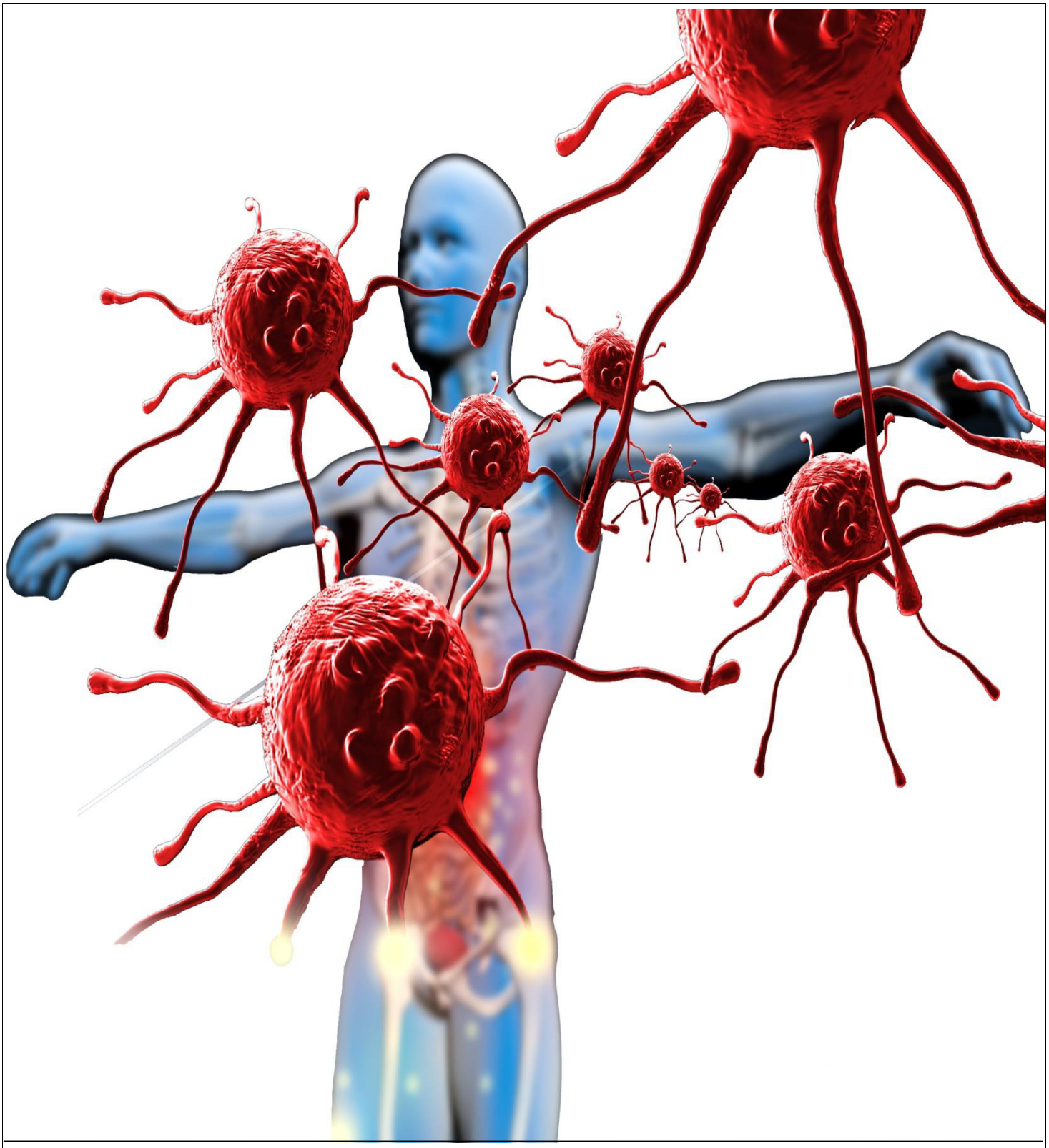

IMMUNOLOGY

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#19

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Immunodeficiency Disease

Defects in one or more components of the immune system can lead to serious and often fatal disorders called immunodeficiency diseases.

There are 2 varieties of these diseases:

*Inherited

*Acquired: that you get in a certain stage of your life due to various etiologies; HIV causing Acquired Immunodeficiency Syndrome (AIDS), however it's not the only or most important cause since the acquired diseases could be due to malnutrition, or chronic diseases like diabetes and chronic infections like Tb. We'll focus on the inherited diseases and not talk about the acquired in details.

Congenital (inherited) immunodeficiencies

The etiology of some of these diseases is well known but it's not in others.

The defect could be in any of the arms of the immune system:

Defects in Complement

Defects of phagocytic cells & lymphocytes

Defects of Humoral immunity (immunoglobulins)

Defects in complement& its regulation: it's rare occurring in one in a million maybe. Any component of the complement system could be affected but the commonest of them all is **C2 deficiency** happening in 1 in 20,000 live births (however it's not a high incidence).

2 genes on each chromosome, one or 2 could be defected and you can have a defect in all of them.

Another deficiency is in **complement 1 (C1) and Complement 4 (C4)**

*Patients with these deficiencies (the classical pathway) don't necessarily suffer from increased susceptibility to bacterial infections because the Alternative pathway is intact, and the mannose pathway would be also activated. But they will suffer **from immune complex diseases** such as systemic lupus erythematosus SLE… because they did not clear the immune complexes efficiently.

Deficiencies **Complement 3 (C3)** will lead to recurrent Pyogenic (bacterial) infections.

*Deficiency of C3 is rare but important since C3 is required in both the classical and alternative pathways.

Factors that can be deficient are: Factor B, Factor H, Factor I,

Perperdin which is X-linked immunodeficiency since the gene for it is on the X chromosome.

*Patients also have recurrent infections.

Deficiency could be in the **terminal pathway that is from C5 to C8** (C9 is not that important in the formation of membrane attack complex (MAC)

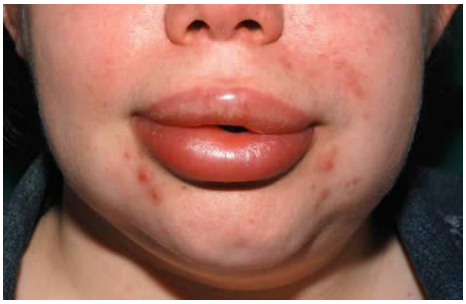
*Patients have Neisseria infections.

Deficiencies in complement regulators:

C1 inhibitor "C1-INH" (that binds to activated C1r and C1s blocking their action): dominant inheritance affecting the classical pathway

85% of these cases there is an incidental production of C1-INH that is not enough to actually inhibit C1 activation, and 15% have no C1-INH at all.

This condition is called **Angioneurotic Edema**, where the patient has swelling of mucosa and skin (usually near eyes and mouth), it could also reach larynx thus obstructing the airways.



-What is the cause of this edema? Some people say it is the product of C2 (Since C1-INH inhibits C1 that activates both C4 and C2). On the other hand C-INH has a dual purpose; it inhibits the kinase system, so when C1-INH is deficient this leads to continuous activation of the kinase system which is responsible for increasing permeability and the result is edema and swelling.

Deficiency of membrane bound regulators of complement activation:

Deficiency in

* **Decay accelerating Factor (**DAF that accelerates the dissociation of both classical and alternative pathway C3 convertase bound to cell surface**) *Homologous Restriction Factor or C8 Binding Protein (HRF** that act on C8 and C9**)**

* **CD59 (**that block C9 binding to C8 preventing MAC formation)

All are present on RBC surfaces to protect them from lysis by MAC.

(Although red blood cells, white blood cells and platelets are targeted by complement, red blood cells are particularly vulnerable to lysis by MAC because they are non-nucleated)

***This predisposes RBC to undergo hemolysis by complement activation leading to what is called **PNH Paroxysmal NocturalHemoglobinuria**

- Paroxysmal because it is episodic, nocturnal because it happens at night when blood PH drops a little, and hemoglobinuria because of the Hb found in blood and that appears in urine.

***Complement Receptor 1 (CR1) deficiency:** CR1 is present on RBC to remove immune complexes from blood to spleen, so patients are more susceptible to immune complex diseases like SLE.

We finished with Complement deficiencies and here is a summary.

DeficienciesinComplement	Deficiency	Signs Diagnosis
Classicpathway	Clq,Clr,Cls,C4,C2	Markedincreasein immunecomplex diseases
Bothpathways	C3	Recurrent infections, immune complexdisease
	C5,C6,C7,orC8	RecurrentNeisseria infections
Deficiencies in complem-entregulatory proteins	Cl-INH(hereditaryangioedema)	OveruseofC1,C4,or C2, Edemaatmucosalsu

Phagocytic cells defects (neutrophils and lymphocytes):

1) Chronic Granulomatous Disease (CGD) :

*Two thirds of cases are X-linked while one third is inherited as autosomal recessive.
*Incidence is one in a million, not that common.

*Appears early in life (in childhood), and is quiet fatal
*Patients mainly have recurrent pyogenic infections.

Etiology of the disease:
Neutrophils and phagocytes are unable to produce **reactive oxygen compounds** (Respiratory burst, (most importantly the superoxide radical and hydrogen peroxide) because of a deficiency in the **cytochrome oxidase enzyme (NADPH oxidase**). 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).

2)Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) :
It is a very common disease especially in the Mediterranean area, and has protective mechanism against malaria.
Patients don't actually suffer from immune diseases but rather the red blood cells are affected because they lack a nucleus and thus can't compensate for the deficient enzyme. RBC will undergo hemolysis.

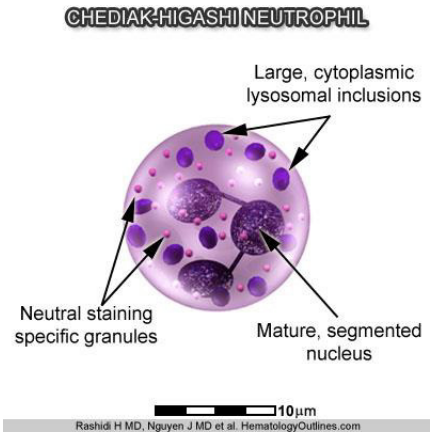
3)Myeloperoxidase deficiency:
Macrophages are unable to produce myeloperoxidase (an antimicrobial enzyme formed mainly by neutrophils which acts to produce hypochlorous acid (HOCl) from hydrogen peroxide(H_2O_2) and chloride anion (Cl^-)), eventually the phagocytes are not able to kill and get rid of the bacteria.

4**) Leukocyte Adhesion Deficiency (LAD**):
The Adhesion molecule deficient is Beta-2 integrin subunit, called CD18 and this is involved in the formation of **Beta2 integrins**found on neutrophils and leukocytes and which allow them to adhere to blood vessels endothelium for migration (diapedesis) to tissues.
*The result is recurrent and chronic infections.

5) Chédiak–Higashi syndrome

* It's an autosomal recessive disease
*abnormality in phagosomes and lysosomes; impaired bacteriolysisdue to failure of phagolysosomeformation that is the failure of fusion between phagosomes and lysosomes.

* They make inclusion bodies inside cells however these are not really effective in bacteria killing
*This disease is associated with other cells not just leukocytes, for example affects melanocytes impeding melanin production and patients will be either Albino or Albino-like (very blonde not white). It also affects neurons leading to neuropathy.



6) Hyper IgE syndrome (Job Syndrome):

*very rare syndrome

*Autosomal recessive, the etiology is specifically a defect in STAT gene signaling pathway

*Patients have coarse faces

*Dermatological manifestations like Eczema

*High IgE, and this may be because of TH2 cells producing a lot **of IL-4 leading to the production of IgE** (because basically TH1 cells can't produce IFN gamma responsible for shutting down TH2 response.)

*Recurrent abscesses formed by staphylococcus aureus

*Retain Primary teeth (it's hard to replace their primary teeth)

Disease	MolecularDefect(s)	Symptoms
Chronicgranulomatous disease(CGD)	DeficiencyofNADPHoxi-dase	Recurrentinfectionswith Bacteria

	failureto generatesuperoxideanion, other02radicals	
Leukocyteadhesion deficiency	AbsenceofCD18-common chainoftheleukocyte integrins	Recurrentandchronic infections
Chediak-Higashisyndrome	Granulestructuraldefect	Recurrentinfectionwith Bacteria Partial albinism
Glucose-6-phosphate dehydrogenase(G6PD)	Deficiencyofessentialenzyme G6PD	
Myeloperoxidasedefi-ciency	Granuleenzymedeficiency	Infections since the bacteria is not phagocytized
Job'ssyndrome	Defect in STAT gene pathway IL-4>> high IgE	Coarsefacies,bacterialabsecces by staph. Aureus ,retainedprimaryteeth ,high IgE,eczema

Defects of B- lymphocytes (Humoral immunity):

1)Brutonagammaglobulinemia (also called Brutonhypogammaglobulinemia):

* X-linked inherited in a recessive manner, so occurs in males not females.

*Symptoms start to appear after the first 4 or 5 months of life, before that, the baby has no antibodies from his bone marrow, only igG from his mother (maternal protection). After 4 months of life, the baby loses protection and now has no antibodies and will suffer from recurrent pyogenic infections.

Etiology: Deficiency of Bruton's tyrosine kinase (BTA) thus arresting the maturation of B cells at the (pre- B cell) stage (A pre-B cell has only M chain in the cytoplasm) that is in the bone marrow, so they will not reach the mature or even the immature B cell.

If you examine the blood of the baby, you will NOT find any B cells. All the secondary immune tissues are not effective, like adenoids or lymph nodes therewill be no secondary or primary follicles; there will be only T cells)

*No imuunoglobulin or very little immunoglobulin in the serum. So all would be reduced; IgA, IgM, IgE will be absent and IgG will be very low.

Treatment: you can treat patients by giving babies multi injections of immunoglobulins, and treat infections with antibiotics.

2)Transienthypogammaglobulinemia of infancy:

It's quite the same manifestations where the baby has recurrent infections after the age of 5-6 months when maternal protection by IgG is no longer present.

*IgG is in higher concentrations than in Bruton. And if you examine Adenoids and secondary lymphoid tissues they have normal architecture.

*The main difference is that in Transient hypogammaglobulinemia B cells are present in blood but they are not mature, while they are not present in Brutonagammaglobulinemia.

* It may last up to 18 months to 2 years sometimes, but then it will resolve without treatment, it is self-limiting. But of course you have to give antibiotics to prevent the complications of the infections.