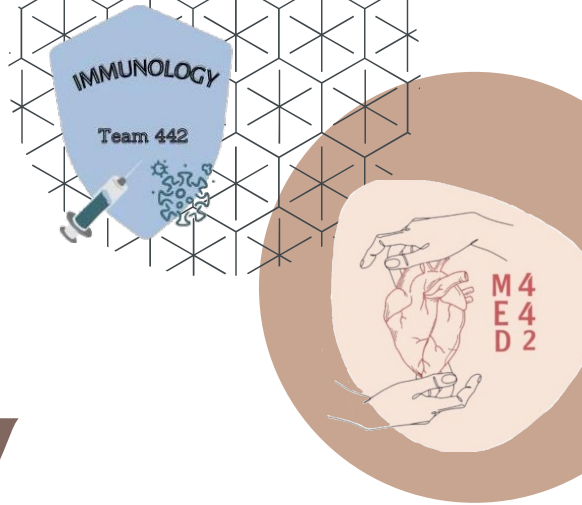
Foundation block

KSU



Immunodeficiency disorders

W7
L6

Color index :

- Main text
- Important
- Dr notes
- Females slides
- Male slides
- Extra

Editing File

Objectives

- Identify the immunodeficiency is due to defect in the immune function.
- Describe the classification of immunodeficienc.
- Explain the presentations of different types of immunodeficiencies (e.g. recurrent infections).
- Understand the varieties of immune system deficiencies involving defects in: T cells, B cells, phagocytes and complement.
- Know the laboratory investigations for immunodeficiency disorders.

Immunodeficiency

Definition : A state in which the ability of the immune system to fight infectious disease is compromised or entirely absent
***A person who has an immunodeficiency is called immuno-compromised**

is considered to be present when infections are:

01 Frequent and severe

02 Caused by opportunistic microbes
bacteria, viruses, fungi

03 Resistant to antimicrobial therapy. ability of a microbe to resist the effects of medication

Secondary (Acquired)

- Malnutrition
- Viral and Bacterial Infections(Aids)
- Excessive Proteins Loss e.g (Burns, nephrotic syndrome) cause damage to kidney which lead to protein loss
- Immunosuppressive Therapy (Corticosteroids) Treatment that lowers the activity of the body's immune system

Classification of Immunodeficiency (ID)

Primary (Congenital) Genetic Mutation:

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

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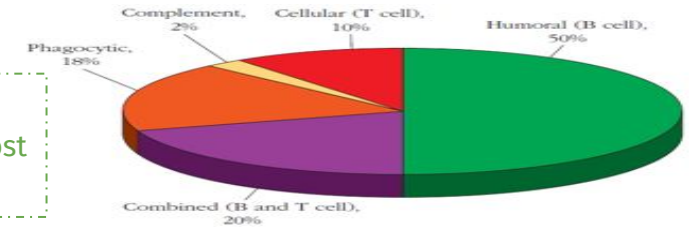
Distribution of primary



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

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, glomerulonephritis
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	N/A
Regulatory T cells	N/A	Autoimmune disease

- T-cells
- B-cells

Acquired Immunity
(adaptive)
affected by secondary

the effect of primary and secondary

Natural Immunity
(innate)
affected by primary

- Phagocytic cells unable to engulf or kill the antigen
- Complement proteins

T-cell defects

1

A congenital defect is characterized by: Low T-cell amounts
- Absence or underdevelopment of the Thymus gland (hypoplasia)
- Hypoparathyroidism causes tetany which is involuntary muscles constriction,Ca affected (hypocalcemia)
- Facial abnormalities
- Cardiovascular abnormalities

DiGeorge Syndrome (Congenital Thymic Aplasia)

2

Features of DiGeorge syndrome:
- Extreme susceptibility to viral protozoal, and fungal infections.
- Profound depression of T-cell numbers.
- Absence of T-cell response
- Children may present with tetany

3

Management of DiGeorge syndrome:

Fetal thymus tissue graft (14 weeks old)

graft: is the surgical transplant of living tissue

*438

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)

B-cell defects are characterized by:

- Complete absence of B cells or Plasma cells.
- Low or absent of immunoglobulins (Igs)
- Selective absence of certain Igs.

It's genetically transmitted
(Autosomal recessive)
(X linked) making males show manifestation (express the disease) and females acting as normal carriers

Management of immunoglobulin deficiencies:

Periodic intravenous immunoglobulin (IVIG) reduces infectious complications.

B-cell Defects (Gammaglobulinaemias)

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

Dr note:
يصيب الرجال فقط XLA
ما يصيب النساء يكونون فقط carries

- The most common type, 80% to 90%.
- Defect in Bruton Tyrosine Kinase (BTK). (The reason for the other name)
  Agammaglobulinemia is a group of inherited immune
- The defect involves a block in maturation of pre- B- cells to mature B-cells in bone marrow.

Features of XLA:

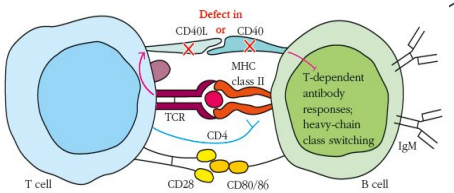
- Reduced B-cell counts to 0.1 % (normally 5%-15%)
- Absence of Immunoglobulins
- Affected children suffer from recurrent pyogenic bacterial infections

Selective immunoglobulin deficiency (Congenital disease)

- IgA deficiency (1:700)
- 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

B-cell Defects (Gammaglobulinaemias)

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 & B-cell 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 & B-cell 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.

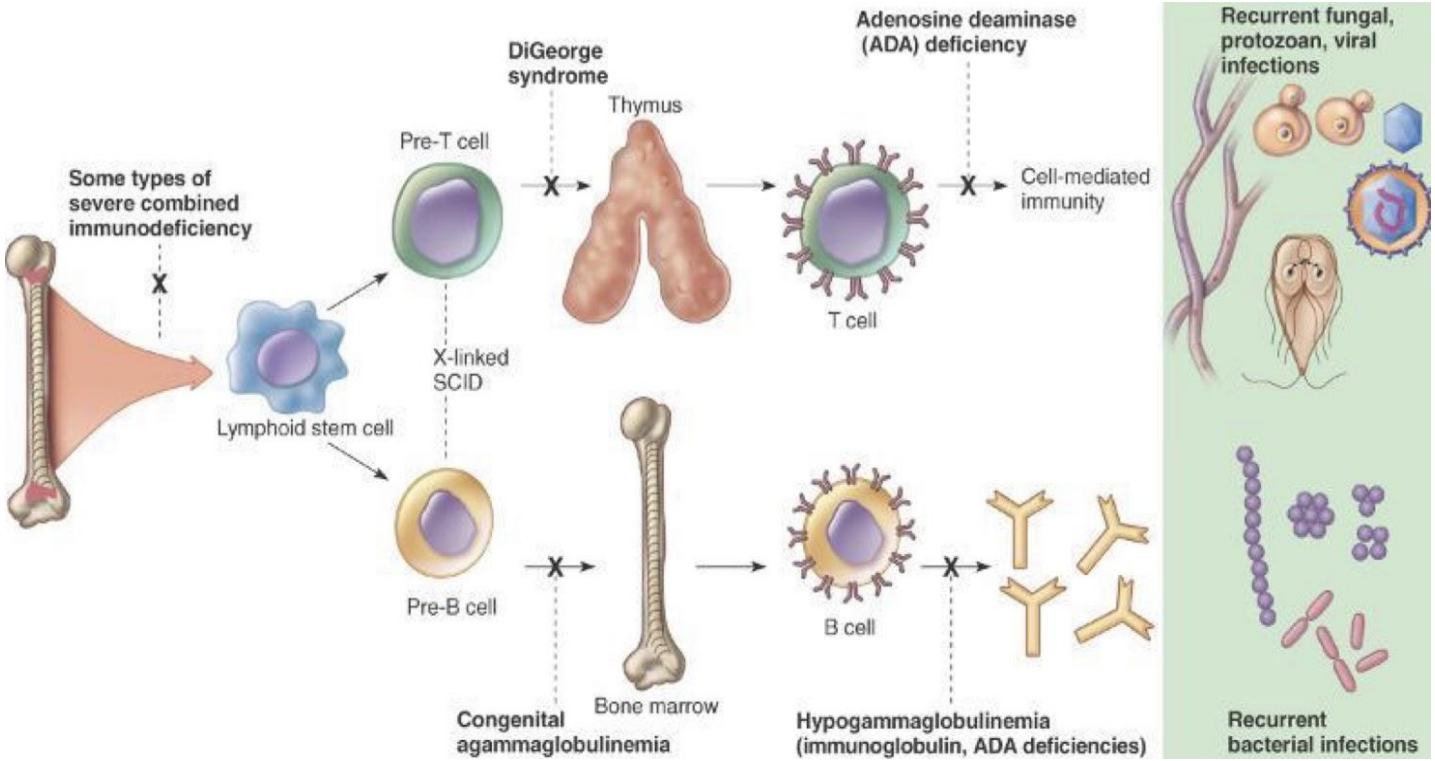
Deficiency in cytokine signaling:

- 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).

Features of SCID:

Increased susceptibility to; viral, fungal bacteria protozoal infection (starting at 3 months of age)

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
Congenital agammaglobulinemia
B cell
X
Hypogammaglobulinemia (immunoglobulin, ADA deficiencies)
Recurrent fungal, protozoan, viral infections
Recurrent bacterial infections

Leukocyte Defects

Qualitative defects (Related to function)

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

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 إلى مكان العدوى لقتل البكتيريا

Quantitative defects (Related to numbers)

Congenital Agranulocytosis

other name : Kostmann's Syndrome

- Defect in the gene inducing G-CSF (Granulocyte Colony Stimulating Factor) note 439 : important for producing granulocytes (play a major role in bacterial infections)
- Features : pneumonia (التهاب الرئة) , otitis media, abscesses

**Note

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

Thanks to Teams 441,439 and 438 <3

Complement Deficiency

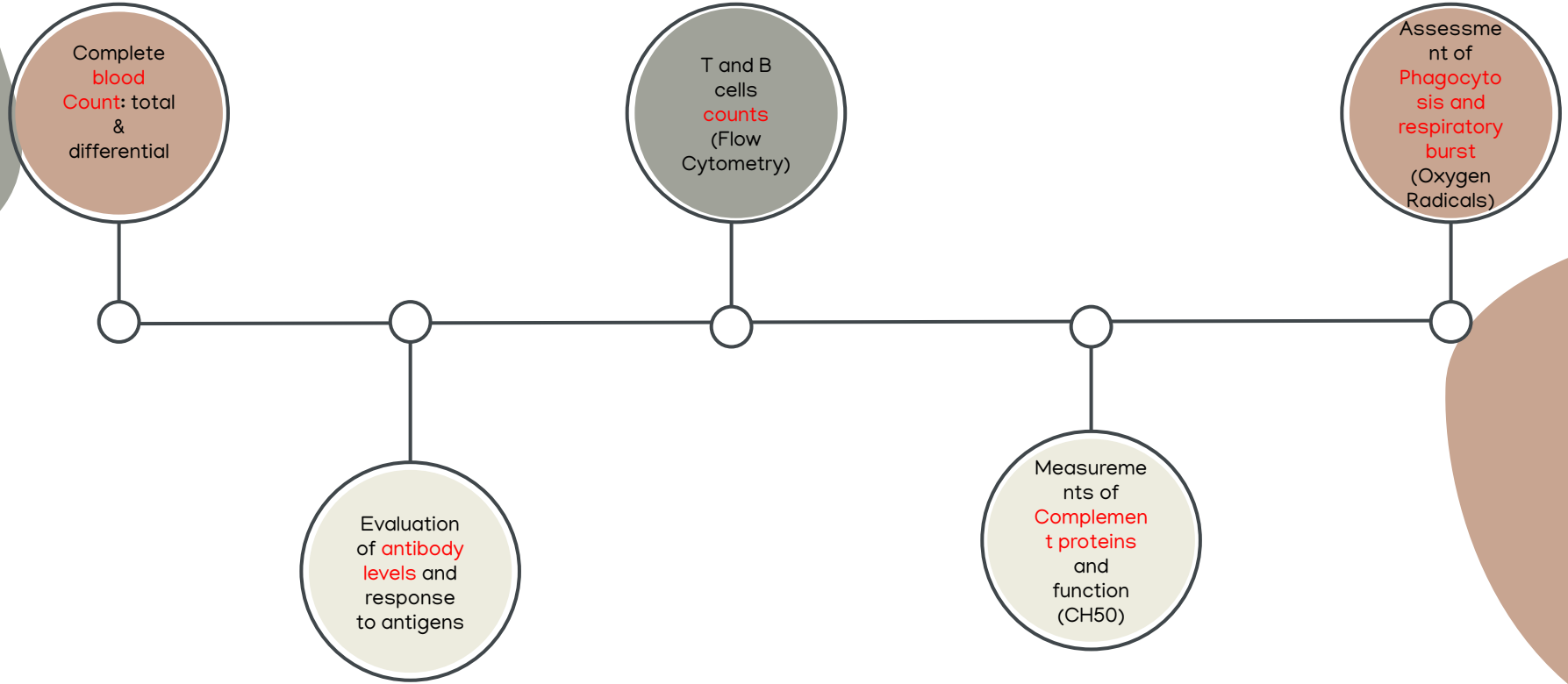
Deficiency in	Components	Deficiency lead to
Classical pathway	C1, C2, C4	Immune-complex disease
Alternative pathway	Factor D Factor B	Infection with pyogenic bacteria and neisseria Spp. No immune-complex disease
MB-lectin pathway	MBL, MASP 1, MASP 2 C2, C4	Bacterial infection (Mainly in childhood)
C3b deposition	C3	Infection with pyogenic bacteria and neisseria Spp. Sometimes immune-complex disease
Membrane attack complex components	C5, 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

**What are the membrane attack components?
C5B, C6,C7,C8,C9

Laboratory diagnosis of ID (Immunodeficiency)



Take Home Messages :

1. Immunodeficiency may be congenital or acquired.
2. It can involve any component of the immune system such as cells, antibiotics, complement, etc.
3. Most common presentation of immunodeficiency is recurrent infections that may be fatal due to delay in diagnosis and lack of appropriate therapy

MCQ

Q1: Excessive protein loss is an example of			
A- Primary ID	B- Secondary ID	C- Both A, C	D- None is correct
Q2:Burton's hypogammaglobulinemia is marked by			
A- Complement defect	B- Cellular (T cells)	C- Humeral (B cells) defect	D- Phagocytic defect
Q3: Which of the following is caused by a defect in the gene inducing G-CSF			
A -Congenital Agranulocytosis	B- Leukocyte adhesion deficiency	C- Chronic granulomatous disease	D) A&C
Q4: which one of the following is characterized by recurrent life-threatening & granuloma formation?			
A- congenital agranulocytosis	B- leukocyte adhesion deficiency	C- chronic granulomatous disease	D- SCID

1:B
2:C
3:A
4:C

More HARD Questions

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★ Special thanks to Immunology Team (441).

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