, people with problems in the classical pathway do not suffer from serious recurring infections, but they are more prone to developing immune-complex diseases, such as "Systemic Lupus Erythematosus" due to reduced clearance of complexes by CR1 which can bind "C3b and C4b as they're present in the complexes".

C4 is coded for by 2 genes; two alleles on the maternal chromosome and two alleles on the paternal chromosome. All four of these are active in a normal person, so a complete deficiency, where all of the genes are non- functioning, is very rare! The amount of c4 produced may vary greatly. For example, if all genes are functional there will be a large amount of c4 produced. If only one gene is functional, we will have a low concentration of c4 in the serum.

The level of c4 in the serum of a diseased person is low due to the high activity of the complement system (they will be consumed). So, if you come across low level of c4, take into consideration that this may be a result of **less functional genes** rather than consumption by the classical pathway due to a normal infection.

Alternative pathway deficiencies

Deficiencies of the alternative pathway include deficiencies of c3, Properdin (this is a sex-linked deficiency), Factor D and Factor B (rare). If these deficiencies are present, the patient will suffer from **repeated infections**. You may also have a deficiency in the terminal components; c5, c6, c7, c8 or c9. A deficiency in one of these components means MAC (membrane attack complex) will not be produced and the patient will be more prone to develop infection, especially infection by the gram-negative cocci, Neisseria (both gonococci and meningococci).

***There are a variety of control proteins that may be deficient**:*

***C1 inhibitor deficiency**:

C1 inhibitor usually prevents unnecessary activation of c1. If c1 inhibitor is deficient, c1 will be continuously activated which will in turn activate c4 which then goes on to activate c2.By the time we get to the c3 convertase, a c4 binding protein is finally able to inactivate it. So in a person with c1 inhibitor deficiency, c2 and c4 will be consumed with no regulation from the c1 inhibitor. This leads to a low reading of c4 and c2 in the serum of a c1 inhibitor-deficient patient.

Angioneurotic edema is a disease in which swelling occurs, as a result of extravasation of fluid from the blood vessels to the extra vascular compartment. This disease produces swelling around the eyes, in the face, and in various places in the body. It is not very serious; however, it may be fatal if swelling in the larynx occurs and compromises breathing.

The **causes** of this disease are debatable, but there are various theories:

1) C1 inhibitor deficiency. C1 inhibitor normally prevents activation of a cascade of proteins leading to the swelling of angioneurotic edema. Low levels of c1 will be found in the serum.
2) C2 is split into c2a –the active form- and c2b. It is thought that c2b or a breakdown product of c2b may be responsible for the increased permeability of the blood vessels.
3) May be due to activation of the kinase system which increases permeability of blood vessels.

It is a genetic form of angioedema. Inheritance is supposedly dominant. In 85% of cases we will find that one allele does not work while the other still functions and produces c1 inhibitor, however because it is a dominant disease, one functional allele is not enough to cover up for the non-functional allele. In the other 15% of cases, one allele is functional while the other allele produces a **non-functional form of the protein.**

This may sometimes be **acquired** in cases where a missense mutation occurs at the gene which codes for the **Hageman Factor**.

*__Other regulatory proteins that may be deficient__:

Factor I and factor H.

This will lead to continuous activation of the complement system and lead to the depletion of c5 and c3. So when you need c3 to fight infection, it will be present in much lower levels.

*__Deficiency of cell-bound (membrane anchored) regulatory proteins:__

These include CD59, HRF and DAF. These proteins are cell bound and are usually attached to a common molecule which anchors them to the membrane. A lack of these proteins will lead to certain diseases like **PNH, Paroxysmal Nocturnal Hemoglobinuria.** Sometimes this disease may occur as a deficiency of CR1.

If these regulatory proteins are absent the RBCs will be more susceptible to MAC (the function is to protect cells from MAC), and will be lysed. RBCs are more susceptible to MAC because they are non-nucleated, unlike the other nucleated body cells which are more resistant.

Phagocytic cell abnormality: Chronic Granulomatous Disease

- Appears very early in childhood
- Autosomal recessive
- Very rare, incidence: 1 in 1,000,000.

Etiology:
Neutrophils and phagocytes are unable to produce respiratory bursts because of a deficiency in the cytochrome oxidase enzyme. **Respiratory Burst** is the rapid release of reactive oxygen species (superoxide radical and hydrogen peroxide) from different types of cells. In cases where the enzyme is absent or inactive the cell is unable to produce a respiratory burst and in turn is unable to kill bacteria. Macrophages will not carry out their jobs properly and will form granulomas. They also cannot eradicate infection very quickly (that's why it is called **Chronic** Granulomatous Disease); the disease is usually fatal and kills the diseased person within the first year of life.

Diagnostic test:
We test for this disease using the NBT test (Nitro blue tetrazolium test). Nitro blue tetrazolium is a colorless chemical, when mixed with normally functioning neutrophils will produce a blue color. If neutrophils are unable to produce respiratory bursts, the NBT will remain colorless- showing that it's non functional.

*Other cases which have problems with respiratory bursts:

G6PD deficiency

G6PD deficiency is an X-linked recessive hereditary disease characterized by abnormally low levels of glucose-6-phosphate dehydrogenase; people who are deficient usually suffer from favisim. G6PD deficiency is the most common human enzyme defect. All cells have a deficiency in the enzyme. Deficiency affects lymphocytes so they can't produce respiratory burst.

Myeloperoxidase deficiency

An enzyme found in leukocytes, its deficiency affects respiratory burst → immunodeficiency.

Leukocyte Adhesion Deficiency (LAD)

A disease defined by a lack of leukocyte extravasation from blood into tissues (diapedesis). It affects leukocytes and has two types.

LAD 1:

- Due to the absence of Beta 2 integrin (CD18). Integrins are present on leukocytes and are known to participate in cell adhesion as well as cell-surface mediated signaling. CD18 is present in several cell surface receptor complexes found on white blood cells, including: LFA 1, MAC1 (CR3), p150/p95 (CR4). Each one of those 3 is made up of 2 chains: alpha and beta. The beta chain is common in all of them and is the integrin beta chain beta 2 (CD18), that's why they are known as beta 2 integrins. The Alpha chain could be either CD11a or CD11b or CD11c.

LAD2:

- Neutrophils bind to E-selectins (expressed on endothelial cells) in order to undergo rolling during diapedesis. In this condition, the ligand on neutrophils which binds to this selectin is not present, therefore there is no adhesion.

Chédiak–Higashi syndrome

- It's autosomal recessive
- affects many cells **including** leukocytes (not only leukocytes)
- accumulation of large granular inclusions in the cytoplasm of the cells which are believed to be caused by lack of fusion of lysosomes with phagosomes (supposed to form phagolysosomes)
- will have repeated infections
- Other cells affected may be affected. For example, melanocytes will not produce melanin → albinos. Nerve cells will also be affected leading to nerve defects.

Job syndrome (Hyper IgE Syndrome):

- Etiology not very well known
- Staphylococcal abscesses on skin because of reduced immunity but at the same time the patient has high levels of IgE. This could be due to dysfunction of T-regulatory cells which produce a lot of IL-4, therefore, leading to the production of IgE. Recently, there is evidence that it's caused by defects in STAT3 and DOCK8 which are involved in intracellular signaling.