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

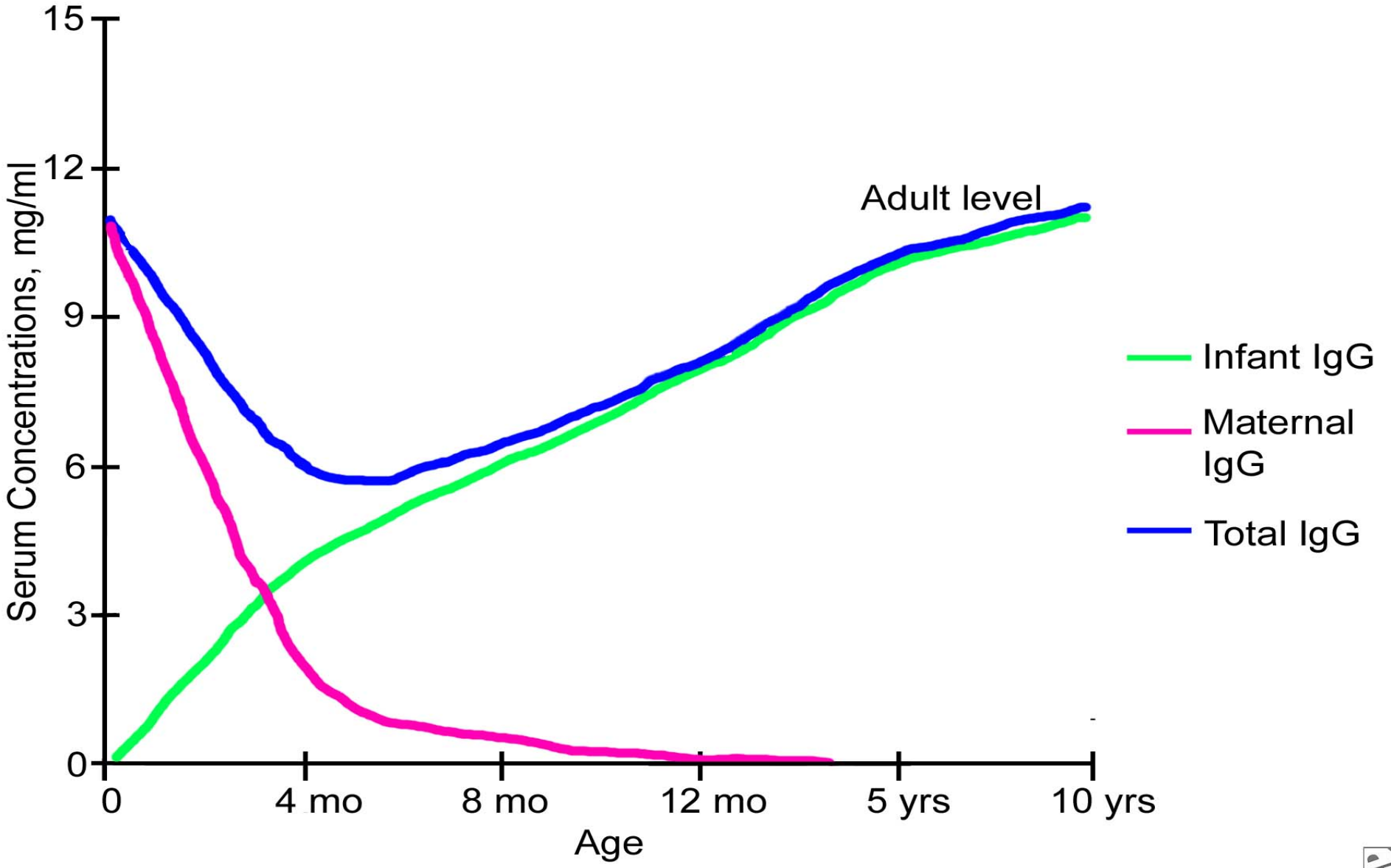
B- Cell (Antibody) Deficiency

- 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



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)

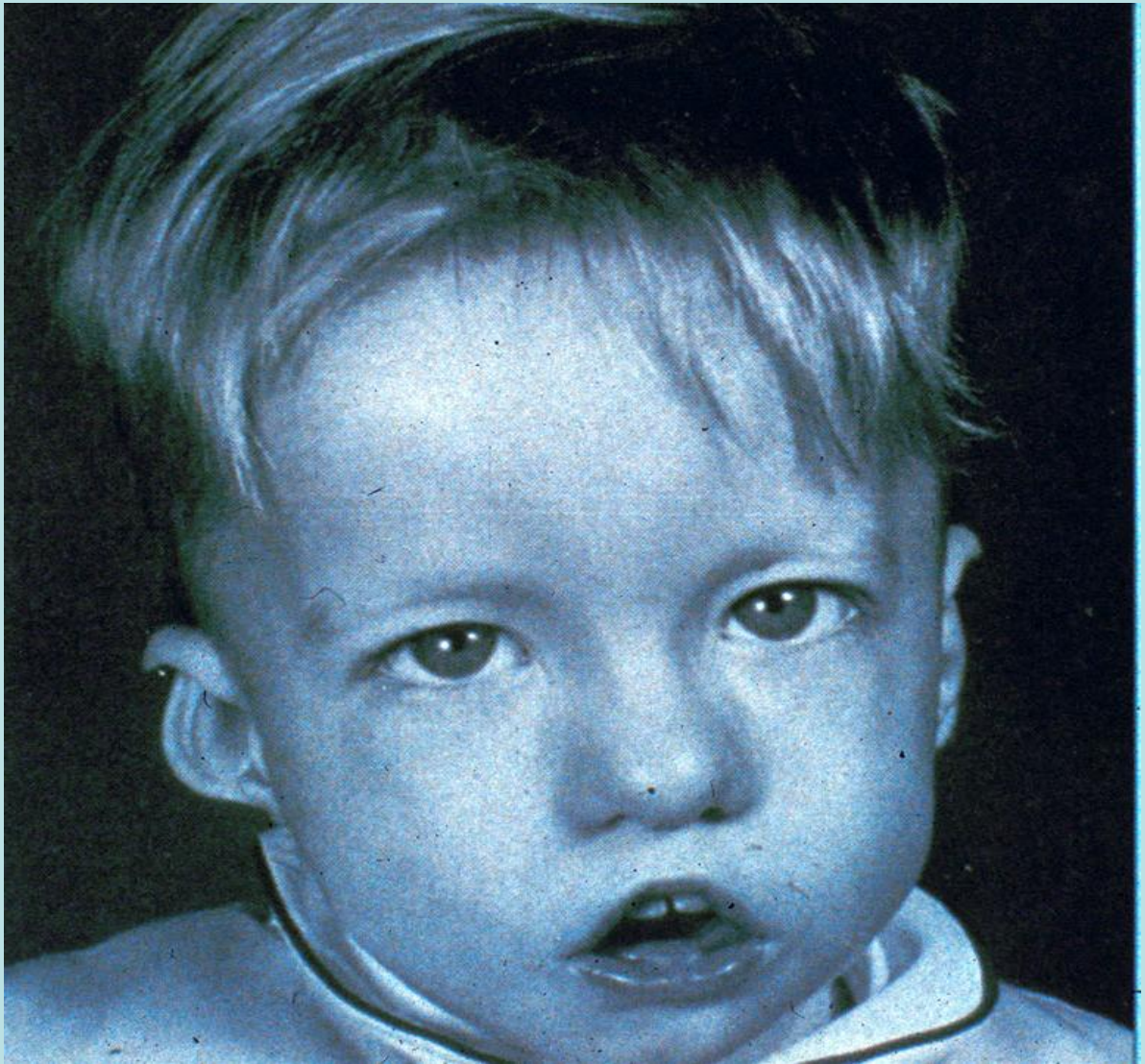
- Congenital T cell defects presents within the first few months of life:
  - Severe mucocutaneous candidiasis
  - URI, diarrhea, failure to thrive
  - Infection following vaccination

- It results from dysmorphogenesis of the third and fourth pharyngeal pouches during early embryogensis (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).
- Extrathymic 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

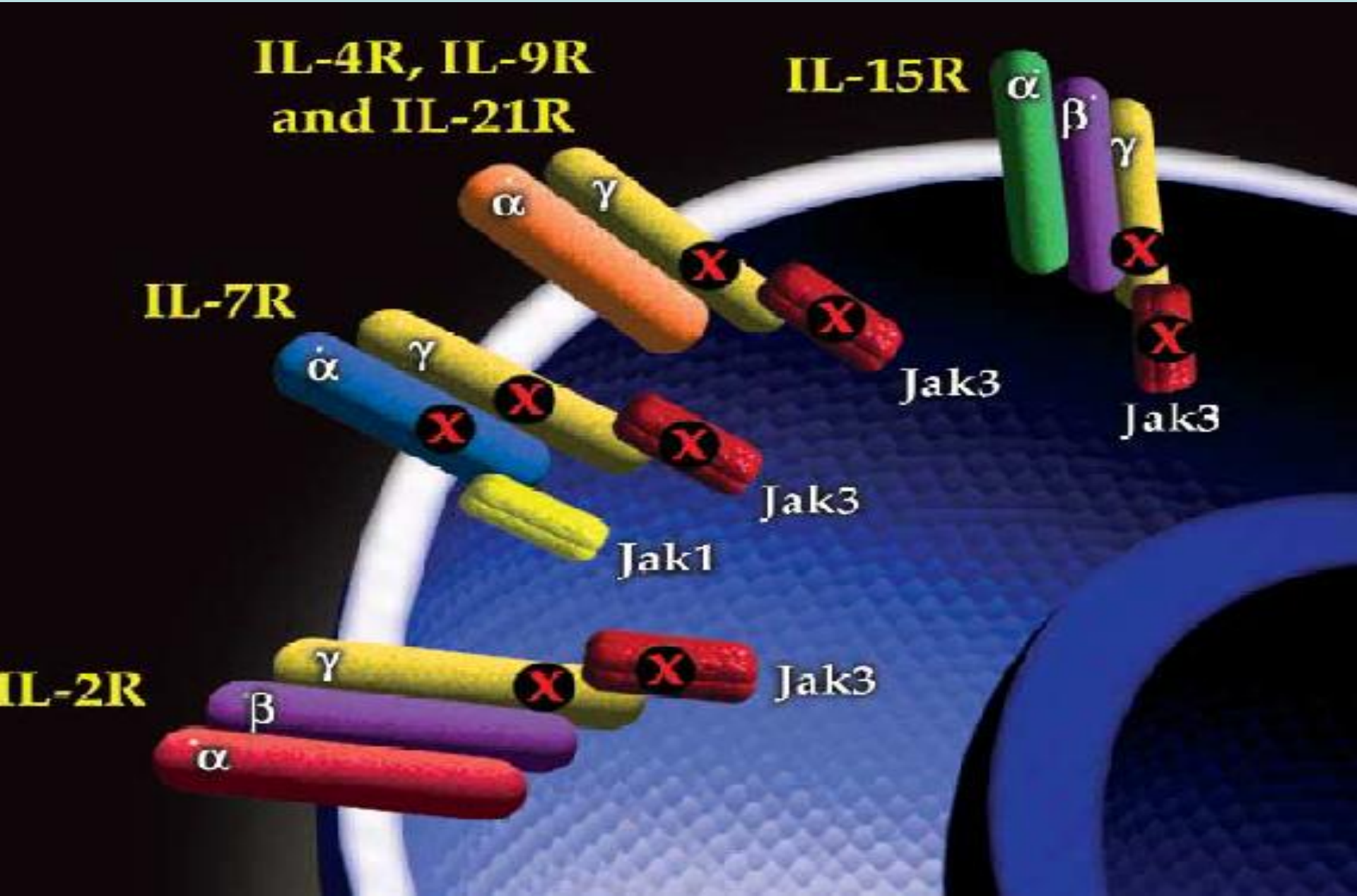
- SCID is a rare fatal syndrome of quite diverse genetic origin.
- X- linked SCID is the most common form.
- frequent episodes of diarrhea, pneumonia, otitis, sepsis and cutaneous infections.
- Extreme wasting usually develops after infections and diarrhea begin.
- Persistent opportunistic infections 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 (γc) 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.

Combined Immunodeficiency



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

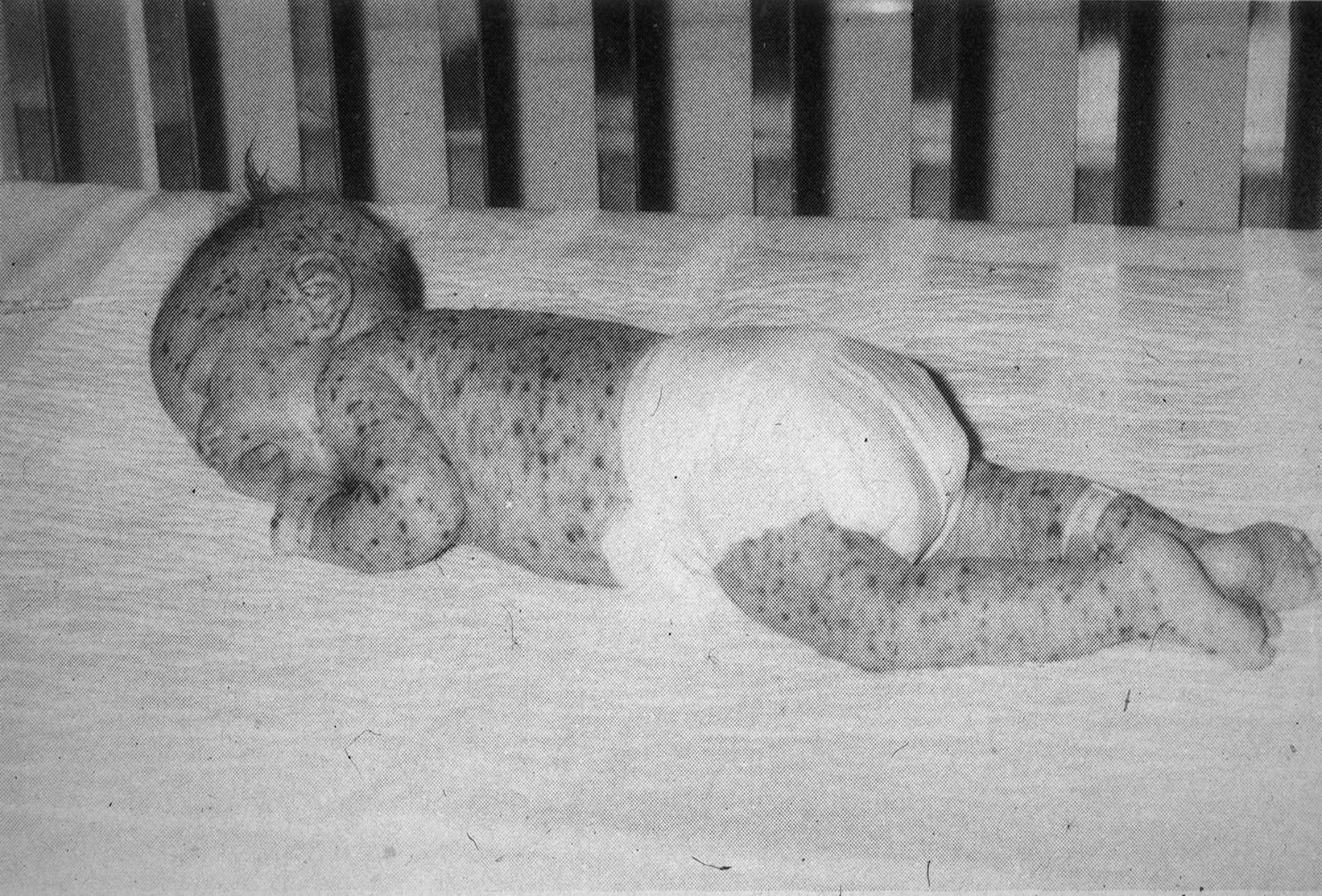


Fig 2-2.—Progressive varicella in infant with severe combined immunodeficiency.

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

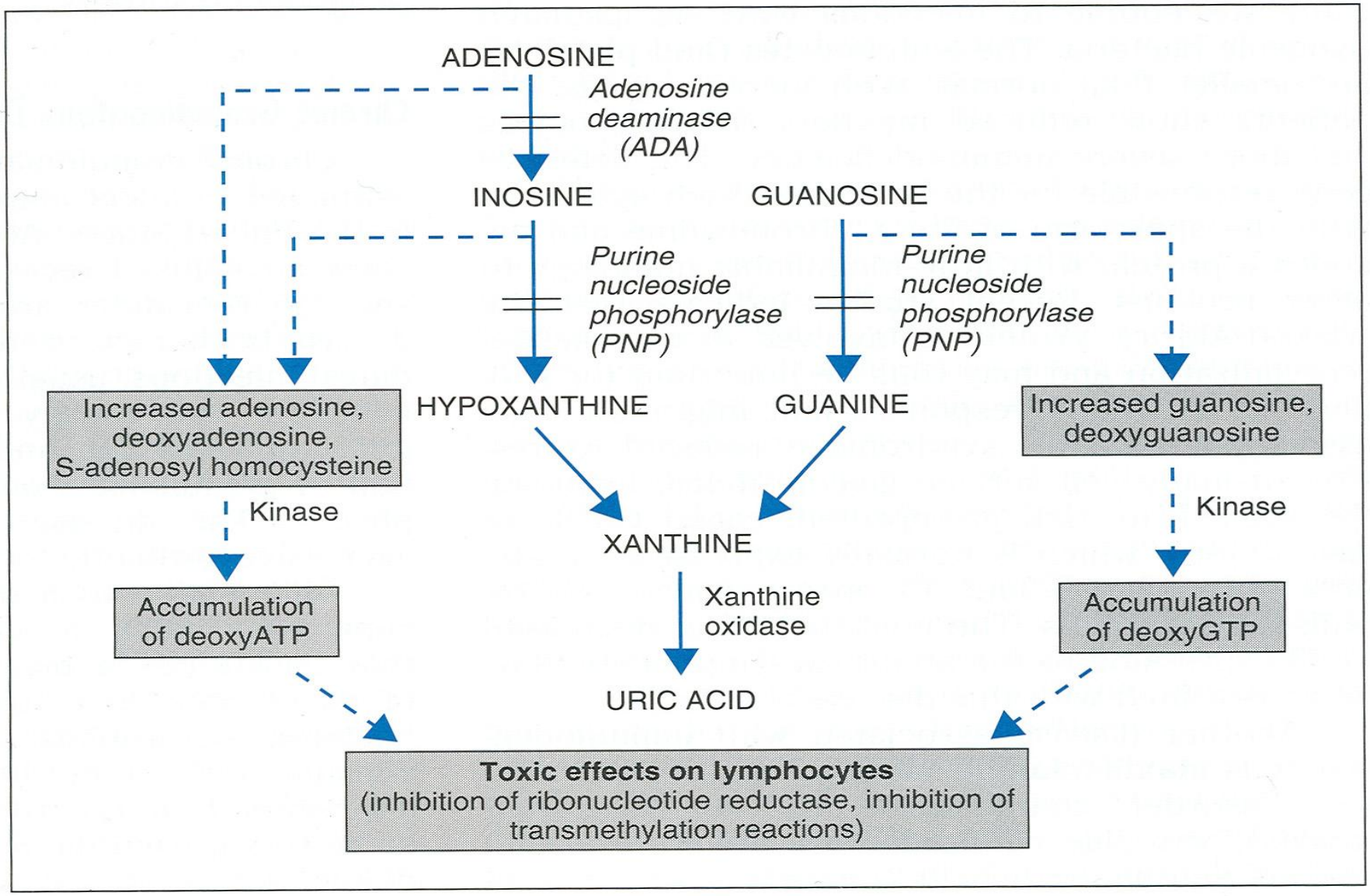
- ADA deficiency affects primarily T cell function due to marked accumulation of toxic purine metabolites.

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

- Lymphopenia is more profound than with other types of SCID (<500/mm^3), 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



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 γc.

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 H_2O_2 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 H_2O_2 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 hetrodimers: 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