Immune deficiency disorders

Immunology Unit
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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 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.
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 said to be immuno-compromised
A boy with congenital ID lived in a bubble for 12 years before he died.
Immunodeficiency is considered to be present when infections are:

- Frequent and severe
- Caused by opportunistic microbes
- Resistant to antimicrobial therapy
Classification of ID

Primary
(Congenital)

Genetic Mutation
Monogenic (Single gene)
Polygenic (Multiple genes)

Secondary
(Acquired)

Malnutrition
Viral and Bacterial Infections
(AIDS)
Immunosuppressive Therapy
(Corticosteroids)
Excessive Proteins Loss
(Burns, nephrotic syndrome)
Primary or Acquired Can Affect

Natural Immunity
- Phagocytic Cells
- Complement Proteins

Acquired Immunity
- T cells
- B cells
Distribution of Primary Immunodeficiencies

- Complement: 2%
- Cellular (T cell): 10%
- Humoral (B cell): 50%
- Phagocytic: 18%
- Combined (B and T cell): 20%
## Pattern of infections and symptoms associated with primary immunodeficiencies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Opportunistic Infections</th>
<th>Other Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Antibody</td>
<td>Sinopulmonary (pyogenic bacteria)</td>
<td>Autoimmune disease (autoantibodies, inflammatory bowel disease)</td>
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<td></td>
<td>Gastrointestinal (enterovirus, giardia)</td>
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<tr>
<td>Cell-mediated immunity</td>
<td>Pneumonia (pyogenic bacteria, <em>Pneumocystis carinii</em>, viruses)</td>
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<tr>
<td></td>
<td>Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)</td>
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<tr>
<td>Complement</td>
<td>Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)</td>
<td>Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)</td>
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<tr>
<td>Phagocytosis</td>
<td>Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)</td>
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<tr>
<td>Regulatory T cells</td>
<td>N/A</td>
<td>Autoimmune disease</td>
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</tbody>
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T-cell defects
DiGeorge Syndrome (Congenital Thymic Aplasia)

A congenital defect that is marked by:

- Absence or underdevelopment of the Thymus gland (hypoplasia)
- Hypoparathyroidism
- Facial abnormalities
- Cardiovascular abnormalities
Features 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
Management of DiGeorge syndrome

Fetal thymus tissue graft
(14 weeks old)
B-cell defects

(Gammaglobulinaemias)
Patients with B-cell defects are subject to:

Recurrent bacterial infections

but

Display normal immunity to most viral and fungal infections

Why ???
Diverse spectrum ranging from:

- Complete absence of B-cells
- Complete absence of plasma cells
- Low or absent immunoglobulins
- Selective absence of certain immunoglobulins
- Genetic Transmission
  - **Autosomal recessive**
  - **X-linked disease:**
    - Females: carriers (normal)
    - Males: manifest the disease
X-linked agammaglobulinaemia (XLA) or Bruton’s hypogammaglobulinaemia (Congenital disease)

The most common type, 80 to 90 percent

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 percent (normally 5-15 percent)

- 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
X- linked hyper-IgM Syndrome (Congenital disease)

Characterized by:

- Low IgG, IgA & IgE
- Variable IgM levels most frequently high
Management of immunoglobulin deficiencies:

*Periodic intravenous immunoglobulin (IVIG) reduces infectious complications
Severe Combined Immunodeficiency (SCID) (Congenital disease)

Causes of SCID:

Enzyme deficiencies:

1. ADA (adenosine deaminase) deficiency
2. PNP (purine phosphorylase) deficiency

Toxic metabolites accumulate in T and B cells
Features of SCID

- Increased susceptibility to viral, fungal, bacterial protozoal infections (starting at 3 months of age)
Management of SCID

1. Infusion of purified enzymes
2. Gene therapy
Leukocyte defects

Quantitative

Qualitative
Quantitative Defects

Congenital agranulocytosis:

Defect in the gene inducing G-CSF (granulocyte colony stimulating factor)

Features:

- Pneumonia, otitis media, abscesses
Qualitative Defects (Congenital disease)

A. Defect in chemotaxis
   Leukocyte adhesion deficiency (LAD)
   Defect: in the adhesion molecules responsible of leukocyte trafficking and migration to sites of infection

B. Defect in intracellular Killing
   Chronic granulomatous disease:
   Defect: in the oxidative complex responsible for producing superoxide radicals
Chronic granulomatous disease (CGD) (Congenital disease)

Neutrophils lack the "respiratory burst" upon phagocytosis

- Characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation
Complement Deficiency
Deficiency of all complement components have been described C1-C9.
Laboratory diagnosis of ID

1. Complete **blood count**: total & differential
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