Primary Immunodeficiency Diseases
Introduction

- **Immunodeficiency States**
  - **Primary**
    - Congenital
    - Genetic
  - **Secondary** – acquired
    - Infections, particularly viruses
    - Malnutrition or malabsorption
    - Medications – corticosteroids, chemotherapy
- Respiratory tract is often involved, but other organ systems may also be affected.
- Otolaryngologists may be exposed to a higher incidence of these problems.
Primary Immunodeficiency

- Immunodeficiency occurs when one or more of the components of the immune system is defective.

- Most immunodeficiency diseases are inherited manifesting as recurrent or overwhelming infections in young children.

- They are inherited of different patterns, mostly recessive or X-linked.

- They follow embryologic abnormality and may be due to enzymatic defects, or of unknown etiology.
Studies of these disorders have revealed:

- the role of the immune system in maintaining health.
- interactions between different cell types in the generation of the immune response.
- the molecular basis of immune processes.

They provided the necessary information for diagnosis, genetic counseling and gene therapy.
Primary immunodeficiency diseases are characterized by:

- Undue susceptibility to infection.
- Autoimmune diseases and excessive production of IgE antibodies.
- Increased incidence of malignancy.
- With the exception of selective IgA deficiency, genetically determined immunodeficiency is rare.

- B-cell defects far outnumber those affecting T-cells, phagocytic cells, or complement proteins.

- During childhood, there is a 5:1 male: female sex predominance for these disorders.

- This ratio reverses so that there is a slight predominance (1:1.4) in women in adulthood.
Types of Primary Immunodeficiency Disorder

- Humoral defects: impaired antibody production but cellular immunity is usually intact
  - Molecular defect of B cells
  - Failure of interaction of T and B cells

- T - Cell defects
- Combined humoral and T - Cell defects
- Phagocytic dysfunctions
- Complement deficiencies
B- Cell (Antibody) Deficiency

- Characterized by decreased immunoglobulin levels and recurrent infections.

- The primary abnormality may be a defect in B cell maturation and development or in its response to antigenic stimulation.

- Physiologic B cell deficiency occurs, usually at 6-9 months of age and should be differentiated from the B cell deficiencies.
Trends in immunoglobulins

- There is a physiologic nadir in serum IgG concentration at 4-6 months.

- Among the IgG subclasses, IgG2 & IgG4 are lower in childhood and increase gradually to adult values.

- Serum IgA concentrations are the last to rise to adult values and are the first to decline in most primary immunodeficiencies.
IgG Antibody Levels Vary with Age

Serum Concentrations, mg/ml

Age

Adult level

- Infant IgG
- Maternal IgG
- Total IgG
X-Linked Agammaglobulinemia: Burton’s agammaglobulinemia

- XLA gene had been precisely mapped to Xq21.2-22.2 and the gene product is an intracellular signaling tyrosine kinase named Bruton tyrosine kinase (btk).

- BTK is expressed in all stages of B cell lineage except the plasma cell.

- BTK is also present in monocytes, megakaryocytes, platelets, and mast cells but not in T and NK cells.

- It appears to be necessary for pre-B cell expansion and maturation into surface Ig- expressing immature B cells.
Today, more than 600 different mutations in btk gene have been recognized.

An autosomal recessive form had been reported in females resulting from mutations in the heavy chain gene on chromosome 14.

Very low Concentrations of immunoglobulins of all isotypes, circulating B cells are usually absent but Pre- B cells are present in reduced numbers in the bone marrow.

Onset by 6-18 months of age, absence of tonsils and lymph tissue, 25% have neutropenia as well, and collagen vascular disease may develop later.

Rx with IV immune globulin q2-4 weeks is associated with normal growth rate and life span.
Immunodeficiency with Hyper IgM

- A rare X-linked or autosomal condition. The abnormal gene was localized to Xq26. Some acquired forms are seen after lymphoma, anemia and post-rubella.

- B cells from such patients have the capacity to synthesize IgG and IgA normally when cultured with a switch T cell line.

- This suggests that the defect is in T-lineage cells. Defect is in a T cell surface molecule for class switching from IgM to other classes.

- The gene product is CD154 on activated helper T-cells which interacts with CD40 on B Cells, leading to isotype switching.
Immunodeficiency with Hyper IgM

- The presence of the condition in females indicates that this condition has more than one genetic cause. In those patients, the condition truly is a B-cell defect.

- Opportunistic infections in the first 2 years.

- Very low serum IgA, IgG, and IgE but either a normal or, more frequently, a markedly elevated concentration of polyclonal IgM. Normal B cell numbers, but no memory B cells.

- Rx is IVIG, steroids to prevent lymphoproliferative disease, plasmapheresis for hyperviscosity, BMT.
Common Variable Immunodeficiency

- CVID is a heterogeneous group of disorders with intrinsic B-cell defect or a B-cell dysfunction related to abnormal T-cell B-cell interaction.

- CVID is associated with infections, autoimmunity and malignancy

- Similar clinically to XLA with normal numbers of circulating Ig - bearing B- cells but they do not differentiate into immunoglobulin- producing cells.

- Recent studies showed a lack of protein kinase C activation and translocation to the plasma membrane when CVID B- Cells are stimulated with phorbolester or anti-μ.
Lack of inducible costimulator (ICOS) expression by activated T cell which is associated with lack of T cell help for B cell differentiation, class switching and memory B-cell generation.

Depressed T-cell function has been reported in other patients.

It is suspected to have a common genetic basis with selective IgA deficiency (first degree relatives of patients with selective IgA deficiency may develop CVID).

In 10-20% of families another member have selective IgA deficiency.
Abnormalities include; reduction in class switching, defect in somatic hypermutation, reduced production of cytokines, increased apoptosis in B and T cells, and defects in CD27 and CD134 Ligand, important in promoting B cell differentiation into plasma cells.

Bimodal distribution: 5-15 yrs. and 25-45 yrs with almost equal sex distribution.

Sporadic, but some familial cases were reported.

There is > 400 – fold increase in lymphoma in affected women in the 5th and 6th decades of life.

Total IgG is low and T cells may be decreased. Treated with IVIG q2-4 weeks, most patients respond.
Selective IgA Deficiency

- The most common well-defined immunodeficiency: 1 in 700, Whites. 1 in 5000 Asians (1:333 among some blood donors).

- An isolated absence or near absence (< 10mg/dl) of serum and secretory IgA

- Familial clusters, but no genetic defect found.

- Autosomal inheritance; in most families this appears to be dominant with variable expressivity

- Possible cytokine defect in plasma cells
Selective IgA Deficiency

- Links with CVID and IgG subclass deficiency. Occurs in pedigree with CVID patient (susceptibility genes in the MHC Class III region).

- Although it has been diagnosed in apparently healthy individuals, it is commonly associated with ill health (Infections and malignancy).

- Predisposes to sinopulmonary infections, autoimmune disorders (RA, lupus), and malignancy.

- Drug induced (reversible) from penicillamine, sulfasalazine, captopril, phenytoin, thyroxine, valproic acid and dilantin.
Selective IgA Deficiency

- Diagnosis made in children over 4 years with IgA levels less than 7 mg/dl, normal IgG and IgM.

- Most patients are asymptomatic. Children with levels of 5 mg/dl usually recover.

- One study linked IgA deficiency with atopy and it has been associated with anaphylaxis during blood transfusion (1/3 of patients have anti-IgA).
Selective IgA Deficiency

- Severe or fatal anaphylactic reactions due to IgE anti IgA antibodies have been reported.

- IgG anti- IgA are present in the sera of as high as 44% of patients (remove IgA rapidly from circulation).

- Rx: prophylaxis and treatment of infections

- IVIG if IgG is low (Risk of anti-IgA production)
IgG Subclass Deficiency

Four subclasses:
- IgG1 (67%-70%) – soluble protein antigens
- IgG2 (20%-23%) – deficiency is more common in children and males
- IgG3 (7%) – deficiency is more common in women
- IgG4 (3%)

One or more subclass may be defective, IgG2 is most commonly affected and most important are those involving IgG1 or IgG3.
IgG Subclass Deficiency

- Diagnosis: low concentration in one or more subclass with normal total IgG

- Assess child’s response to tetanus and *H. influenzae* vaccination for help in making diagnosis

- Most patients are asymptomatic, but it may be associated with recurrent bacterial infections with common pathogens, frequent URI, diarrhea, allergies, asthma, vasculitis or other autoimmune disease
X-Linked Lymphoproliferative Disease (XLP) (Duncan’s Disease)

- It is a recessive trait characterized by an inadequate immune response to infection with EBV.

- Affected individuals are apparently healthy until they experience infectious mononucleosis.

- Immunologic studies demonstrated elevated IgA or IgM and/or variable deficiency of IgG1 and IgG3.
The mean age at presentation is less than 5 years.

The most common (75%) form of presentation is severe mononucleosis, which is fatal in 80% of cases.

Primary cause of death is extensive liver necrosis caused by polyclonally activated alloreactive cytotoxic T cells that recognize EBV – infected autologous B-cells.

Most patients surviving the primary infection develop global cellular immune defects involving T, B, and NK cells, lymphoma, or hypogammaglobulinemia.
Hyper IgE (Job’s syndrome)

- Recurrent infections with elevated IgE and eosinophilia

- Skin and respiratory tract (usually lower) infections and anti-staphylococcus IgE is specific for Job’s syndrome

- Failure of primary dental exfoliation, scoliosis, hypertelorism, protruding mandible, broad bulbous nose, skin abscesses and positive family history

- Differential diagnosis for elevated IgE:
  - Allergy – Atopy
  - Parasitic disease and other infections
  - Malignancy
  - Skin disease, smoking, drugs, RA, burns
Evaluation of antibody (B cell)

1. Protein electrophoresis
2. Quantitation of IgG, IgA, IgM and IgD
3. Isohemagglutinin
4. Specific antibody response
5. B cell quantitation
6. B cell markers (CD19)
T Cell Deficiency

- DiGeorge Syndrome
- Defects in CD3/TCR
- Defects in signaling, Defects in ZAP-70
- Defects in Cytokine production as IL-2 and IFN gamma
- Defects in Cytokine response
DiGeorge Syndrome (Congenital thymic aplasia or hypoplasia)

- Congenital T cell defects presents within the first few months of life:
  - Severe mucocutaneous candidiasis
  - URI, diarrhea, failure to thrive
  - Infection following vaccination

- It results from dysmorphogenesis of the third and fourth pharyngeal pouches during early embryogenesis (6-12 weeks).

- Hypo- or aplasia of the thymus and parathyroid glands but hypoplasia is more common.
Other structures forming at that period are frequently affected.

Some children have partial DiGeorge’s syndrome.

It has occurred in both males and females.

Microdeletions of 22q 11.2 (DGCR region) have been shown in a majority of patients.

Immunodeficiency, hypocalcemia, and neonatal tetany.
DiGeorge Syndrome
Rarely familial but three cases of apparent autosomal dominant inheritance have been reported.

Another deletion on chromosome 10p13 has been identified.

Thymic transplantation for the complete form (fetal thymus <14 weeks of gestation).

Extrathyemic tissue, ectopic thymus tissue and ectopic parathyroid were suggested to explain spontaneous improvement.
Evaluation of T-Cell Immunity

1. Total lymphocyte count
2. DTH
3. Lymphocyte transformation assay
4. Total T cell count using Anti-CD3
5. CD4 and CD8 subset counts
6. Cytokine production
Severe Combined Immunodeficiency

- SCID is a rare fatal syndrome of quite diverse genetic origin.

- X-linked SCID is the most common form.

- Frequent episodes of diarrhea, pneumonia, otitis, sepsis and cutaneous infections.

- Extreme wasting usually develops after infections and diarrhea begin.

- Persistent opportunistic infections lead to death.
Elevated percentage of B cells but these B cells do not produce immunoglobulins. Absent T, NK and Ig synthesis.

Due to mutation in the gene coding for common chain ($\gamma_c$) shared by the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15 which play a role in signal transduction through activation of Jak-3.

XSCID is a pediatric emergency requiring bone marrow transplantation (HLA identical or haploidentical) with 95 % survival rate.
Common Features of Severe Combined Immunodeficiency (SCID)

- Failure to thrive
- Onset of infections in the neonatal period
- Opportunistic infections
- Chronic or recurrent thrush
- Chronic rashes
- Chronic or recurrent diarrhea
- Paucity of lymphoid tissue
Fig 2-2.—Progressive varicella in infant with severe combined immunodeficiency.
Autosomal – Recessive Severe Combined Immunodeficiency Diseases

- Mutated genes on autosomal chromosomes have been identified in three forms of SCID:
  - Adenosine deaminase (ADA) deficiency
  - Janus Kinase 3 (Jak3) deficiency.
  - Recombinase activating genes 1 and 2 (RAG1 or RAG2) deficiency.
Adenosine Deaminase Deficiency

- ADA deficiency affects primarily T cell function due to marked accumulation of toxic purine metabolites.

- Certain distinguishing features of ADA deficiency include rib cage and multiple skeletal abnormalities.

- Lymphopenia is more profound than with other types of SCID (<500/mm³), but NK function is normal.
The gene encoding ADA was mapped to chromosome 20q13 –ter.

Mutation in this genes results in marked accumulations of adenosine, 2 – deoxy adenosine and 2-O-methyladenosine.

Adenosine and deoxy adenosine are apparent suicide inactivators of the enzyme S-adenosylhomocysteine hydrolase (SAH).

Treatment of choice is bone narrow transplantation.
ADA deficiency

ADENOSINE → Adenosine deaminase (ADA) → INOSINE → Purine nucleoside phosphorylase (PNP) → GUANOSINE → Purine nucleoside phosphorylase (PNP) → GUANINE → Increased guanosine, deoxyguanosine

HYPOXANTHINE → Kinase → HYPOXANTHINE → XANTHINE → Xanthine oxidase → URIC ACID

Accumulation of deoxyATP

Accumulation of deoxyGTP

Toxic effects on lymphocytes (inhibition of ribonucleotide reductase, inhibition of transmethylation reactions)
Janus Kinase 3 Deficiency (Jak3)

- Elevated B cells and very low percentages of T and NK cells.
- Related to defective function of the multiple types of cytokine receptor that share $\gamma_c$.

RAG 1 or RAG2 Deficiency

- Complete absence of T- or B- cell function.
- Such mutations result in a functional inability to form antigen receptors through genetic recombination.
Combined Immunodeficiency

- low but not absent T-cell function.

- Serum immunoglobulins may be normal or elevated but antibody-forming capacity is impaired in the majority of cases.

- Other findings include neutropenia and eosinophilia
Purine Nucleoside Phosphorylase Deficiency (PNP)

- PNP deficiency does not lead to as severe immunodeficiency as in ADA deficiency.

- Two thirds of patients have neurologic abnormalities.

- Most patients have normal or elevated serum immunoglobulin levels with profound lymphopenia.

- Marked T cell deficiency but increased NK cell count and function.

- The gene encoding PNP is on chromosome 14q13.1.
Cartilage – Hair Hypoplasia

- Short – limbed dwarfism, and fine sparse light hair and eyebrows with frequent and severe infections.

- Three patterns of immune dysfunction have emerged, defective antibody – mediated immunity, defective cellular immunity (most common) and SCID.

- NK cells are increased in number and function.

- It is an autosomal recessive disorder and the defective gene maps to chromosome 9q21 – p13.
Immunodeficiency with Thrombocytopenia and Eczema (Wiskott – Aldrich Syndrome)

- An X-linked recessive syndrome characterized by eczema, thrombocytopenic purpura with normally appearing megakaryocytic but small defective platelets and undue susceptibility to infection.

- Patients have an impaired humoral immune response to polysaccharide antigens (Low or absent isohemagglutinins).

- The mutated gene responsible for this defect was mapped to Xp11.22 –11.23
Ataxia Telangiectasia

- Associated with neurologic, endocrinologic, hepatic and cutaneous abnormalities.

- Progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy and variable humoral and cellular immunodeficiency.

- Low CD3+ and CD4+ T cells.

- Selective IgA deficiency in 50-80% of patients.
Defective DNA repair and frequent chromosomal abnormalities (breakages) frequently involving the genes that encode TCR on chromosome 7 and the immunoglobulin heavy chain on chromosome 14.

It follows autosomal recessive pattern of inheritance.

The mutated gene maps to chromosome 11q22-23 which encodes a DNA – dependent protein kinase localized to the nucleus and involved in mitogenic signal transduction, meiotic recombination and cell cycle control.
Defective Expression of Major Histocompatibility Antigens

MHC Class I Antigen Deficiency

- Class 1 MHC antigens are not detected on any cells in the body.

- Mutation in the gene encoding the antigenic peptide transporter protein (TAP1 and TAP2).
Defective Class II MHC Expression
Bare lymphocyte syndrome

- Autosomal recessive
- Fail to express HLA–DP,DQ,DR on APC and in response to IFNγ
- Very low CD4+ but normal or elevated CD8+ T cells.
- Mutation in genes encoding proteins that regulate class II MHC transcription
- Transcription factor RFX5 or CIITA
- May result in defective positive selection of T cell in thymus and reduction of T CD4+
- Affected individual are deficient in DTH response and in antibody response to T dependent antigens.
Phagocytic Dysfunctions

- **Extrinsic**: chemotaxis, opsonization, Immunosuppression.

- **Intrinsic**: Quantitative: neutropenia.
  Qualitative: CGD, MPD, G6PD

- **Chronic Cranulomatous Disease (CGD)**

- **Rare**

- **X-linked (65%)** or **autosomal recessive (35%)**.

- Defective respiratory burst; No generation of H2O2 due to abnormal NADPH Oxidase (Cytochrome b558).
NADPH Oxidase is made up of four proteins:
- gp 91 phox / membrane
- P22 phox / membrane
- P47 phox / Cytosolic
- P67 phox / Cytosolic

- Gp 91 → X-linked → ≈ 65%
- P22 phox = chromosome 16 → ≈ 5%
- P47 phox = chromosome 7 → ≈ 30%
- P67 phox= chromosome 1 → ≈ 5%
Clinical Presentation
- Onset by 2 years.
- Recurrent bacterial and fungal infections.
- Draining Lymphadenopathy, hepatospleno-megaly, pneumonia, osteomyelitis and abscesses

G6PD Deficiency
- X-linked.
- Deficient generation of H2O2 or failure to oxidize via shunt
MPO Deficiency
- Failure to utilize H2O2 generated.
- Most common Neutrophils disorder – 1/2000
- Defective fungal killing, worse with DM

Neutrophils disorders
- characterized by gingivitis, oral ulcers, skin or visceral infections with staphylococci
- Delayed presentation

Tuftsin Deficiency
Leukocyte Adhesion Deficiencies (LAD)

LAD –1

- Due to a mutation in the gene on chromosome 21q22.3 encoding CD18, a 95 – Kda beta subunit shared by three adhesive heterodimers: LFA-1, CR3 and P150,95

- The alpha chains of these three proteins (chromosome 16) are not expressed because of the abnormal beta chain.

- Inability of cells to adhere to vascular endothelium and migrate out of the intravascular compartment.

- All cytotoxic lymphocyte functions are markedly impaired as well as immune cell interaction and immune recognition.
LAD-2

- Absence of neutrophil sialyl–Lewis X, a ligand of E-selectin on vascular endothelium

Chediak – Higashi syndrome

- Lysosomal transport protein defect with leukocyte adhesion defect.

- Oculocutaneous albinism and giant lysosomal granules in Neutrophils and most of other cells of the body, including melanocytes.

- Complete absence of cytotoxic T-lymphocytes and NK cell activity as a result of abnormal lysosomal granule function. Abnormal chemotaxis.

- Autosomal recessive (1q42-43).
Complement Defects

- Recurrent systemic bacterial infections
- Best screen is total hemolytic complement (CH50 assay)
- Pneumonia is common with early defects in the classical and alternative pathways
- Recurrent Neisseria bacteremia and meningitis with late component defects (C5-9)
- Early complement defects are associated with collagen vascular disease and lupus
- Other components such as C3 or C4 can be defective
Complement and Infection

Classical Pathway

Autoimmunity; Occasional Infections

Pyogenic Infection

C3

C1 C4 C2

C3b B P

C5 C6 C7 C8 C9

Pyogenic Infections

Late components

Recurrent Neisserial Infections

Alternative Pathway