IMMUNOLOGY 444

MED444 KING SAUD UNIVERSITY

EDITING FILE

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INTRODUCTION TO IMMUNODEFICIENCY

Color Index:

Main Text

Important

Female Slides

Male Slides

Dr's Notes

Extra

OBJECTIVES

01

Identify that Immunodeficiency is due to a defect in the immune function.

02

Describe the classification of Immunodeficiency.

03

Explain the presentations of different types of Immunodeficiencies (e.g. recurrent infections).

04

Understand the varieties of immune system deficiencies involving defects in :

- T cells, B cells, phagocytes and complement.

05

Know the laboratory investigations for immunodeficiency disorders

WHAT IS IMMUNODEFICIENCY?

(Immunodeficiency (ID) : is a state in which the ability of the immune system to fight infectious disease is compromised (weakened) or entirely absent .

A person who has an immunodeficiency is called '**Immunocompromised**'

Immunodeficiency (ID) is considered present when infections are:

1- Resistant to antimicrobial therapy

2-Frequent and severe

3-Caused by opportunistic microbes

A boy with congenital ID lived in a bubble for 12 years before he died

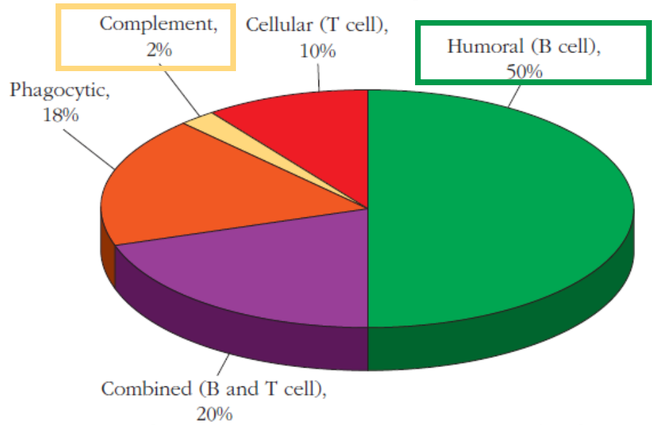
CLASSIFICATION OF IMMUNODEFICIENCY

Primary (Congenital)

Genetic mutation:

- Single gene (Monogenic)
- Multiple genes (Polygenic)

Distribution of Primary immunodeficiencies



For example: defect of Humoral B cell (adaptive immunity) is the most common (50%)

Secondary (Acquired)

- Malnutrition
- Viral and bacterial infections (AIDS)
- Immunosuppressive therapy (Corticosteroids)

Corticosteroids anti-inflammatory drugs so it lowers the immune system

- Excessive protein loss

(burns, nephrotic syndrome—>protein loss in urine)

Primary and **Secondary** immunodeficiencies can affect

- NATURAL IMMUNITY (INNATE) **PRIMARY**
  - COMPLEMENT PROTEINS
  - PHAGOCYTIC CELLS
- ACQUIRED IMMUNITY (ADAPTIVE) **SECONDARY**
  - B LYMPHOCYTES
  - T LYMPHOCYTES

PATTERN OF INFECTIONS AND SYMPTOMS ASSOCIATED WITH PRIMARY IMMUNODEFICIENCIES

Disorder	Opportunistic infections	Other symptoms
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune diseases (autoantibodies, inflammatory bowel disease
Cell-mediated immunity	Pneumonia (pyogenic bacteria, pneumocystis carinii,viruses) Gastrointestinal (viruses), mycoses of Skin and mucous membranes (fungi)	N/A
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune diseases (systemic lupus erythematosus (الذئبة الحمراء), glomerulonephritis
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	N/A
Regulatory T cells (Treg)	N/A	Autoimmune disease

T-CELL DEFECTS

DiGeorge Syndrome

(Congenital *primary* Thymic Aplasia)

01

A congenital defect that is <u>marked</u> by:

- Absence or underdevelopment of the Thymus gland(hypoplasia)
  Low T-cells amount
- Hypoparathyroidism
- Facial abnormalities
- Cardiovascular abnormalities

Note:
Hypoplasia: is when an organ doesn't reach its full size (developmental disorders)
Hypoparathyroidism could cause "tetany" which is involuntary muscles constriction, Ca affected (hypocalcemia)
It is a deletion of small piece of chromosome 22.

02

<u>Features</u> of DiGeorge syndrome:

- Children may present with tetany in the complete form:
- Extreme susceptibility to viral, protozoal, and fungal infections.
- Profound depression of T-cell numbers.
- Absence of T-cell responses.

03

<u>Management</u> of DiGeorge syndrome

- Fetal thymus tissue graft transplant(14 weeks old)

B-CELL DEFECTS (GAMMAGLOBULINEMIA)

Patients with B-cell defects are subject to

recurrent bacterial infection **BUT** display normal immunity to most viral and fungal infections.

Because the T cells are not affected. only B cells work in the case of bacterial infection and T cells work in cases of viral infections.

Diverse spectrum ranging from:

- Complete absence of B-cells
- Complete absence of plasma cells_
- Low or absent immunoglobulins (Igs)
- Selective absence of certain immunoglobulins (Igs)

It's genetically transmitted

- Autosomal recessive (X linked)
- making **males** show manifestation (express the disease)
- **females** acting as normal carriers

Management of immunoglobulin deficiencies:	Periodic intravenous immunoglobulin (IVIG) reduces infectious complications.

B-CELL DEFECTS (GAMMAGLOBULINEMIA)

01

X-linked agammaglobulinemia (XLA) or Bruton's hypogammaglobulinemia (Congenital disease)

The most common type, 80% to 90%.
Defect in Bruton Tyrosine Kinase (BTK).
The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow.

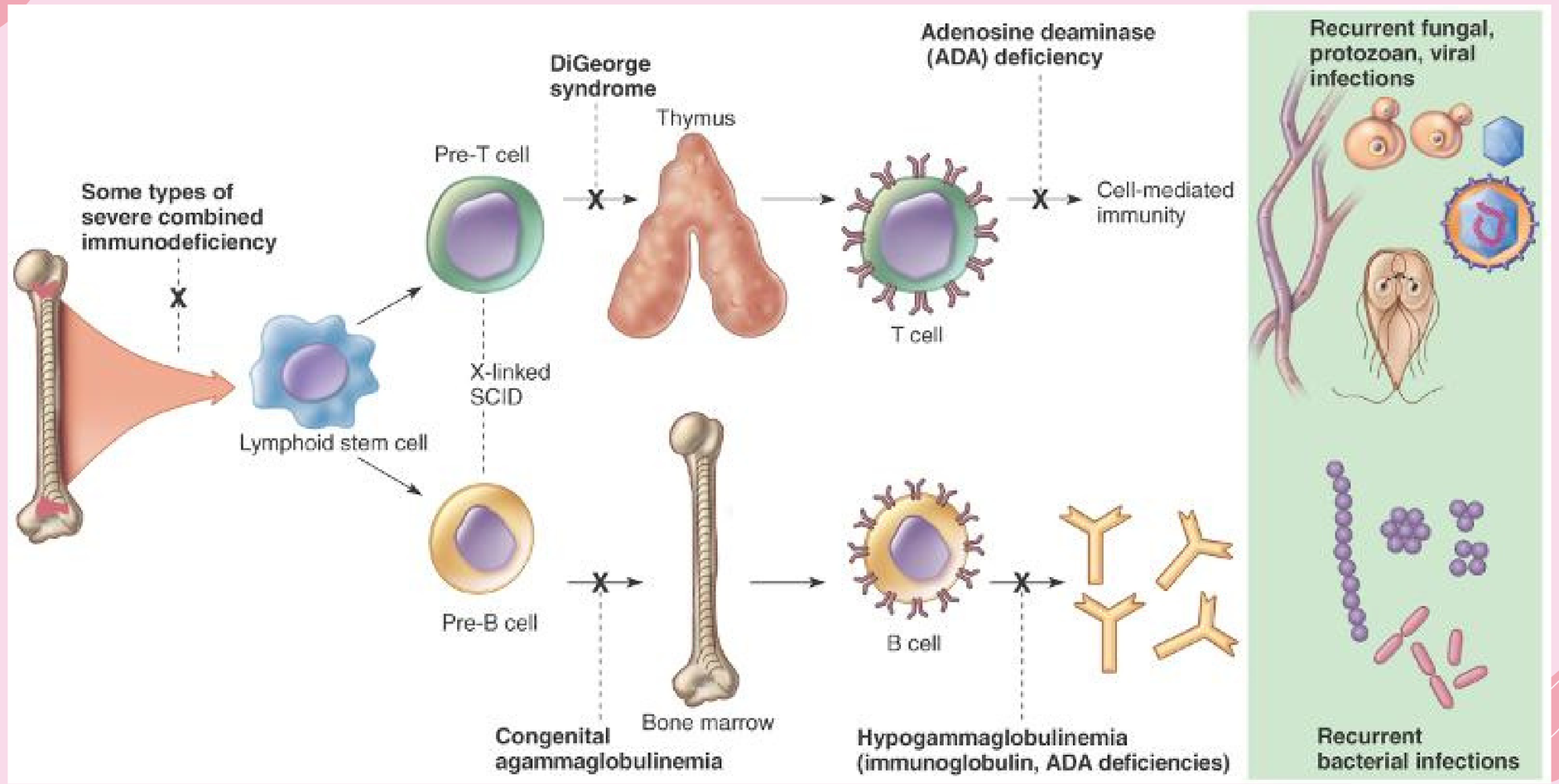
Features of XLA:
Reduced B-cell counts to 0.1 %
(normally 5%-15%)
Absence of Immunoglobulins
Affected children suffer from recurrent pyogenic (pus producing) bacterial infections.

02

Selective immunoglobulin deficiency (Congenital disease)

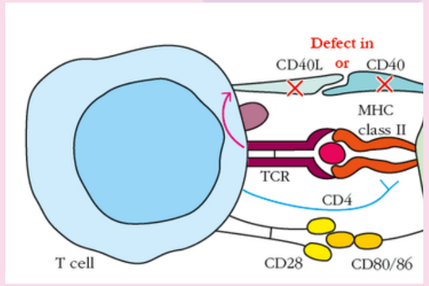
IgA deficiency (1:700) (at every birth)
Most are asymptomatic but may have increased incidence of respiratory tract infections (R.T.I).
Some have recurrent R.T.I and gastrointestinal tract symptoms.

Summary


Some types of severe combined immunodeficiency
X
Lymphoid stem cell
Pre-T cell
DiGeorge syndrome
X
Thymus
T cell
Adenosine deaminase (ADA) deficiency
X
Cell-mediated immunity
X-linked SCID
Pre-B cell
X
Bone marrow
B cell
X
Congenital agammaglobulinemia
Hypogammaglobulinemia (immunoglobulin, ADA deficiencies)
Recurrent fungal, protozoan, viral infections
Recurrent bacterial infections

B-CELL DEFECTS(GAMMAGLOBULINEMIA)

X-linked hyper IgM syndrome (congenital disease):



Characterized by:

- Defective CD40L/CD40 interaction B cell class switching fails.
- Variable **IgM** levels most frequently **high**.
- Low IgG, IgA & IgE. Team 439:(remember the word AGE)

Common variable immunodeficiency disorders:

Disorders of unknown etiology

Characterized by:

- Presentation in childhood or later in life.
- Recurrent respiratory tract infections due to immunodeficiency.
- Reduction in the levels of one or more antibody isotype with normal B cell numbers.
- Impaired B-cell responses to antigen.

BOTH T AND B CELLS DEFECTS

Severe Combined Immunodeficiency (SCID)

- Congenital
- Increased susceptibility to : viral , fungal, bacterial protozoal infectious (starting at 3 months of age) SCID found mainly in babies from 3-6 months
- causes:

Enzyme deficiencies :

1.ADA (adenosine deaminase) deficiency

-Catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine , respectively (Which interferes with DNA synthesis).

2.PNP (purine phosphorylase) deficiency

-Toxic metabolites accumulate in T and B cells.

- Management :

1.Infusion of purified enzymes.

2.Gene therapy

BOTH T AND B CELLS DEFECTS

Severe Combined Immunodeficiency (SCID) Cont.

●Reticular Dysgenesis (RD)
- Initial hematopoietic cell development is blocked by defects in the adenylate kinase 2 gene (AK2)
- Apoptosis of myeloid and lymphoid precursors
- Severe reductions in circulating leukocytes
- Impairment of both innate and adaptive immunity
- Susceptibility to infection by all types of microorganisms
- Without aggressive treatment children die in early, infancy

●Deficiency in cytokine signaling:
- Defects in the gene encoding for common gamma chain of the IL-2, IL-4, IL-7, IL-9.
- IL-15 and IL-21 receptors.
- This leads to widespread defects in B-cell , T-cell and NK-cell development. NK-cell (Natural Killing Cell)

LEUKOCYTE DEFECTS

Quantitative defects (Related to numbers)

Congenital Agranulocytosis
other name : Kostmann's Syndrome

●Defect in the gene inducing G-CSF(Granulocyte Colony Stimulating actor)
note 439 : important for producing granulocytes (play a major role in bacterial infections)

●Features : pneumonia , otitis media , abscesses

**Note
-patient with deficiency in the G-CSF , what's the defect ?
Quantitative congenital agranulocytosis defect

Qualitative defects (Related to Function)

A) Defects in chemotaxis
_Leukocyte Adhesion Deficiency
-Defect in the adhesion deficiency molecules responsible of leukocyte trafficking and migration to sites of infection

مسؤولة عن تحريك كريات الدم البيضاء الى مكان العدوى لقتل البكتيريا

B) Defects in intracellular killing
Chronic Granulomatous Disease (CGD)
-congenital disease
-Defect in the oxidative complex responsible for producing superoxide radicals
-Neutrophils lack the "Respiratory burst" upon phagocytosis
-characterized by recurrent life-threatening and granuloma formation
These severe infection include : skin and bone infection + abscess in internal organs such as: lung , liver and brain

Go back to lecture 2 for a clear explanation on the pathways

COMPLEMENT DEFICIENCY

Deficiency in	Components	Deficiency lead to
Classical pathway	C1 , C2 , C4	Immune-complex disease
Alternative pathway	Factor D Factor B	Infection with pyogenic bacteria and neisseria Spp. No immune-complex disease
MB-lectin pathway	MBL , MASP 1 , MASP 2 C2 , C4	Bacterial infections (Mainly in childhood)
C3b deposition	C3	Infection with pyogenic bacteria and neisseria Spp. Sometimes immune-complex disease
Membrane attack complex components	C5b , C6 , C7 C8 , C9	Infection with neisseria Spp. Only

**Note

-immune-complex disease caused of ? Deficiency in Classical pathway

-Patient came with infection with neisseria only , what's the deficient in this patient ?
Membrane attack complex components

LABORATORY DIAGNOSIS OF ID (IMMUNODEFICIENCY)

Assessment of **Phagocytosis and respiratory burst** (Oxygen Radicals)

Measurement of **Complement proteins** and function (CH50)

T and B cells **counts** (Flow Cytometry)

Evaluation of **antibody levels** and response to antigens

Complete **blood Count** : total & differential

TAKE HOME MESSAGES

01 Immunodeficiency may be congenital or acquired

02 It can involve any component of the immune system such as cells, antibodies, complement etc.

03 Most common presentation of immunodeficiency is recurrent infections that may be fatal due to delay in diagnosis and lack of appropriate therapy

MCQ'S

ANSWERS:
1-D 2-A

1 DEFFICINECY IN ALTERNATE PATHWAY

A	c3	B	C5B	C	MBL	D	Factor D

2 X- LINKED HYPER-IGM SYNDROME (CONGENITAL DISEASE) CHARACTERIZED BY?

A	low IgG iL-10	B	high IgG	C	defective cd30L/cd30	D	Defects

MCQ'S

ANSWERS:

3-D 4-D

3 MEMBRANE ATTACK COMPLEX COMPONENTS MADE OF?

A	C5 , C6 , C7,C8,C9	B	C5a , C6 , C7,C8,C9	C	C5 , C6a, C7a,C8a,C9a	D	C5b , C6 , C7,C8,C9

4 WHAT IS THE CAUSE OF PRIMARY IMMUNODEFICIENCY?

A	Malnutrition	B	Aids	C	immunosupressive therapy	D	Genetic mutation

MCQ'S

ANSWERS:

5-A 6-D

5 WHAT IS ASSOCIATED WITH ABSENCE OR UNDERDEVELOPMENT OF THYMUS?

A	Digeorge syndrome	B	XLA	C	IgA deficiency	D	BTK

6 IN B-CELLS DEFECT THERE WILL BE

A	Virus infection	B	Protozoal infection	C	bacterial infection	D	both B & C

MEET THE TEAM

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