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Immunology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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Immunodeficiency disorders

- in the next 2 lectures. we will study primary and secondary Immunodeficiency disorders.

➢ Introduction:

❖ The function of the immune system is to discriminate between self and non-self entities and to protect the body from the harmful non-self entity like (microbes/toxins/ altered cells as malignant cells/etc.)

❖ Immune system is composed of cells (PMNS, macrophages, dendritics in innate and B, T lymphocytes in adaptive) and molecules (CS, TLR in innate and antibody, MHC, TCR in adaptive).

❖ Immunodeficiencies (IDs) are a group of diseases caused by **quantitative** (decrease the number) and/or **functional** changes in different mechanisms involved in both the innate and the adaptive immune response.

❖ primary immunodeficiency **(very rare)**: Immunodeficiency resulting from an **inherited** genetic or developmental defect in the immune system.

❖ Secondary immunodeficiency **(more common)**, also known as **acquired** immunodeficiency, is the loss of immune functions that results from **exposure to an external** agent (infection or drug). Also, Secondary immunodeficiency can be **reversed** if we remove the factor that underlays it then restore the normal function.

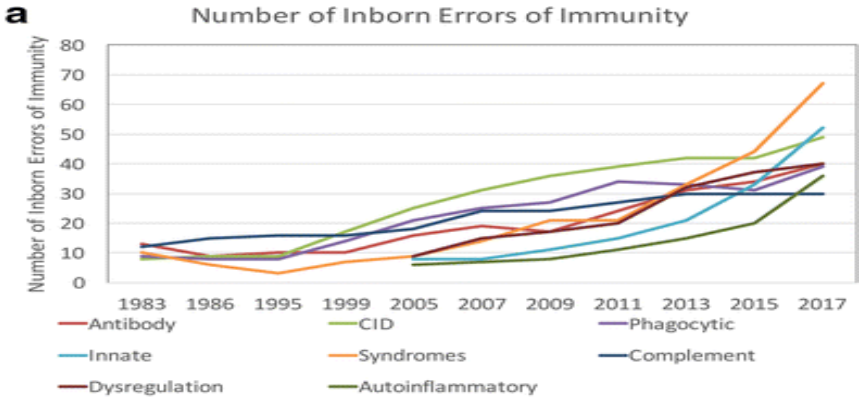
❖ HIV is the most important cause of Secondary immunodeficiencies.

• primary immunodeficiency

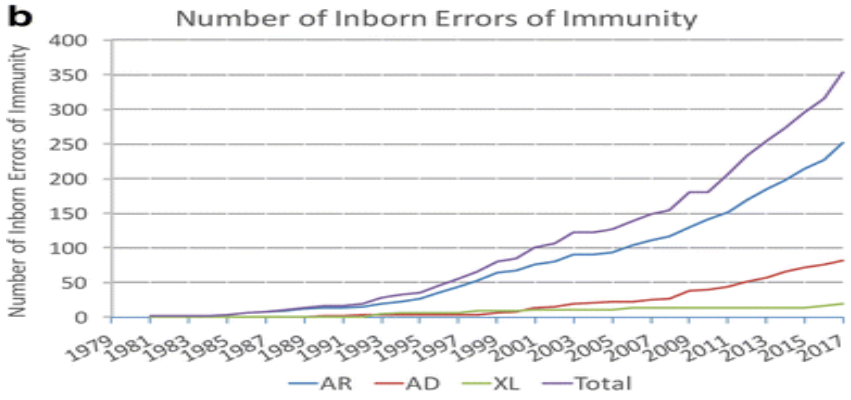
✓ To date, over 300 different types of primary or inherited immunodeficiency have been identified.
✓ Most of these disorders are **monogenic** (caused by defects in a single gene) and are extremely **rare**.
✓ Primary immunodeficiency diseases vary in severity from mild to nearly fatal (**the earlier is much more severe**).

✓ Due to the **complex** interconnections of the immune response, defects in one pathway can also **manifest** in other arms of the immune response, and different gene defects can produce the same phenotype, **making strict categorization complicated**. -for example, T cell which interacts with B cell continuously, a defect on T cell also affects B cell, for this reason, it's **not strict**-, so when we say there is a defect on one component doesn't mean the other components are not defected.

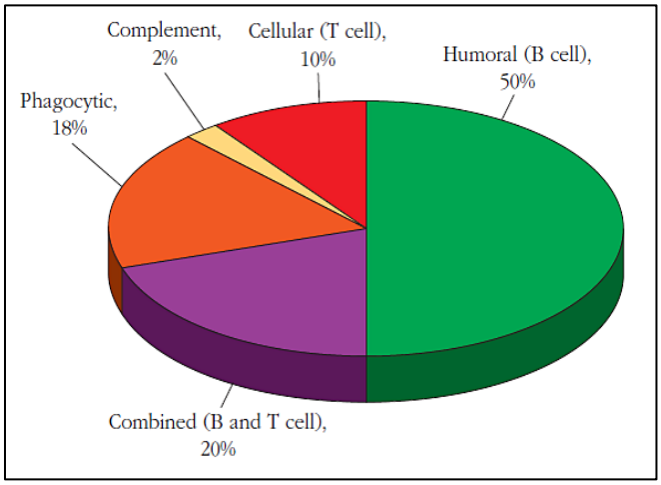
- (a): identification of primary immunodeficiency increases overtime especially in the last (10-20) years due to advances in sequencing technology.



- (b): primary immunodeficiencies can be autosomal dominant or syndromes or other, but the **most** is due to **autosomal recessive deficiency.**



- **PIDs** (primary immunodeficiencies) can be **loosely** categorized as affecting either innate or adaptive responses and are often grouped by the specific components of the immune system most affected. (**look at the order**)
- **The most common cause is humoral (B cell)**.



- When should we investigate a possible IDs?

important

. Clinical Signs That Suggest a Primary Immunodeficiency Disease

Positive family history
Infections in multiple anatomic locations
Increasing frequency and severity of infections with age
Recurrent serious infections with common pathogens
Serious infections with unusual pathogens

About the table above:

- ✓ Positive family history is the **strongest** predictor of an underlying ID.
- ✓ Increasing **frequency and severity of infections with age**: mostly seen in babies and B cells, when infected they **unable to mount** the infection, so infection becomes severe.
  - ➢ in the **neonate**, for six months babies are protected by passive immunity, which comes from the mother (maternal transfer antibody, IgA and mainly IgG).
  - ➢ IgG has subclasses (1,2,3). **Subclass 2 has the minimal ability to cross the placenta** and bind to the neonatal Fc receptor.
- ✓ Recurrent serious infection with common pathogen:(normally respiratory, trachea and other infections by a common bacteria or virus takes 4 days to complete resolution. but in patient with **PIDs**, it becomes **more severe and it takes longer time.**
- ✓ The last sign: if a patient comes to your clinic with an **opportunistic pathogen** he **mostly** has (**IDs**). opportunistic pathogens like candida infection, pseudomonas respiratory infection, mycobacterium intracellulare and JC virus which cause (PML).

But why they are unable to mount the infection?

In babies, the main Ig is IgG which has a half-life of 3 weeks, so it decreases until a point there is no enough antibody to mount the infection.

For example: if the baby takes 100 IgG it becomes 50 after 3 weeks and 25 after 6 weeks, reaching 6 months with few IgGs.

How to diagnose PIDs:

1. **History**: ask for **positive history family** (the strongest sign for underlying PID), ask for a previous infection (if ever have multiple infections).
2. **Physical examination**: if the patient has a syndrome, a disease in development or abnormality will be **observed** by physical examination. Also, when lymph nodes (which contain B cell) are exposed to infections they will normally enlarge, but patients with PIDs will not be palpable. (absent lymph node indicates B cell defect)
3. **CBC & DIFFERENTIAL**: perform complete blood count (CBC) for white blood cells, red blood cells, platelets,etc. . Then, to know which type is defected, we **use blood differential test** for PMNs, lymphocyte, monocyte. (defect in PMNs (neutropenia), defect in lymphocyte (Lymphopenia). However, in differential we can't discriminate between types of lymphocytes (B, T and NK cells), in such case B cells could defect and the total is normal, we use Flow Cytometry method to find out which defect.
4. **Quantitative IGS** (immunoglobulins): concentration of immunoglobulins respectively from the highest to the lowest in normal adult (IgG, IgA, IgM, IgD, IgE), if all defect this indicates B cell defect. (also, we can measure the number of subclasses for Igs, for example, the most common IgG subclass deficiency is IgG2).
5. **Review of previous culture result**: we have to know the type of organism and severity from the culture.
6. **Titers of administrated vaccine**: to test the immune response, in normal immune response there is a production of IGs.
7. **Lymph enumeration** using FCM: discriminate (B cells by CD19, T cells toxic and helper by CD3, NK cells by CD16 (**FcγRIII**) and CD56).
8. **Skin testing**: mainly to see the function of **T** cells.
9. Measure the complement activity, total complement activity in classical pathway, specifically if there is a defect in the terminal pathway, for example, if (c5-c9) defect there is no formation of MAC, **CH50 will be abnormal**. Also, we can do quantitation for components of the complement system (C3 and C4 have the highest concentration, **C4 is the most common complement deficiency**).

CH50: An assay to determine the function of the classical pathway of complement.

10. Phagocyte studies NBT: phagocytosis is not enough to kill the organisms, neutrophils must be activated to give the “respiratory burst” to generate (**ROS**) that kill the organism . Patients with chronic granulomatous disease are unable to mount this respiratory burst, so they engulf the bacteria but without killing it .(the test which used to investigate this case is NBT).
11. Enzyme studies: if there is a defective enzyme or mutations that make them non-functional.

pattern of illness associated with PIDs:

- ✓ The **pattern** of infection gives an indication which component of the immune system is defective, in our adaptive immune system we have **B cells for extracellular organisms** (mainly bacteria) and **T cells for intracellular organisms** (viruses and fungus). So, when a patient is continuously infected with encapsulated bacteria this indicates a B cell defect, another patient continuously infected with recurrent (candida, viral and fungal) infections this indicates T cell defect.
- ✓ Defect in **regulatory** T cells causes **loss** of **peripheral** tolerance.
- ✓ About the **terminal** component of the complement system specifically (C5-C9): if there is a defect in one of them, **the propensity to develop severe Neisseria infection and Meningococcal infection increases.**

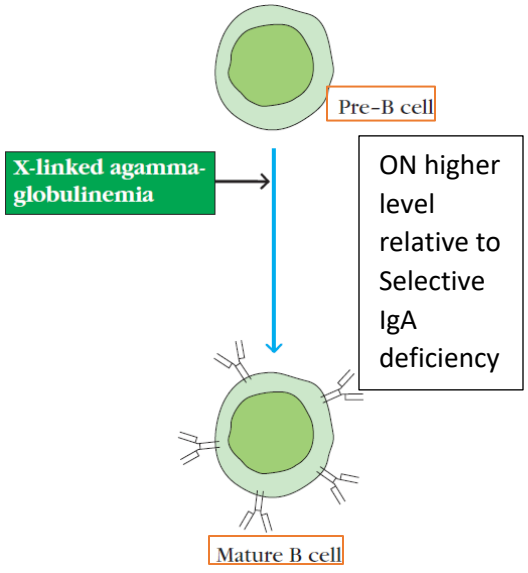
important

Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystis carinii*, viruses) Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)	
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	
Regulatory T cells	N/A	Autoimmune disease

- **PIDs (selected examples)**
  - **defect of the B cell system:**

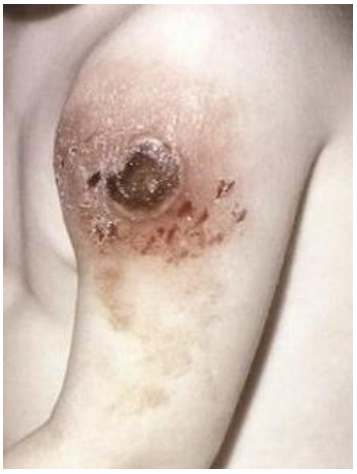
✓ **<u>Selective IgA deficiency</u>** is **the most common congenital immunodeficiency**, occurring in about 1 in 500 persons of American-European descent. Individuals with selective IgA deficiency typically exhibit **normal levels of other antibody isotypes** and may enjoy a full life span, troubled only by a greater-than-normal **susceptibility to infections of the respiratory and genitourinary tracts (mucosal surfaces)**, the primary sites of IgA secretion. Although the genetic defect has not been established, it is hypothesized that lack of IgA is caused by **impaired differentiation of lymphocytes to become IgA-producing plasma cells**.

✓ **<u>X-Linked Bruton's Agammaglobulinemia</u>**



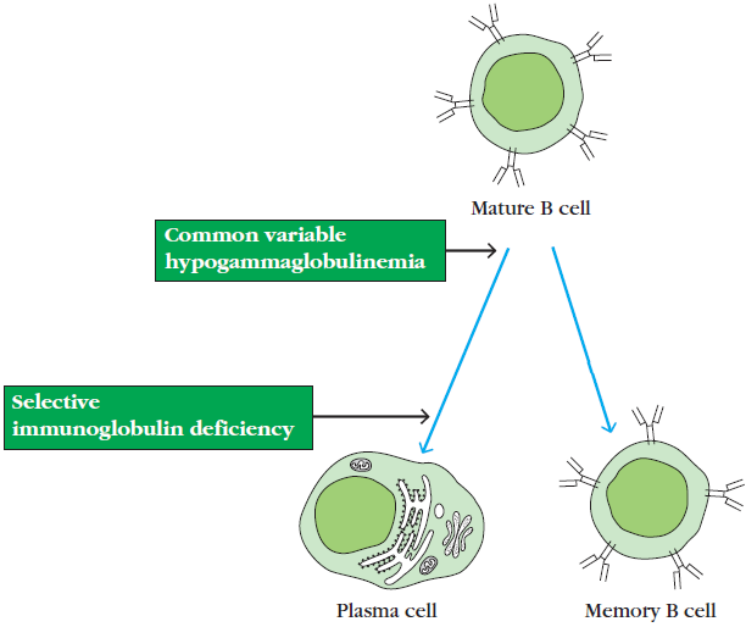
- first described in 1952, is an X chromosome-linked, so this syndrome **affects males almost exclusively (on the female as a carrier)**. Patients with X-linked agammaglobulinemia **lack** circulating mature CD19 positive **B cells** and exhibit a deficiency or **lack of immunoglobulins of all classes**. Furthermore, they have no plasma cells in their lymphoid tissues, but **they do have pre-B cells in their bone marrow**. Because of the lack of B cells, the tonsils and adenoids are small or entirely absent, and lymph nodes lack normal germinal centers. T cells are normal in number and function.
- X-linked agammaglobulinemia results from arrested differentiation at the **pre-B cell stage**, leading to a **complete absence of B cells and plasma cells**.

- The underlying genetic mechanism is a deficiency of an enzyme called the **Bruton tyrosine kinase (Btk) in B-cell progenitor cells**.
- Lack of the enzyme apparently causes a failure of V_H gene rearrangement.
- Patients most commonly develop **Sino-pulmonary infections** caused by **encapsulated** organisms such as streptococci, meningococci, and Haemophilus influenzae, because of lack of IGs which is important for opsonization. Other infections seen include bacterial otitis media, bronchitis, pneumonia, meningitis, and dermatitis.
- Present-day use of **Prophylactic antibiotics and replacement** therapy in the form of passively administered antibodies (by IV injection) can make this disease quite manageable.



✓ **<u>Common variable immune deficiency (CVID)</u>**

- CVID encompasses the largest group of **<u>symptomatic</u>** primary immunodeficiencies, with an estimated incidence between 1:10,000 and 1:50,000.
- Patients usually begin to have symptoms in their 20s and 30s, but the age at **onset ranges from 7 to 71 years of age**. Respiratory tract infection by common bacterial strains is the most common symptom.
- **Diagnosis by exclusion and if there are 2 or more classes of IGs in a low level.**



➢ defect of the T cell system

✓ **DiGeorge Anomaly:**

- Developmental abnormality of the third and fourth pharyngeal pouches that affects thymic development. Specifically, most patients show a deletion in **chromosome 22, region q11**.
- The severity and extent of the developmental defect can be quite variable. Many patients with a partial DiGeorge anomaly have only a minimal thymic defect and are thus near normal immune function.
- However, 20% of children with a defect of the third and fourth pharyngeal pouches have a severe decrease in T-cell numbers. These children tend to have severe, recurrent viral and fungal infections. Severely affected children usually **present in the neonatal period with tetany**, **which is the most common presentation** (caused by **hypocalcemia** resulting from hypoparathyroidism) or manifestations of cardiac defects.

NOTE:

The most common **ID** is protein malnutrition which is **SID** and the most common **PID** is B cell defect specifically selective IgA deficiency.