University of Basrah, Medical College, Microbiology Department

Microbiology/ 3rd Year M.B.CH.B. Students

Part V: Basic & Clinical Immunology (17 hours)

Lecture 15

Duration: 1 hour

Immunodeficiency Diseases

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Reference: Roitt's Essential Immunology 13th Edition

For more detailed instruction, any question, cases need help please post to the group of session.

Key definitions

Pathogen-associated molecular patterns (PAMPs): particular molecular patterns that are typically associated with infectious agents. PAMPs after being recognized trigger activation of the innate immune system.

Pattern recognition molecules: present either as cell-associated receptors (PRR) on the surface of the immune cells [Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-1-like receptors (RIRs)] or soluble molecules [complement, mannose binding lectin, C-reactive protein, and lysozyme]. Pattern recognition molecules can recognize the PAMPs.

(NADPH): nicotinamide adenine dinucleotide phosphate

NK cells: natural killer cells play important roles in surveillance & subsequent destruction of infected cells & production of cytokines such as IFN-γ.

Factor I: a protein regulates the complement system activation by cleaving cell-bound or fluid phase C3b & C4b

MyD88: adaptor protein is required for signaling through a number of Tool-like receptors (TLRs).

IL1R-associated kinase-4 (IRAK4): involved in signaling through IL-1 & IL-18 receptors, also through a number of Tool-like receptors (TLRs).

Hereditary angioedema: a disorder characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body develop swelling are the limbs, face, intestinal tract, and airway.

Learning objectives (LOs)

Definition of immunodeficiency	LO.1
Deficiencies of pattern recognition receptor (PRRs) signaling	LO.2
Phagocytic cell defects	LO.3
Primary immunodeficiency affecting other cells of innate response	LO.4
Complement system deficiencies	LO. 5
Cytokines & cytokine receptor deficiencies	LO.6
Examples of congenital immunodeficiency	LO.7
Secondary (Acquired immunodeficiency)	LO.8
Laboratory investigation of immunodeficiency	LO.9

LO.1

What is immunodeficiency?

"State in which the immune system is unable to respond appropriately and effectively to infectious microorganisms"

Infections suggesting underlying immune deficiency defined as:

SPUR

S: Severe

P: Persistent

U: Unusual

R: Recurrent

LO.1

What makes an individual "immunocompromised"?

Factors that cause defective Immunity:

1. **Congenital (Intrinsic defect)-----** **Primary immunodeficiency**
   - **Single-gene disorder**
   - **Polygenic (??)**
   - **HLA Polymorphisms**

2. **Acquired-------** **Secondary immunodeficiency**

(Diseases or conditions affecting immune components)

LO.2

Deficiencies of pattern recognition receptor (PRRs) signaling:

Examples:

1. MyD88 deficiency:

- **Patients with MyD88 deficiency suffer from severe life-threatening infections with pyogenic bacteria (pneumococci & *Salmonella*).**

2. IL1R-associated kinase-4 (IRAK4)

- **IRAK4 deficient individuals, Gram +ve pyogenic bacteria (*Streptococcus pneumonia* & *Staphylococcus aureus*) are most commonly seen.**

LO.3

Phagocytic cell defects

Chronic Granulomatous Disease:

Monocytes & neutrophils fail to produce reactive oxygen intermediates; defect in (NADPH) oxidase system.

Patient suffers from relatively restricted range of infectious pathogens.

The most common are:

- ***Staphylococcus aureus***
- ***Candida albicanus***
- ***Aspergillus fumigatus***

LO.4

Primary immunodeficiency affecting other cells of innate response

- NK cells (susceptible to viral and mycobacterial infections)
- Dendritic cells
- Monocytes
- Mast cells (defect in certain gene causes cold urticaria in which patient's mast cells spontaneously degranulate in cold temperatures.

LO. 5

Complement system deficiencies

1. Lacking Factor I ------- inability to destroy C3b lead to continual activation of the alternative pathway
   - very low C3 & Factor B levels
   - Normal C1, C4 & C2 levels

Repeated life-threatening infection with pyogenic bacteria.

2. Defect in C1 inhibitor ------- hereditary angioedema

3. Deficiencies in C1q, C1r, C1s, C2, C3, & Factor I ---------- can all predispose to development of immune-complex mediated autoimmune diseases (SLE).

4. Patients deficient in components of MAC exhibit increased susceptibility to disseminated *Neisseria gonorrhae.*

5. Patients with MASP-2 deficiency have increased pyogenic infections (such as *Streptococcus pneumonia).*

Q: Reduced levels of MBL are fairly common but does not result in a detectable increase in infections in most cases. Explain Why?

LO.6

Cytokines & cytokine receptor deficiencies

Examples:

Mutations in the genes encoding:

1. **IL-10, IL-10 R1 & IL-10 R2 lead to defective regulation of myeloid cells & development of inflammatory bowel disease.**
2. **IL-17 ------ increased susceptibility bacterial infections & candidiasis.**

LO.7

B-cell deficiencies:

Infantile agammaglobulinaemia (Bruton's syndrome)

- **pure B cell deficiency syndrome.**
- **X- linked due to lack of tyrosine kinase, which results in failure of B cell development and few or absent B cell count with low immunoglobulin levels.**
- **patient presented with repeated pyogenic infection.**

(LO.7)

Clinical case example of Bruton's disease:

- 12-month-old boy with 4 episodes of severe gram-positive bacterial pneumonia in the last 6 months.

Age | Frequency | Severity | Microbes | When?

- Had recurrent diarrhea (Giardia lamblia) & his tonsils are barely detectable.

Microbes

- Below the norm for height and weight.

Failure to grow

- Recommended pediatric immunizations (low IgG & low B cells).

Lab.

- Has 3 healthy sisters aged 3, 5, & 7 years. The family lost a boy at 10 months of age due to bacterial pneumonia 8 years ago.

Family history

(LO.7)

IgA deficiency

- **The most common immunodeficiency.**
- **Very low IgA level with normal B cell count.**
- **Some have recurrent infections, especially of the sinuses and lung, caused by pyogenic bacteria.**
- **Anti-IgA antibodies can be detected in about one-third of the patients.**

(LO.7)

T- Cell Deficiencies

Thymic Aplasia (Digeorge Syndrome)

- **Severe viral, fungal and protozoal infections occur early in life.**
- **Frequent infection episodes.**
- **Absence of T cells while B cells have normal count but defective function.**

(LO.7)

Hyper IgM syndrome

- **This syndrome characterized by low levels of IgG, IgA, and IgD in association to a marked elevation of IgM.**
- **The helper T cells have a defect in the surface protein CD40L that interact with CD40 on the B cell surface.**
- **This results from inability of B-cell to switch from the production of IgM to other classes.**

(LO.7)

Combined immunodeficiency

Severe combined immunodeficiency disease (SCID)

- **Recurrent infections caused by bacteria, viruses, fungi and protozoa occur in early infancy (3 months).**
- **Deficiency of both B-cell and T-cell function.**
- **It is inherited disease due to defect in differentiation of an early stem cell.**

(LO.8)

Secondary (Acquired immunodeficiency)

1. Immunodeficiency caused by drugs

Drugs causing neutropenia, when neutrophil count <500ul, it predispose to severe infections caused by pyogenic bacteria and enteric gram-negative rods.

- **Cytotoxic drugs in cancer chemotherapy;**
- **Immunosuppressive drugs in autoimmune disease;**
- **Corticosteroids**

2. Immunodeficiency caused by infection

- In patients with AIDS, human immunodeficiency virus (HIV) alters T cell immunity and allows further infection with opportunistic pathogens.

- Certain bacteria release toxins that function as super antigens

3. Other causes of Immunodeficiency

- **Renal failure**
- **Diabetes**
- **Malnutrition**
- **Liver Failure**

(LO.9)

Laboratory investigation of immunodeficiency (1)

(Look for secondary immunodeficiency General):

- **Full blood count and differential**

Tests of humoral (antibody) immunity

Tests for Cell mediated immunity

Tests for phagocytic cells

Tests for Complement

Definitive tests:

Molecular testing and Gene mutations

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Thank You