Immunology 23

NOTE: when we talk about deficiency of sth, either this thing is completely absent, or present in very little amounts, or it is almost non-effective.

B cell immunodeficiencies: immunodeficiencies affecting the humoral aspect of the immune system:

Bruton Agammaglobulinemia:

- Bruton refers to the name of its discoverer.
- It is inherited in an x-linked recessive manner.
- The pathological manifestation of the disease is the absence of mature B cells as B cells are arrested at the stage of the pre-B cell (the pre-B cells have μ chains but there's no expression of BCRs on their surfaces).
- B cells tend to be found in large numbers in the bone marrow without any trace –not present- in the blood.
- In the lymph nodes, there will be no secondary or primary follicles, there will be only T cells.
- Of course, there will be no plasma cells and thus, low levels of immunoglobulins are usually observed:
    - IgG < 200 mg/ 100 mL… 100mL = 1dL… Note: normal IgG range in blood is between 700 & 1700 mg/dL.
    - IgM and IgA are nonexistent.
- The manifestations of the disease appear at the age of 6 months because maternal antibodies protect infants in the period between birth and the age of six months.
- At the age of 5 – 6 months, the infant starts having recurrent infections.
- The cell-mediated immunity is intact and is able to fight against some bacterial and viral infections.
- So, dead -NOT live- antigens and toxoids will not be able to interact with pre-B cells that lack BCRs and, as a result, there will be no production of specific antibodies.
- Treatment is usually achieved with intravenous or intramuscular human immunoglobulins:
    - IV: less painful; given once a month; Igs must not form aggregates in the serum.
    - IM: usually given when the administered Igs are able to form aggregates in the serum.
    - Aggregation of Igs in the serum can activate the complement system.

- Also, antibiotics are necessarily given when the patients have an infection.

Transient hypogammaglobulinemia of infancy:

- Manifestations start to appear at the age of 5 – 6 months after the maternal Igs are gone.
- The pathology of this disease is caused by the delayed development of the immune system in some babies, so, by 6 months of age, the maternal Igs are gone, but still the baby doesn't have mature lymphocytes yet and the amount of self produced Igs are not enough… this case can last from few months to 2 years.
- These individuals are not said to be immunodeficient; because there is nothing wrong with their immune system/ response, it's just not mature enough yet.
- The maternal Igs cease to exist before the newborn can produce his own Igs.
- These individuals tend to suffer from recurrent infections until their immune system kicks in and starts working properly – they'll recover completely & be back to normal- usually by the age of 1.5 - 2 years.
- To differentiate between transient hypogammaglobulinemia and agammaglobulineamia, one can check for the presence of B cells in the blood.
- Transient cases:
    - Will have some B cells in the blood.
    - IgG titer would be 300 – 350 mg/ 100 mL … still below normal but won't reach as low as 200 as in cases of agammaglobulinemia
    - IgM and IgA are also found in the blood in normal levels.
    - When these individuals are challenged with antigens –toxoids-, specific antibodies are produced against these toxoids.
    - Rule: Always when we find someone who is immunodeficient & we want to challenge them with an antigen, we DON'T use live viruses, bacteria, etc… we always use sth that is killed, for example the toxoid is an inactive toxin, so it can be used in these cases.

Selective Ig deficiencies:

- IgA-selective immunodeficiency:

- The most common of all immunodeficiencies (1 in 700 individuals).
- B cells bearing IgA on their surface are present in the blood but, for an unknown reason/ mechanism, they are not able to convert to

plasma cells & produce free IgA molecules… so the patient doesn't have IgA at all.

- These individuals usually have a normal life with the exception of suffering from easily controllable recurrent upper respiratory tract infections.
- They are prone –have predisposition- to have autoimmune diseases (increased incidence of AI diseases in these patients) and allergies.
- Allergies are probably caused by the absence of IgA in the GIT secretions resulting in allowing allergins –which are normally neutralized by IgA- to pass through the GI barrier & get access to the body producing some allergic reactions.
- Another important manifestation of this disease is the individuals' ability to produce allergic reactions against IgA upon exposure to it, since they don't have IgA in their bodies (i.e.production of IgE against IgA).
- In cases of blood transfusion:
  - The first time causes sensitization against IgA.
  - Consequent transfusions can cause anaphylaxis.
  - So to be on the safe side, these individuals are only given packed RBCs -that have been washed- with no serum because RBCs lack IgA from their surfaces.

- IgG-selective immunodificiency:

- Can be selective for any of IgG1, IgG2, IgG3 or IgG4.
- These people will probably suffer from recurrent infections, but those with the selective IgG4 deficiency are usually ok; because IgG4 has the least concentration out of the 4 subtypes of IgG in the serum.
- IgG2 & IgG3 deficiencies are the commonest.
- IgG1 deficiency is the most serious of them all because IgG1 is the most common in the blood.
- IgG3 deficiency can also be serious but IgG2 and IgG4 deficiencies are usually of less seriousness.

- IgM-selective immunodeficiency:

- IgM is not produced while all other Igs can be found normally in blood.
- This contradicts the sequential theory of production of antibodies, i.e. that IgM is produced first before switching to other Igs.

- X-linked hyper-IgM syndrome:

- This is due to abnormality in T cells not B cells.
- The CD40 ligand (which is present on T cells & connects with CD40 on B cells and promotes switching) is absent from the surfaces of T cells and, thus, after IgM is produced there will be no class switching/ isotypes production other than IgM...
- Individuals have better responses to T-independent antigens – which will give rise for the production of IgM - than to T-dependent ones, since the response to such antigens is impaired...
- There will be very little IgG & IgA & there'll be an increase in IgM conc.
- CD5 cells will still produce IgM.

Acquired hypogammaglobulinemia of adulthood (Good syndrome):

- Usually appears in adults 30-40 years of age and is associated with thymoma (tumor of the thymus).
- The patients will present with a shadow in their mediastinum; due to the tumor behind the sternum.
- The relation between thymoma and hypogammaglobulinemia is not really understood.
- Disturbance of T cell function leading to hypogammaglobulinemia is observed, which maybe the reason behind such association/relation.
- It is believed in this syndrome that cells are arrested in the bone marrow and don't mature into B cells… what's the relation between this and the syndrome itself along with the thymoma? WE DON'T KNOW :-/
- Thymoma is also associated with other problems such as myasthenia gravis.
- Treatment: removal of the tumor, but unfortunately it doesn't guarantee that if you remove the tumor, you'll get rid of the immunodeficiency.

Common variable immunodeficiency:

- This disease is more common than other immunodeficiencies.
- Symptoms vary in severity and are not usually constant.
- Normal B cells are present but they are not able to become plasma cells.
- Symptoms (recurrent infections) can appear in early childhood or as late as 15 – 20 years of age.

T cell immunodeficiencies:

DiGeorge syndrome: the most common of them:
- In most of the cases, there is a deletion in parts of one of the chromosomes of the 22nd pair, which participates in the causation of this syndrome.
- It is a congenital disease that occurs during the fetal development & affects all the tissues developing from the 3rd and 4th branchial pouches.
- Affected tissues include the thymus, parts of the heart, the lower aspect of the face and the parathyroids.
- Manifestations:
    - Absence of the thymus and parathyroids.
    - Congenital abnormalities of the heart.
    - Deformed faces (fish-like faces especially at the mouth region).
- Clinical symptoms:
    - Recurrent infections; especially intracellular (viral and protozoal) infections.
    - Hypocalcemia due to parathyroids deficiency and tetany (contraction of muscles due to hypocalcemia).
    - Pls differentiate between tetany & tetanus, tetanus is the contraction of muscles due to the toxin of clostridium tetanus.
- There are no thymic cells to educate T cells, so you may have some T cells which are normal but are present in very small numbers, that's why they don't function normally.
- Usually, as a rule, the inheritance of this disease doesn't involve a complete absence of the thymus, usually there'll be some remnants of the thymus –cells scattered there-, that's why the T cells are normal but small in number, the remnants of the thymus can proliferate and take over the function of the thymus, and that explains why some of the patients in the past used to recover in the age of 3-5 years and become completely normal as far as the immunodeficiency is concerned.
- Reduced numbers of T-lymphocytes which affects the action of Igs -since they need help from T cells- is observed in these cases.
- Treatment is usually done by thymic transplants into ill babies & they should recover.

Chronic mucocutaneous candidiasis:
- Some, not all, T lymphocytes are affected; more specifically the TCRs are affected.
- Affected T lymphocytes are the ones that are reactive with candida.

- These individuals are liable to have candida infections on skin, nails, pharynx & vagina … i.e. chronic mucocutaneous infections, BUT they're resistant to candida septicemia – blood infection with candida -.
- Also, these patients tend to have multiple autoimmune endocrinopathy, i.e. they might have autoimmune diseases which affect the endocrines, as in diabetes, and this maybe has something to do with mutations in the AIRE gene which end up with multiple endocrinopathies which are autoimmune in nature.
- Some people say that the thymus itself is an endocrine gland & thus it's involved in conjunction with these endocrinopathies.

** All primary immunodeficiencies discussed so far are congenital, except for the Good syndrome, and thus are called primary (because they're congenital/ inherited).
** This finishes the T-cell abnormalities.

**Combined immunodeficiencies, affect both humoral & cell mediated immunity, it either affects directly the B & T cells, or sometimes the effect is on T cells but it reflects on the function of B cells& they won't function normally, now in this case when you have a combination of B & T cells affected, this is:

Sever combined immunodeficiencies (SCID):

- These are all severe diseases and are treated with bone marrow transplantation.
- You have to be careful with these people; you shouldn't give them a live vaccine – only dead vaccines-
- You have to be careful when you give them blood products, why? Because of the risk of GVH (Graft Versus Host), because such patients don't have an immune system at all, so if you give them blood with T lymphocytes, these can mount an aggressive attack against the person himself, so if you want to give them blood, you give them blood which has been eradiated, i.e. eradiation will kill all the live cells –leukocytes-.

- Classical SCID:
  - The first 50%:
    - These are X-linked recessive.
    - These are due to deficiency of the gamma chain of the interleukin 2 receptor:
      - A trimolecular receptor.
      - Alpha chain is CD25.

        - If the gamma chain - a growth promoter - isn't present, then IL 2 receptor won't work & this impairs the function of both B and T cells.
- The other 50%:
    - They are autosomal recessive.
    - They are of multiple etiologies:
        - The absence of recombination activation genes 1 and 2 (RAG1 and RAG2 defects) which are necessary for the production of TCRs and BCRs, thus B & T cells will be affected.
        - Deficiency of the adenosine de-aminase enzyme which is involved in the purine metabolism by removing toxic metabolites that may accumulate… thus in case of its deficiency, there'll be accumulation of toxic products of purine metabolism & this will prohibit the DNA synthesis & the B & T cells won't be able to multiply.
        - Deficiency of PNP (Purine Nucleoside Phosphorylase), another enzyme which if deficient, there will be build up of toxic metabolites that affect the growth of B & T cells.
        - Deficiency of the Janus kinase 3 (also called just another kinase) which is responsible for signal transduction into the cell.

- Bare lymphocyte syndrome:

- Lymphocytes lack MHC molecules.
- Can cause the absence of MHC-I, MHC-II or both.
- The genes that are involved in the HLA molecules synthesis are normal, but the expression on the surface is impaired due to deficiency in one or more of the proteins responsible for MHC expression… thus there will be problems with antigen presentation & even the T cells will not develop properly.
- Associated with immunodeficiency.
- All the cells of the body will be affected depending on the class absent, if MHC I, then all cells in the body are affected, if MHC II, then all APCs are affected, if both, then every single nucleated cell is affected.

Genetic abnormalities affecting the immune system and other systems:

Wiskott-Aldrich syndrome:

- It is X-linked.
- The protein involved is referred to as WASP (Wiscott-Aldrich syndrome protein), which is deficient in this syndrome.
- WASP helps in transduction of signals to the inside of the leukocytes & it is present on all cells coming from the bone marrow.
- WASP deficiency causes:
    - Immunodeficiency due to malfunctioning B & T cells.
    - Abnormally small platelets which are also small in number, resulting in thrombocytopenia and bleeding.
    - Eczema: an allergic manifestation that can be associated with immunodeficiency.
- Bone marrow transplant can be curative.

Ataxia telangiectasia:

- Ataxia means loss of balance.
- Telangiectasia means the presence of abnormal blood vessels in places they should not be, like in the sclera or any other part in the body –where there is normally no BVs- .
- The abnormality is caused by a defect in DNA repair, it is a rare (1/200000) inherited disease.
- The cerebellum is affected causing ataxia.
- Telangiectasia is often observed on the face and it resembles vascular birthmarks, which may help in the diagnosis.
- It will affect the immune system, these individuals are immunodeficient.
- It can affect the speech.

**The last 3 mentioned disease are SCID too.

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