جامعة الملك سعود
King Saud University

Immunodeficiency disorders

Color code:
Important in red
Extra in blue

Immunology
MED438

Reviewed by Razan AlRabah & Khalid Alkhani

For team error adjustments, click here

Objectives

- Identify that Immunodeficiency is due to a defect in the immune function.
- Describe the classification of Immunodeficiency.
- Explain the presentations of different types of Immuno-deficiencies (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

Definition

Immunodeficiency Disorders: 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 said to be immuno-compromised

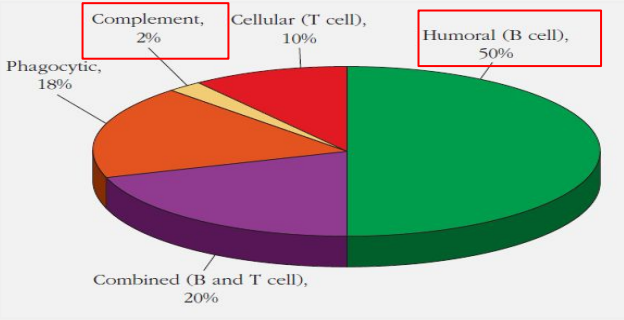
Immunodeficiency is present when:

- Infections are frequent and severe
- Infections are caused by opportunistic microbes (pathogenic normal flora)
- Infections are resistant to therapy (difficult to treat)

Immunodeficiency Classifications

Primary (congenital/present at birth):

1. Genetic Mutation (Monogenic or Polygenic)



Distribution of Primary ID

Secondary (Acquired):

1. Malnutrition (loss of nutrients even when consumption is adequate)
2. Viral and Bacterial infections (AIDS: only virus that attacks helper T cells)
3. Immunosuppresive therapy (corticosteroids: drugs that resemble cortisol and reduce the activity of the immune system)
4. Excessive protein loss (burns: loss of interstitial fluid, nephrotic syndrome: protein gets filtered in urine)

They Affect:

1- Innate (natural) Immunity:

- Phagocytic cells
- Complement proteins

2- Acquired Immunity:

- T cells (recall: AIDS attacks CD4 cells, which are the heart of the immune system)
- B cells (The main deficient part in primary immunodeficiency)

Pattern of infections and symptoms associated with primary immunodeficiencies

Not that important. For your own read. Just recall that B cells are associated with pyogenic infections while T cells are associated with viral, fungal, and protozoal infections

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

Source: Adapted from H. M. Lederman, 2000, The clinical presentation of primary immunodeficiency diseases, Clinical Focus on Primary Immune Deficiencies. *Towson, MD: Immune Deficiency Foundation* **2**(1):1.

T-cell Defects

DiGeorge Syndrome (Congenital Thymic Aplasia)

Features	Definition	- Congenital defect marked by the absence (aplasia) or underdevelopment (hypoplasia) of the Thymus gland. (this will affect the maturation of T-cells)
	Symptoms	- Hypoparathyroidism (causes tetany and hypocalcemia) - Facial abnormalities - Cardiovascular abnormalities
	Development (complete form)	- Extreme susceptibility to viral, fungal, and protozoal infections - Major decrease in T cells (results in absence of T cell response-No CMI)
Management	- Fetal Thymus Tissue Graft (14 weeks old) graft: is the surgical transplant of living tissue	

Flowcytometry is used to test for this condition because it counts the number of B and T cells separately, whilst a CBC only gives the WBC count in general

B-cell Defects

Agammaglobulinaemias

Note:
When B cells are defected, T cells are not affected.
But not vice versa

Characterized by:

- Complete absence of B cells or Plasma cells, resulting in low Igs.
- Selective absence of certain Igs (such as IgA deficiency)

It is transmitted genetically (mainly monogenic) (autosomal/X-linked*) and can cause recurrent bacterial infections.

B cell Defects include the following:

1. X-linked Agammaglobulinaemia (XLA) Or Bruton's hypogammaglobulinaemia

Features	Definition	- Most common congenital disease marked by a defect in Bruton Tyrosine Kinase (BTK), disturbing the maturation of B cells.
	Causes	- Reduced B cell count to 0.1% (normally 5-15%) - Absence of Igs - Recurrent pyogenic (pus-producing) bacterial infections
Management	- Periodic IV immunoglobulin (IVIG) injection	

*X-linked transmission is more common in males (females can be normal carriers)

B-cell Defects

2. Selective Immunoglobulin Deficiency (IgA deficiency)

Features	Definition	- Congenital disease marked by IgA deficiency (most common SID 1:700)
	Symptoms	Mostly Asymptomatic, but may result in: - Respiratory tract infections (RTI) - GIT symptoms
Management	- Periodic IV immunoglobulin (IVIG) injection	

3. X-linked Hyper-IgM Syndrome

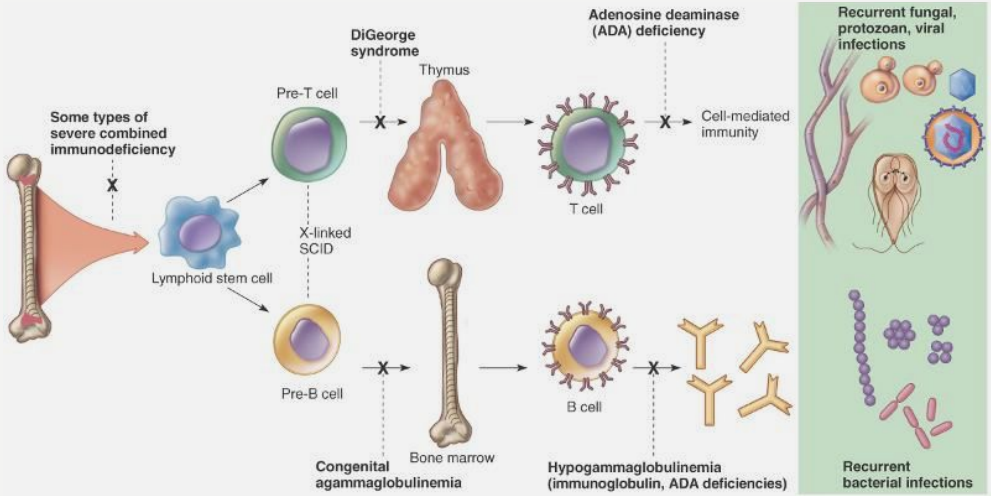
Features	Definition	- Congenital disease marked by: High IgM levels Low IgG, IgA, & IgE levels.
Management	- Periodic IV immunoglobulin (IVIG) injection. (depends on half life of Ig)	

Note: The B cell normally switches from producing IgM to producing IgA or IgG. In this syndrome, the B cells will lack this ability, leading to high levels of IgM

Combined B and T cell Defects

Severe Combined Immunodeficiency (SCID)

Features	Definition	- Congenital disease marked by the following enzyme deficiencies: 1. ADA (adenosine deaminase) → (important in DNA synthesis) 2. PNP (purine phosphorylase) → (important in detoxifying cell metabolites)
	Development	- Increased susceptibility to viral, bacterial, fungal and protozoal infections
Management	- Infusion of purified enzymes and gene therapy	



Leukocyte Defects

Quantitative

Definition

- Congenital agranulocytosis: acute condition involving lowered WBC count
- Defect in the gene inducing factor G-CSF (granulocyte colony stimulating factor)

Can Cause

- Pneumonia
- Otitis Media (ear inflammation)
- Abscess

Qualitative

Defect in Chemotaxis

- Deficiency in Leukocyte Adhesion (**LAD**).
- Affects migration of leukocytes to infection sites.

Defect in intracellular killing

- Chronic Granulomatous Disease (**CGD**)
- Defect in production of superoxide radicals (pathogen gets engulfed but survives phagocytosis)

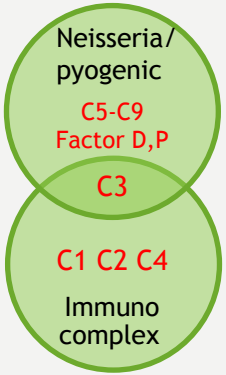
Recall that ROS have an important role in killing pathogens during phagocytosis

- Neutrophils lack respiratory burst
- Causes recurrent bacterial/fungal infections
- Granuloma formation

Complement Deficiency

Deficiency in	Components (that form C3 convertase)	Deficiency leads to
Classical pathway	C1 C2 C4	immune-complex disease
MB-lectin pathway	C2 C4 MBL MASP1/2	(MBL) Leads to bacterial infections
Alternative pathway	Factor D+P	Neisseria/pyogenic bacteria infection, no immuno-complex
C3b deposition (all pathways)	C3	Neisseria/pyogenic bacteria infection, sometimes immuno-complex
Membrane Attack Components (all pathways)	C5 C6 C7 C8 C9	Neisseria only

Deficiencies



Laboratory diagnosis of ID

1. Complete blood count : total & differential (to differentiate the WBCs)
2. Evaluation of antibody levels and response to antigens
3. T and B cells counts (Flowcytometry)
4. Measurement of complement proteins and function (CH_{50})
5. Assessment of phagocytosis and respiratory burst (oxygen radicals)

Take Home Message

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

Quiz:

1. A patient was presented to the clinic with cardiovascular and facial abnormalities. It was found that his serum calcium level was low. What might he have?

a) Dystrophic calcification
b) Di George Syndrome
c) Bruton Tyrosine Kinase deficiency
d) SCID

2. Which of the following diseases is mostly asymptomatic?

a) XLA
b) Hyper IgM Syndrome
c) IgA Deficiency
d) IgM Deficiency

3. A patient's cells failed to detoxify their metabolic wastes. What condition is this characterized by and how is it treated?

a) Adenosine deaminase deficiency--IVIG Injection
b) Bruton Tyorsine Kinase deficiency--Gene therapy
c) SCID--Blood transfusion
d) Purine phosphorylase deficiency--Purified enzyme injection

4. Which of the following leads to pathogen survival of phagocytosis?

a) Macrophage deficiency
b) Neutrophil deficiency
c) Superoxide deficiency
d) PATRICIA

5. Which of the following could cause otitis media?

a) G-CSF deficiency
b) hyposoupism
c) hyperhowardism
d) GC-OOF deficiency

6. A deficiency in which of the following will lead to a Neisseria infection only?

a) Alternative pathway
b) Membrane attack complex
c) Classical pathway
d) Staphylothomas traineus

1.B 2.C 3.D 4.C 5.A 6.B

Team Leaders:

Sedra Elsirawani

Ibrahim Aldakhil

Team Members:

1. Noura Alturki
2. Lama Alzamil
3. Shahad Althaqeb
4. Leena Alnassar
5. Joud Aljebreen
6. Renad Alkanaan
7. Shahad Bin Selayem
8. Sara Alflaij

1. Alwaleed Alsaleh
2. Muhannad Makkawi
3. Abdullah Basamh
4. Hashem Halabi
5. Amjad Albaroudi
6. Abdulrahman Alhawas
7. Mohammed Alhuqbani

Immunology

MED438