Primary Immunodeficiency disease

Course- SOS in Microbiology
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(Unit IV)

Primary Immunodeficiency disease

- When the system errs by failing to protect the host from disease-causing agents or from malignant cells, the result is **immunodeficiency,** A condition resulting from a genetic or developmental defect in the immune system is called a primary immunodeficiency.
- A primary immunodeficiency may affect either adaptive or innate immune functions.
- Deficiencies involving components of adaptive immunity, such as T or B cells, are thus differentiated from immunodeficiency in which the nonspecific mediators of innate immunity, such as phagocytes or complement, are impaired.

- Immunodeficiencies are conveniently categorized by the type or the developmental stage of the cells involved.
- the two main cell lineages important to immune function are
- 1.Lymphoid -The lymphoid cell disorders may affect T cells, B cells, or, in combined immunodeficiencies, both B and T cells
- 2. Myeloid-The myeloid cell disorders affect phagocytic function.
- The consequences of primary immunodeficiency depend on the number and type of immune system components involved.
- Defects in components early in the hematopoietic developmental scheme affect the entire immune system.

1. Lymphoid Immunodeficiency

- The combined forms of lymphoid immunodeficiency affect both lineages and are generally lethal within the first few years of life; these arise from defects early in developmental pathways.
- They are less common than conditions, usually less severe, that result from defects in more highly differentiated lymphoid cells.

B-Cell immunodeciency- B-cell immunodeficiency disorders make up a diverse spectrum of diseases ranging from the complete absence of mature recirculating B cells, plasma cells, and immunoglobulin to the selective absence of only certain classes of immunoglobulins.

- Patients with these disorders usually are subject to recurrent bacterial infections but display normal immunity to most viral and fungal infections

- **T cell immunodeficiency-** Because of the central role of T cells in the immune system, a T-cell deficiency can affect both the humoral and the cell-mediated responses. The impact on the cell-mediated system can be severe, with a reduction in both delayed-type hypersensitive responses and cell-mediated cytotoxicity.
- Immunoglobulin deficiencies are associated primarily with recurrent infections by extracellular bacteria, but those affected have normal responses to intracellular bacteria, as well as viral and fungal infections.
- By contrast, defects in the cell mediated system are associated with increased susceptibility to viral, protozoan, and fungal infections. Intracellular pathogens such as *Candida albicans, Pneumocystis carinii*, and *Mycobacteria* are often implicated

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- The family of disorders termed SCID stems from defects in lymphoid development that affect either T cells or both T and B cells. Clinically, SCID is characterized by a very low number of circulating lymphocytes.
- SCID results in severe recurrent infections and is usually fatal in the early years of life. Although both the T and B lineages may be affected, the initial manifestation of SCID in infants is almost always infection by agents, such as fungi or viruses, that are normally dealt with by T-cell immunity.
- The immune system is so compromised that even live attenuated vaccines (such as the Sabin polio vaccine) can cause infection and diseas. The life span of a SCID patient can be prolonged by preventing contact with all potentially harmful microorganisms.

WISKOTT-ALDRICH SYNDROME (WAS)

- The severity of this X-linked disorder increases with age and usually results in fatal infection or lymphoid malignancy. Initially, T and B lymphocytes are present in normal numbers.
- WAS first manifests itself by defective responses to bacterial polysaccharides and by lower-than-average IgM levels.
- As the WAS sufferer ages, there are recurrent bacterial infections and a gradual loss of humoral and cellular responses.
- The syndrome includes thrombocytopenia (lowered platelet count; the existing platelets are smaller than usual and have a short half-life), which may lead to fatal bleeding.

INTERFERON-GAMMA–RECEPTOR DEFECT

- This deficiency was found in patients suffering from infection with atypical mycobacteria (intracellular organisms related to the bacteria that cause tuberculosis and leprosy). Most of those carrying this autosomal recessive trait are from families with a history of inbreeding.
- This immunodeficiency points to a specific role for IFN- gamma and its receptor in protection from infection with mycobacteria.

X-LINKED AGAMMAGLOBULINEMIA

- A B-cell defect called X-linked agammaglobulinemia (XLA) or Bruton's hypogammaglobulinemia is characterized by extremely low IgG levels and by the absence of other immunoglobulin classes. Individuals with XLA have no peripheral B cells and suffer from recurrent bacterial infections, beginning at about nine months of age.

X-LINKED HYPER-IgM SYNDROME

- A peculiar immunoglobulin deficiency first thought to result from a B-cell defect has recently been shown to result instead from a defect in a T-cell surface molecule. X-linked hyper- IgM (XHM) syndrome is characterized by a deficiency of IgG, IgA, and IgE, and elevated levels of IgM, sometimes as high as 10 mg/ml (normal IgM concentration is 1.5 mg/ml).
- Although individuals with XHM have normal numbers of B cells expressing membrane-bound IgM or IgD, they appear to lack B cells expressing membrane-bound IgG, IgA, or IgE.

COMMON VARIABLE IMMUNODEFICIENCY (CVI)

- CVI is characterized by a profound decrease in numbers of antibody-producing plasma cells, low levels of most immunoglobulin isotypes hypo gamma globulinemia), and recurrent infections. The condition is usually manifested later in life than other deficiencies and is sometimes called late onset hypogammaglobulinemia or, incorrectly, acquired hypogammaglobulinemia.
- Infections in CVI sufferers are most frequently bacterial and can be controlled by administration of immunoglobulin.

HYPER-IgE SYNDROME (JOB SYNDROME)

- A primary immunodeficiency characterized by skin abcesses, recurrent pneumonia, eczema, and elevated levels of IgE accompanies facial abnormalities and bone fragility.

ATAXIA TELANGIECTASIA

- Although not classified primarily as an immunodeficiency, ataxia telangiectasia is a disease syndrome that includes deficiency of IgA and sometimes of IgE.
- The syndrome is characterized by difficulty in maintaining balance (ataxia) and by the appearance of broken capillaries (telangiectasia) in the eyes.

IMMUNE DISORDERS INVOLVING THE THYMUS

DiGeorge syndrome, or congenital thymic aplasia, in its most severe form is the complete absence of a thymus. This developmental defect, which is associated with the deletion in the embryo of a region on chromosome 22, causes immunodeficiency along with characteristic facial abnormalities, hypoparathyroidism, and congenital heart disease. sometimes called the *third and fourth pharyngeal pouch syndrome.*

2. Myeloid Immunodeficiency

- Immunodeficiencies of the lymphoid lineage affect adaptive immunity. By contrast, defects in the myeloid cell lineage affect the innate immune functions.
- Most of these defects result in impaired phagocytic processes that are
- manifested by recurrent microbial infection of greater or lesser severity.
- There are several stages at which the phagocytic processes may be faulty; these include cell motility, adherence to and phagocytosis of organisms, and killing by macrophages.

REDUCTION IN NEUTROPHIL COUNT

Quantitative deficiencies in neutrophils can range from an almost complete absence of cells, called agranulocytosis, to a reduction in the concentration of peripheral blood neutrophils below 1500/mm3, called granulocytopenia or neutropenia. These quantitative deficiencies may result from congenital defects or may be acquired through extrinsic factors. Acquired neutropenias are much more common than congenital ones.

CHRONIC GRANULOMATOUS DISEASE (CGD)

- CGD is a genetic disease that has at least two distinct forms: an X-linked form that occurs in about 70% of patients and an autosomal recessive form found in the rest.
- This disease is rooted in a defect in the oxidative pathway by which phagocytes generate hydrogen peroxide and the resulting reactive products, such as hypochlorous acid, that kill phagocytosed bacteria.

CHEDIAK-HIGASHI SYNDROME

- This autosomal recessive disease is characterized by recurrent bacterial infections, partial oculo-cutaneous albinism (lack of skin and eye pigment), and aggressive but nonmalignant infiltration of organs by lymphoid cells.
- Phagocytes from patients with this immune defect contain giant granules but do not have the ability to kill bacteria.
- The molecular basis of the defect is a mutation in a protein (LYST) involved in the regulation of I

Complement Defects Result in Immunodeficiency or Immune-Complex Disease

- Many complement deficiencies are associated with increased susceptibility to bacterial infections and/or immune-complex diseases.
- One of these complement disorders, a deficiency in properdin, which stabilizes the C3 convertase in the alternative complement pathway, is caused by a defect in a gene located on the X chromosome intracellular trafficking.