IMMUNOLOGY

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Primary Immunodeficiencies

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Content

Defect in phagocytic cell

Defect in B cell

Defect in T cell

Defect in combined B cell and T cell

Primary Immunodeficiencies

Learning Objectives

Solve problems concerning defects of phagocytic cells and humoral immunity

Demonstrate understanding of deficiencies of complement or its regulation

Use knowledge of defects of T lymphocytes to explain severe combined immunodeficiencies

Primary Immunodeficiencies

Introduction

Immunodeficiency cy diseases may occur with any aspect of immunity , including both the innate and adaptive branches. The symptoms of each disease highlight the importance of that aspect of the immune system on protecting the host. Most of these immune disorders are paediatric in nature and begin to appear around age 6 months. Th s highlights the importance of the protective immunity afforded by maternal IgG, which is nearly depleted by age 6 months and completely depletedby age 12-15 months. Another important aspect of immunodeficiency disease s is that several are X-linked and therefore more common in males than females. Because these diseases reveal the importance of the immune system ’s basic function , they are often heavily tested.

Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Chronic Granulomatous Disease

Molecular Defect

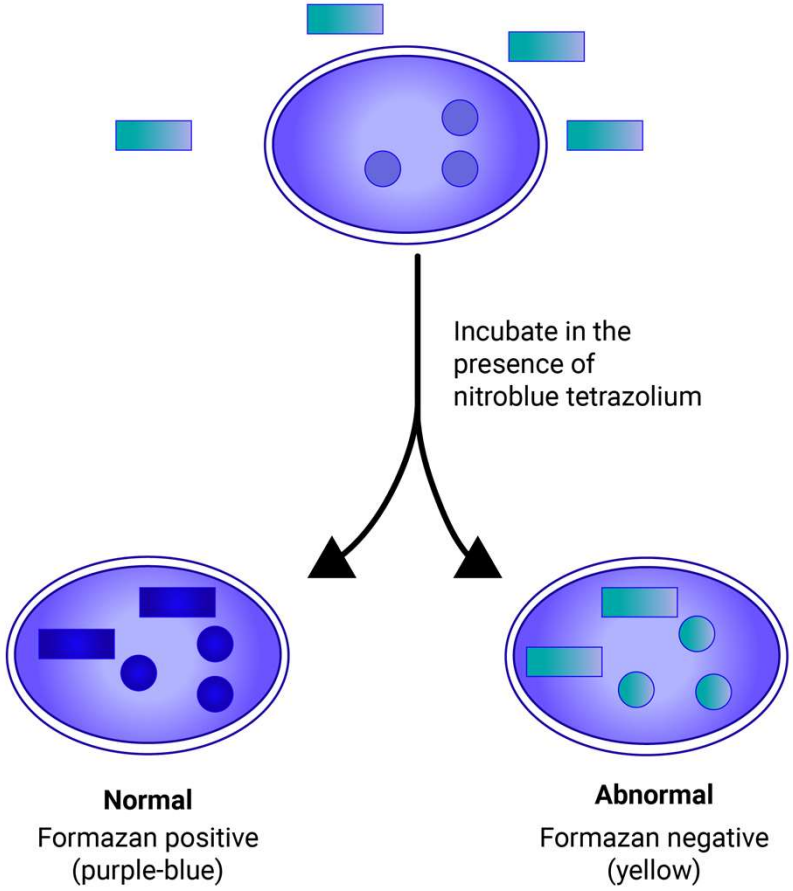
Deficiency of NADPH Oxidase(any of its four-component protein) Failure to generate superoxide anion, other and other O2 radicals.

Symptoms:

Recurrent infection with catalase positive bacteria and fungi.

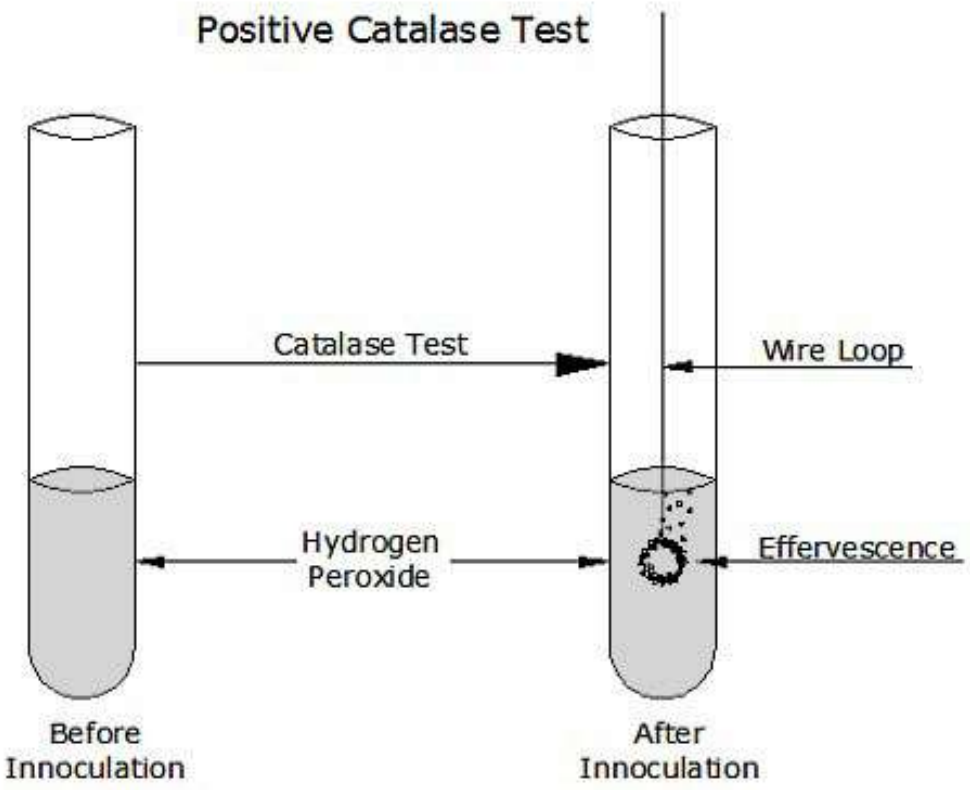
Primary Immunodeficiencies

NBT test



Primary Immune deficiencies

Catalase Positive



Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Leukocyte adhesion deficiency

Molecular Defect

Absence of **CD18**—common β chain of the leukocyte integrins

The 3 integrins that contain CD18: LFA-1, MAC-1 and gp150/95

Symptoms

- Recurrent and chronic infections,
- Failure to form pus,
- Delayed separation of umbilical cord stump

Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Chediak Higashi Syndrome

Molecular Defect

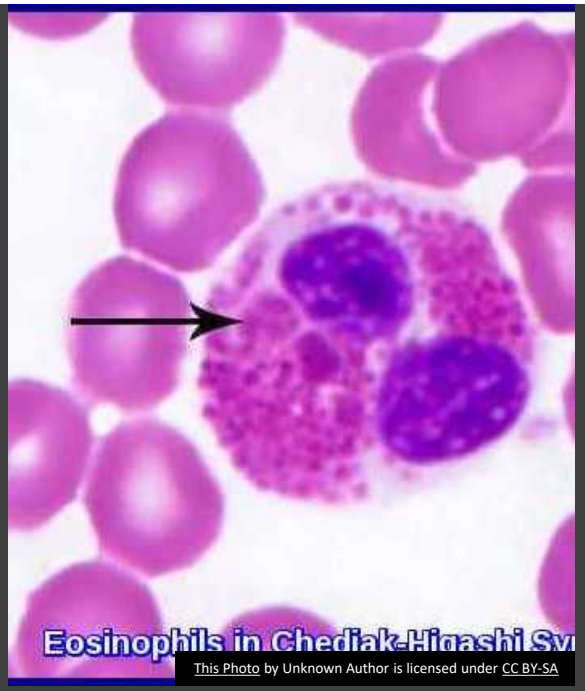
Nonsense mutation in the lysosomal trafficking regulator, CHS1/LYST protein, leads to aberrant fusion of vesicles

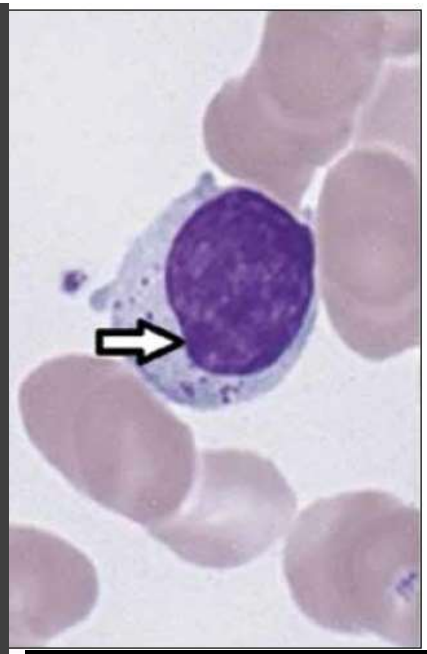
Symptoms

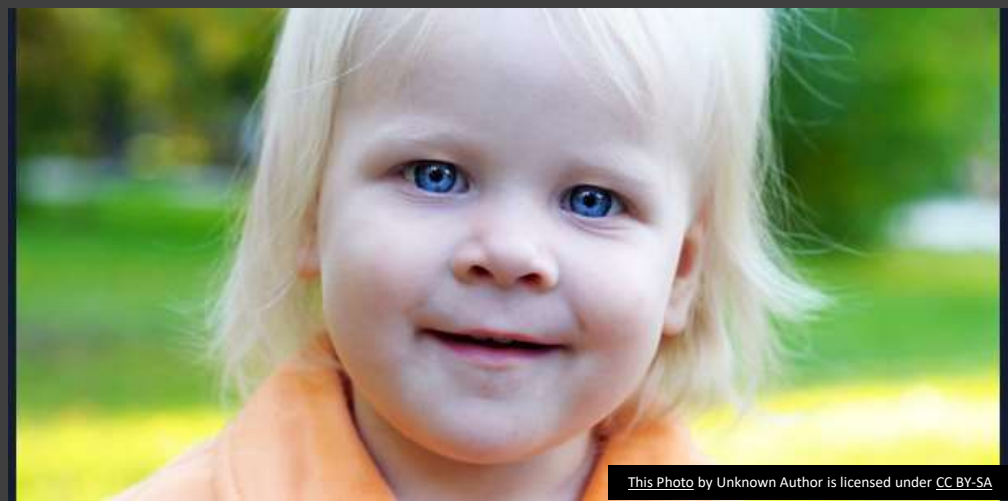
- Recurrent infection with bacteria
- Chemotactic and degranulation defects
- Absent NK activity
- Partial **albinism**

Primary Immunodeficiencies

Chediak Hegashi Syndrome







Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Molecular defect

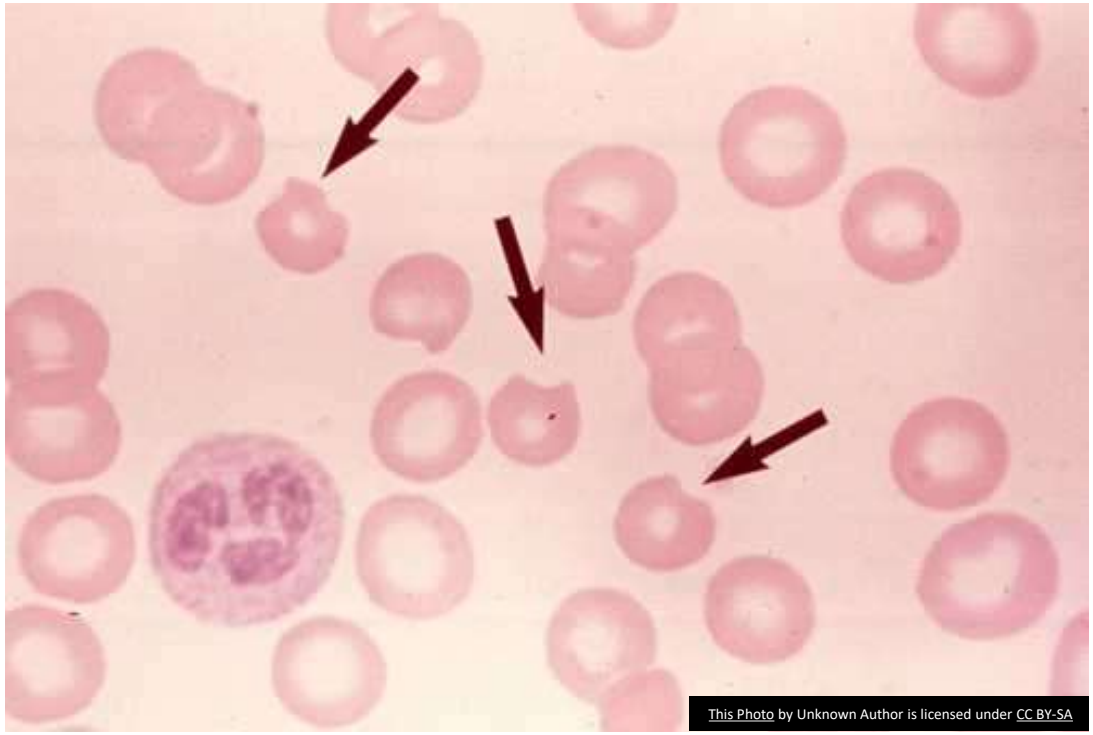
Deficiency of essential enzyme in Hexose monophosphate shunt.

Symptoms

- Same as CGD,
- Associated **Anaemia**

Primary Immunodeficiency

G6PD Deficiency



Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Myeloperoxidase deficiency

Molecular defect

Defect in MPO affects the ability to convert hydrogen peroxide to hypochlorite.

Symptoms

Mild or none

Primary Immunodeficiencies

DEFECTS OF PHAGOCYTIC CELLS

Hyperimmunoglobulin E syndrome(formerly Job syndrome)

Molecular Defect

Defects in JAK-STAT signalling pathway leading to impaired Th17 function: decreased IFN gamma production.

Symptoms

- Characteristic facies,
- Severe & recurrent sinopulmonary infections,
- Pathologic bone fractures,
- Retention of primary teeth,
- Increased IgE,
- Eczematous rash

Primary Immunodeficiencies

B Cell defect

Bruton (X-linked) Agammaglobulinemia

Molecular Defect

Deficiency of the Bruton tyrosine kinase (btk) which promotes pre-B Cell expansion; faulty B-cell development

Symptoms

Increased susceptibility to encapsulated bacteria and bloodborne viruses, low immunoglobulins of all isotypes, absent or low levels of circulating B-cells. B-cell maturation does not progress past the pre-B cell stage while maintaining cell-mediated immunity.

Treatment

Monthly gamma-globulin replacement, Antibiotics for infection

Primary Immunodeficiencies

B Cell Defects

Disease

Hyper IgM Syndrome, Defect in class switch

Molecular Defect

Deficiency of **CD40L** on activated T cells

Symptoms

High serum titres of IgM without other isotypes, normal B and T-cell numbers, susceptibility to encapsulated bacteria and opportunistic pathogens.

Treatment

Antibiotics and Gamma globulins

Primary Immunodeficiencies

Selective Ig A deficiency

Molecular Defect

Multiple genetic Causes

Symptoms

Decreased IgA levels and normal IgM and IgG with elevation of IgE. Repeated **sinopulmonary and gastrointestinal** infections, ↑ **Atopy**

Treatment

Antibiotics, not immunoglobulins

Primary Immunodeficiencies

Disease

Common variable Immunodeficiency

Molecular Defect

Collection of syndromes; several associated genetic defects

Symptoms

Onsets in **late teens**, early twenties; B cells present in peripheral blood, immunoglobulin levels decrease with time; ↑ autoimmunity

Treatment

Antibiotics

Primary Immunodeficiencies

Transient hypogammaglobulinemia O

Transient hypogammaglobulinemia of infancy.

Detected in 5th to 6^{th} month of life, resolves by 16–30 months; susceptibility to pyogenic Bacteria.

Treatment

Antibiotics and in severe cases, gamma-globulin replacement

Primary Immunodeficiencies

Complement Deficiency

Defi iencies in Comple-ment Components	Defi iency	Signs/Diagnosis
Classic pathway	C1q, C1r, C1s, C4, C2	Marked increase in immune complex diseases, increased infections with pyogenic bacteria
Both pathways	C3	Recurrent bacterial infections, immune complex disease
	C5, C6, C7, C8, or C9	Recurrent **meningococcal and gonococcal infections**
Defi iencies in complement regulatory proteins	C1-INH **(hereditary angioedema)**	Overuse of C1, C4, or C2, edema at mucosal surfaces

Primary Immunodeficiencies

DEFECTS OF T LYMPHOCYTES AND SEVERE COMBINED IMMUNODEFICIENCIES

Although patients with defects in B lymphocytes can deal with many pathogens adequately, defects in T lymphocytes are observed globally throughout the immune system. Because of the central role of T cells in activation, proliferation, differentiation, and modulation of virtually all naturally occurring immune responses, abnormalities in these cell lines send shock waves throughout the system. It is often a Herculean clinical effort to dissect the cause-and-effect relationships in such inherited diseases, and their diagnosis is often one of trial and-error, which takes years to unravel.

Although in some cases both B- and T-lymphocyte defects may occur, the initial manifestation of these diseases is almost always infection with agents such as **fungi and viruses** that are normally destroyed by T-cell–mediated immunity. Th B-cell defect, if any, is usually not detected for the fi st few months of life because of the passive transfer of immunoglobulins from the mother through the placenta or colostrum. The immune system is so compromised that even attenuated vaccine preparations can cause infection and disease.

Primary Immunodeficiencies

Selective T-cell deficiency

DiGeorge Syndrome

Heterozygous deletion of chromosome 22q11 . Failure of formation of **3rd and 4th pharyngeal pouches**, thymic aplasia.

Clinical manifestation

Characteristic facies and a clinical triad of cardiac malformations, hypocalcemia and hypoplastic thymus

Primary Immunodeficiencies

Selective T cell deficiency

MHC class I deficiency

Failure of TAP 1 molecules to transport peptides to endoplasmic reticulum

CD8+ T Cells déficient, CD4+ T Cells normal, recurring viral infections, normal DTH, normal Ab production

Primary Immunodeficiencies

Disease

Combined B and T cell Deficiency

Wiskott-Aldrich Syndrome

Molecular Defect

Defect in the WAS protein which plays a critical role in actin cytoskeleton rearrangement.

Symptoms

Defective responses to bacterial polysaccharides and depressed IgM, gradual **loss of humoral and cellular responses, thrombocytopenia, and eczema**

IgA and IgE may be elevated, eczema, immunodeficiency

Primary Immunodeficiencies

Disease

Ataxia telangiectasia

Molecular Defect

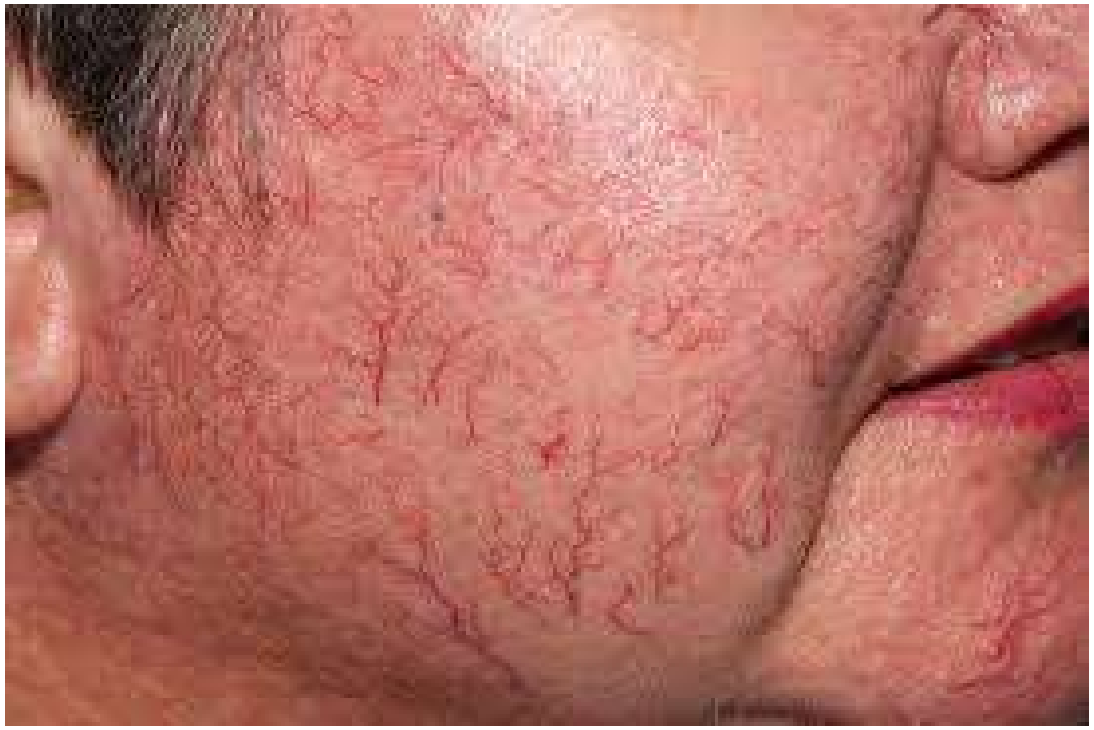
Defect in the ATM kinase involved in the detection of DNA damage and progression through the cell cycle.

Symptoms

Ataxia (gait abnormalities), **Telangiectasia** (capillary distortions in the eye), **deficiency of IgA and IgE** production.

Primary Immunodeficiency

Ataxia telangiectasia



Primary Immunodeficiencies

Complete functional B- and T-cell deficiency Disease

Severe combined immunodeficiency (SCID)

Molecular Defect

Defects in common γ chain of IL-2 receptor (present in receptors for IL-4, −7, −9,−15), X-linked

Adenosine deaminase deficiency (results in toxic metabolic products in cells)

*rag*1 or *rag*2 gene nonsense mutations

Symptoms

Chronic diarrhoea; skin, mouth, and throat lesions; opportunistic (**fungal**) infections; low levels of circulating lymphocytes; cells unresponsive to mitogens.

Clinical overlap with X-linked SCID plus

neurologic deficiency

Total absence B+ T Cells

Primary Immunodeficiencies

Complete functional B- and T-cell deficiency

Primary Immunodeficiencies

Complete functional B- and T-cell deficiency

Disease

Bare lymphocyte syndrome/MHC class II deficiency

Molecular Defect

Failure of MHC class II expression, defects in transcription factors.

Symptoms

T cells present and responsive to nonspecific mitogens, no GVHD, defi ient in CD4+ T cells, hypogammaglobulinemia. Clinically observed as a severe combined immunodeficiency