Immunodeficiency Disorders

- The immune system, which protects the body from disease, works through a complicated web of cells and chemicals. A defect in any one of these parts can damage the body's ability to fight off disease. Such a defect is called an immunodeficiency disease.

**TYPES OF IMMUNODEFICIENCY**

- PRIMARY
- SECONDARY

**IMMUNE SYSTEM**

Innate immunity –
- phagocytic cells, natural killer (NK) cells, complement system, and other plasma factors
Adaptive immunity –
- T and B lymphocytes and their secreted products

- The immune system is not fully mature at birth and may not be well developed in some aspects until a child reaches school age. Even with a well-functioning immune system, young children can have up to six upper respiratory tract infections per year for the first 3 to 5 years of life.
• Typically, children with an intact immune system and no other predisposing factors handle these infections well, with rapid resolution of bacterial infections using appropriate antibiotics.

• Several factors contribute to the risk for infections during childhood -
  – Increased infectious agent exposure, school-aged siblings, peer group
  – Passive smoking
  – Atopy, hyper reactive airway disease
  – Anatomic factors, structural or ciliary defects
  – Foreign body
  – Cystic fibrosis
  – Gastroesophageal reflux

• Primary immunodeficiencies are generally the result of genetic defects in the immune system cells. These disorders are rare, with the exception of IgA deficiency, which occurs with a frequency of approximately 1:500-700 among the white population. The estimated range of prevalence for other primary immunodeficiencies is 1:10,000 to 1:200,000 depending on the specific diagnosis.

• CHARESTERISTICS OF INFECTION
  • Increasing susceptibility to infections
  • Increasing severity of infection
  • Increasing duration of infections
  • Unusual infection
  • Infection with opportunistic agents
  • Continuous illness
  • Dependence to antibiotics
10 WARNING SIGNS OF PRIMARY IMMUNODEFICIENCY

Eight or more new ear infections within 1 year.

Recurrent, deep skin or organ abscesses.

Two or more serious sinus infections within 1 year.

Persistent thrush in mouth or elsewhere on skin, after age 1.

Two or more months on antibiotics with little effect.

Need for intravenous antibiotics to clear infections.

Two or more pneumonias within 1 year.

Two or more deep-seated infections.

Failure of an infant to gain weight or grow normally.

A family history of Primary Immunodeficiency.

PRIMARY IMMUNODEFICIENCY

- 1) B-cell defects
- 2) T-cell defects
- 3) complement system defects
- 4) phagocytic system defects

Antibody deficiencies include:

- X-linked agammaglobulinemia (XLA)
- Common variable immunodeficiency (CVID)
- Selective IgA deficiency (SIgAd)
- Hyper IgM syndrome (HlgM)
- Transient hypogammaglobulinemia of Infancy (THI)
**Cellular deficiencies include:**

- Combined immunodeficiency (CID)
- Severe combined immunodeficiency (SCID)
- Ataxia-Telangiectasia syndrome (AT)
- Wiskott-Aldrich syndrome (WAS)
- DiGeorge syndrome

**Phagocytic disorders include:**

- Chronic granulomatous disease (CGD)
- Leukocyte adhesion defect (LAD)
- Chediak-Higashi syndrome (CHS)
- Swachman syndrome (Swh.S)
- Hyper IgE syndrome (Job syndrome)

**Complement deficiencies**

• B-cell defects are the commonest immune abnormalities, accounting for more than 50% **primary immunodeficiency**. Combined B and T cell defects constitute 20% to 30% cases, followed by phagocytic defects, at 18%, and complement deficiencies, at 2%.

**B-Cell Defect**

- **Age at the onset**: Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood
- **Specific pathogens involved**: Bacteria: streptococci, staphylococci, *Haemophilus, Campylobacter*; Viruses: enterovirus; Fungi and parasites: giardia, cryptosporidia
- **Affected organs**: Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis
- **Special features**: Autoimmunity, lymphoreticular malignancy: lymphoma, thymoma; postvaccination paralytic polio
**T-Cell Defect**

**Age at the onset**
Early onset, usually 2-6 mo of age

**Specific pathogens involved**
Bacteria: mycobacteria
Viruses: CMV, EBV, varicella, enterovirus

**Fungi and parasites:**
Candida; opportunistic infection, PCP

**Affected organs**
Failure to thrive, protracted diarrhea, extensive mucocutaneous candidiasis

**Special features**
Graft-versus-host disease caused by maternal AB or nonirradiated blood transfusion; Postvaccination, disseminated BCG or paralytic polio; hypocalcemic tetany in infancy

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**AGE AT ONSET**

- 2 – 5 months of age – T cell defect (severe combined immunodeficiency )
- 5 – 7 months of age – B cell defect (X linked agammaglobulinemia )
  
Later childhood & adult hood – common variable immunodeficiency
- Younger age at onset – severe the deficiency

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**APPROACH TO A CHILD WITH PRIMARY IMMUNODEFICIENCY**

**MICROORGANISM SUSCEPTIBILITY**

- AGAMMAGLOBULINEMIA -
- encapsulated bacteria - *Streptococcus pneumoniae* or *Haemophilus influenzae*. Complicating septicemia.
- viral meningoencephalitis caused by enteroviruses (coxsakievirus or echovirus)
• *Giardia lamblia* - CVID and IgA deficiency.
• Small-bowel bacterial overgrowth with *Yersinia* and *Campylobacter* – CVID
• bacterial infections and opportunistic infections. *Mycobacterium avium-intracellulare* and *Pneumocystis carinii* severe T-cell defects.

**FAMILY HISTORY**

• A family history of maternal male relatives affected with unusually frequent infections or who died in early infancy should alert the possibility of an X-linked immunodeficiency.
• family history is the presence of relatives with autoimmune disorders, which commonly occurs in families with patients who have CVID and IgA deficiency.

• A negative family history does not rule out this inheritance pattern, a significant rate of new mutations for X-linked disorders exists.

T-cell  
- X-linked SCID (common gamma-chain deficiency)
- X-linked hyper-IgM syndrome
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative syndrome

B-cell  
- Bruton's X-linked agammaglobulinemia
MEDICAL HISTORY

• VACCINE -
  • Adverse reaction to live viral vaccines, Paralytic polio has occurred in patients with B-cell deficiency and in patients with combined T-cell and B-cell immunodeficiency.

• BLOOD TRANSFUSION –
  • Only irradiated blood products should be given to patients with severe T-cell defects because blood transfusions contain lymphocytes that can cause graft-versus-host disease.
  • Patients with complete IgA deficiency can produce IgE antibodies to IgA, so they are at risk for an anaphylactic reaction to plasma or blood transfusions

PHYSICAL EXAMINATION

• a normal physical examination does not rule out an underlying immunodeficiency.
  • In children with X-linked lymphoproliferative disease, symptoms or signs of disease typically do not develop before Epstein-Barr virus infection develops

• Patients with antibody-deficiency syndromes can demonstrate normal growth and development despite frequent and severe RTIs. Antibody-deficiency syndromes can be characterized by asymptomatic periods
PHYSICAL EXAMINATION…

- Some children with underlying immunodeficiency appear chronically ill and underweight. If initial onset of the disease occurs early in life, growth and development may be delayed, leading to failure to thrive.

DYSMORPHIC FEATURES

- In patients with DiGeorge anomaly, abnormalities in the embryologic development of the third and fourth pharyngeal pouches produce dysmorphic features, including hypoplastic mandible, small mouth, hypertelorism and antimongoloid slant, and low-set and posteriorly rotated ears.

SKIN…….

- Skin Findings Associated Immune Defect
  - Eczema and petechiae Wiskott-Aldrich syndrome
  - Telangiectasia Ataxia-telangiectasia syndrome
  - Dermatomyositis-like rash B-cell dysfunction
  - Generalized molluscum contagiosum T-cell deficiency
  - Extensive warts T-cell deficiency
  - Candidiasis T-cell deficiency

DYSMORPHIC FEATURES…

- DiGeorge anomaly also is associated with hypoparathyroidism; an aplastic or hypoplastic thymus; and conotruncal abnormalities of the heart, such as tetralogy of Fallot, ventricular septal defect/atrial septal defect (VSD/ASD), and pulmonic artery atresia or stenosis.
ENT EXAMINATION

• Extensive mucous membrane candidiasis suggests a T-cell defect. Examination of the pharynx and nasal cavities for signs of sinusitis, like, postnasal drainage, or purulent nasal discharge. Tympanic membranes can appear scarred and disfigured as a sign of previous recurrent and chronic infection of the middle ear.

LYMPHIOID SYSTEM

• Absence of tonsils and lymph nodes suggests a severe immunodeficiency, as seen in patients with XLA or SCID.
• Cervical adenopathy and enlarged liver or spleen can be seen in patients with a B-cell deficiency, such as CVID or IgA deficiency.

LYMPHIOID SYSTEM

• Lymphoreticular malignancies occur more commonly in certain primary immunodeficiencies, including Wiskott-Aldrich syndrome, ataxia-telangiectasia, and CVID

SYSTEMIC EXAMINATION

• RESPIRATORY SYSTEM –
• Rales on auscultation of the chest may suggest bronchiectasis occurring as a complication of recurrent lung infections. Digital clubbing points to significant lung disease.
SYSTEMIC EXAMINATION…

- CARDIOVASCULAR SYSTEM –
- Pulmonary hypertension can occur in patients with chronic lung disease

NEUROLOGICAL EXAMINATION

- progressive ataxia in a young child could be the first sign of ataxia-telangiectasia even before immunodeficiency becomes clinically apparent.

NEUROLOGICAL EXAMINATION…..

- Signs of posterior and lateral column involvement of the spinal cord with loss of vibratory sense in the lower extremities, positive Babinski's response, or poor finger coordination can be signs of pernicious anemia complicating the course of CVID or IgA deficiency.

LAB DIAGNOSIS

- CBC, ESR
- B cell defects
- Screening tests
  - 1. IgA, IgG, IgM measurement
  - 2. Isohemagglutinins
  - 3. Antibody titres to tetanus, diphtheria, S. pneumoniae, H. influenzae
ADVANCED TESTS

• B cell enumeration (CD19 or CD20)
• IgG subclass estimation
• IgD and IgE measurement
• In vitro stimulation of B cells to produce immunoglobulins
• Coculture of T and B cells to assess help and suppression

LAB TESTS IN IMMUNODEFICIENCY

• T-Cell Deficiency - screening tests
• Delayed skin tests: e.g., *Trichophyton, Candida*
• Lymphocyte count and
• morphology Chest x-ray for thymic size

Advanced tests

• T-cell enumeration and phenotyping by flow cytometry
• In vitro proliferative responses to mitogens, specific antigens, or allogeneic cells (mixed lymphocyte culture)
• Intracellular cytokine production by flow cytometry
• T-cell cytotoxicity assays

LAB TESTS IN IMMUNODEFICIENCY

• Anemia of chronic disease can develop in patients with chronic infections, whereas pure erythrocyte aplasia can be seen in patients with thymoma and CVID.
Persistent lymphopenia can be a sign of cellular immunodeficiency. Lymphopenia is defined as less than 3000 cells/mm³ in infants, whereas in older children or adults, a total lymphocyte count of less than 1500 cells/mm³ is abnormal.

Thrombocytopenia and small platelet size are characteristic of patients with Wiskott-Aldrich syndrome.

Autoantibodies causing autoimmune hemolytic anemia, thrombocytopenia, or neutropenia can occur in some of the B-cell immunodeficiencies.

Quantitation of serum immunoglobulins (IgG, IgM, IgA) is the first step in evaluating humoral or B-cell immunity
- low IgA level - IgA deficiency or other immunoglobulin deficiency diseases.
- High IgM level - hyper-IgM syndrome

The IgE level commonly is elevated in
- atopy
- Wiskott-Aldrich syndrome.
- Specific antibody titers against glycoprotein antigens, such as tetanus and diphtheria, or polysaccharide antigens, such as pneumococcal polysaccharide, can be assessed