Chapter 1

Introduction

Immune Deficiency Diseases are not rare!
The Eyes See Only What the Mind Knows!

Primary immune deficiencies (PID) are a group of heterogeneous disorders characterized by increased susceptibility to infections, autoimmunity, and malignancy due to a defect in the immune system.

The immune system is akin to an army that constantly protects us from our enemies. In this context, pathogenic microorganisms like bacteria, virus, and fungi can be presumed as our enemies and the white blood cells (neutrophils, lymphocytes) as the soldiers in the army of immune system that protect us. Absence or dysfunction of one of these cells would put an individual at unusually increased risk of infections, these conditions are called 'primary immune deficiencies.'

What are the functions of a healthy immune system?

1. Protection from invading microbes
2. Deletes autoreactive cells and prevents autoimmunity
3. Keeps a check on mutant cells and prevents cancers—*cancer surveillance*

A defect in immune system would therefore predispose an individual to

1. Increased risk of infections
2. Increased autoimmune diseases
3. Increased predisposition for malignancies

Therefore, primary immune deficiencies are better called 'disorders of immune dysregulation'.

What does the term 'Primary' mean?

The term 'primary' in PID means these are genetic diseases. Any component of the immune system—cells, proteins (immunoglobulins), enzymes involved in immune regulation may be at defect causing PID. PIDs are now known as Inborn Errors of Immunity (IEI). It must be noted that immune deficiencies can be secondary to infections like HIV/AIDS or usage of drugs like corticosteroids; however, secondary immune deficiencies are beyond the scope of the discussion of this book.

Basic Components of the Immune System

Before discussing PIDs in-depth, let us quickly revise how the immune system functions to keep us healthy (Fig. 1.1):

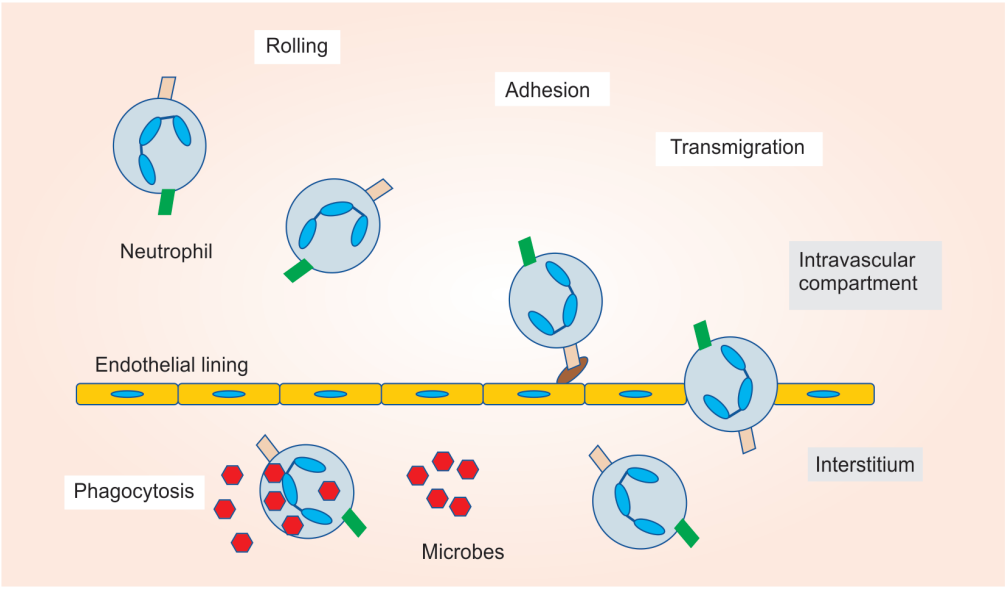
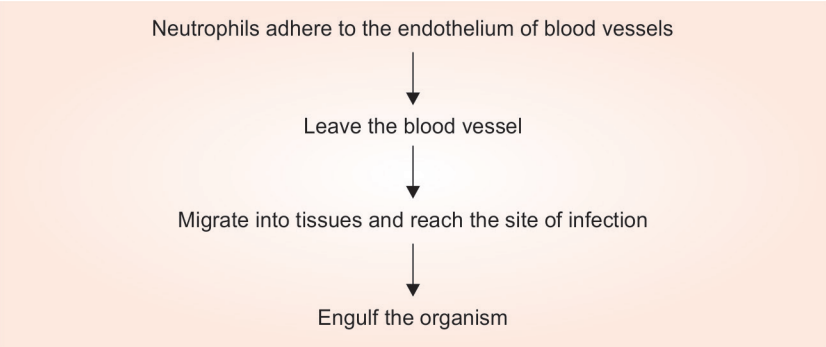


Fig. 1.1: Leukocyte adhesion and extravasation to the site of infection

A. When a microbe enters our body/tissue—tissue macrophages engulf the organism—*phagocytosis.*
B. Neutrophils present in the bloodstream leave the blood vessels to reach the tissues.



C. After phagocytosis, microbes are killed within macrophages and neutrophils. This process needs enzymes like NADPH oxidase.

Clinical implications

a. If neutrophils are absent in an individual, he/she would fail to handle pathogens (bacteria/fungi), e.g. severe congenital neutropenia.
b. If neutrophils cannot adhere to the endothelium, they would not be able to reach infected tissues. This would lead to recurrent infections, e.g. leukocyte adhesion deficiency.
c. If intracellular killing is defective, e.g. NADPH oxidase deficiency, this would lead to persistent infections and autoimmunity, e.g. chronic granulomatous disease.

T Cells and B Cells

a. B cells produce immunoglobulins (IgG, IgA, IgM and IgE) which handle various pathogens (predominantly extracellular bacteria). This is called *humoral (humor in greek meaning body fluid) immunity.*
b. T cells—CD8 T cells kill viral infected cells and play an important role in handling intracellular infections. This is called *cellular immunity*.

Clinical implications

1. Recurrent bacterial infections—think of B cell defect.
2. Viral/fungal infections—think of T cell defect.

Clinical Approach to Immune Deficiency

A systematic approach is needed to arrive to an appropriate diagnosis in a patient with suspected immune deficiency. One must attempt answering the following questions.

1. *Is it an immune deficiency?*
   Presence of warning signs (described in Chapter 3) would be strong pointer towards an immune deficiency.
2. *What is the type of immune defect?*
   B cell/combined/phagocytic/syndrome
3. *What are the organisms?—bacterial/viral/fungal/parasitic*
   Is it the same group of organisms causing recurrent infections? Or is the spectrum of infections very broad?
4. *Family history*—consanguinity, sibling deaths, recurrent infections in parents, issues in maternal uncles or male maternal cousins (X-linked inheritance).
5. Close look at all the previous **hemograms**. Calculate absolute neutrophil and lymphocyte counts (ANC and ALC).
   (congenital neutropenia, cyclic neutropenia can be diagnosed with hemograms.)
6. Look at the thymic shadow in chest radiograph in infants. (If absent, points towards severe combined immune deficiency).
7. Relevant immunological tests—immunoglobulins, lymphocyte subsets (T, B and NK cell counts), nitroblue tetrazolium test (NBT), dihydrorhodamine (DHR) assay.
8. Genetic testing.
9. Functional studies if indicated.

Did you know?

PIDs as a group are 4 times more common than hemophilia and 5 times more common than cystic fibrosis!

SUGGESTED READING

1. de Vries E; European Society for Immunodeficiencies (ESID) members. Patient-centred screening for primary immunodeficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. *Clin Exp Immunol*. 2012; 167(1):108–119.
2. McCusker C, Upton J, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol*. 2018 Sep 12; 14(Suppl 2):61.
3. Ochs HD, Hitzig WH. History of primary immunodeficiency diseases. *Curr Opin Allergy Clin Immunol*. 2012; 12(6):577–587.