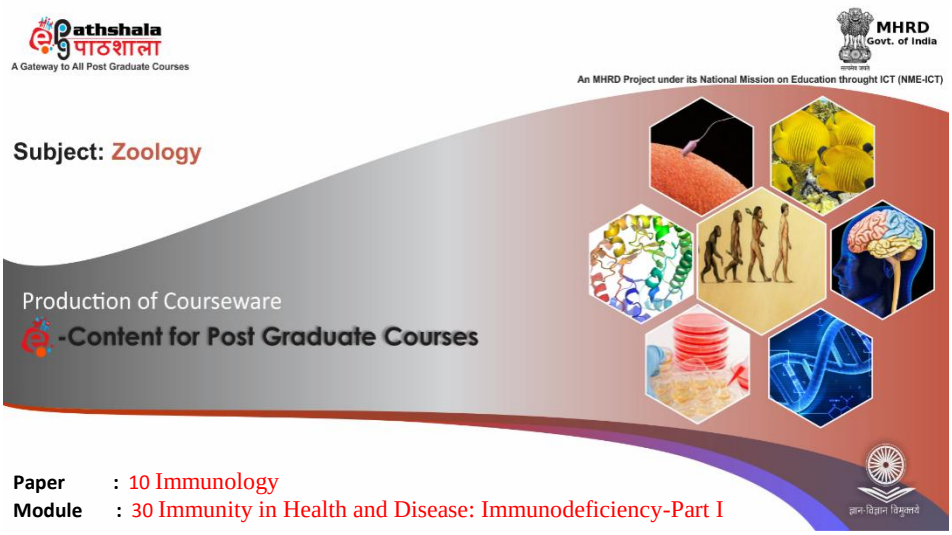

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Contents

6. Prognosis and Prevention of Primary Immunodeficiency Diseases (PID)
7. Management of Primary Immunodeficiency Diseases (PID)
8. Summary

1. Learning Outcomes / Objectives

After studying this module, you shall be able to know more about:

- Immunodeficiency
- Immunodeficiency diseases.
- Mechanism or causes of Immunodeficiency diseases.
- Types of disorders
- Pathogenesis of the Immunodeficiency diseases
- Methods of diagnosis and treatment of Immunodeficiency diseases

2. Introduction

Immunodeficiency is the condition in which the immune system is not able to mount an effective immune response against an antigen. The immune system's ability to fight a pathogen is compromised or entirely absent. This can lead to repeated microbial infections of varying severity. Sometimes it has been seen that the patient can develop enhanced susceptibility to malignancies as well. A person suffering from immunodeficiency is said to be 'immunocompromised'. Such an individual is susceptible to opportunistic infections, in addition to normal infections that could affect everyone. There also seems to be a relationship between person suffering from Immunodeficiency and also having auto immunity through perpetual immune system activation (Grammatikos *et al*., 2012).The severity of the immunodeficiency disease is also dependent on the number of components of immune system getting affected for example in certain disorders there is a deficiency of specific immunoglobulin, mostly IgA or IgG however in certain cases like SCID i.e. severe combined immune deficiency, multiple components of immune system are affected, and this can also cause death.

3. History

The history of Immunodeficiency diseases is interlinked with advances in the fields of clinical physiology, microbiology, pathology along with experimental immunology. However the first case of immunodeficiency may be defined as the one in a strain of guinea pigs in 1919 by Moore at the

Vermont agricultural station in Burlington.It was an autosomal recessive disorder with deficiency of a particular serum protein, which was later established as C4 protein (Moore 1919). The same defect was later found in a colony of outbred Hartley guinea pigs at National Institute of Health (Ellman *et al* 1970). With newer techniques, almost all deficiencies of complement components, regulators and receptors could be characterized (Klemperer *et al*., 1966, 1967; Rosen 2000, Lee and Lau, 2009).

Although during first half of 20th century,many patients with typical symptoms of immunodeficiency disorders such as complement deficiency (Moore 1919), neutropenia (Schultz 1922), ataxia-telangiectasia (Syllaba *et al* 1926), mucocutaneous candidiasis (Thorpe*et al* 1929), Wiskott-Aldrich syndrome (Wiskott 1937) had been reported, the beginning of immunodeficiency is generally considered as 1952, when Odgen Bruton reported the first case of agammaglobulinemia (Bruton 1952).The discovery of agammaglobulinemia by Ogden Carr Bruton is regarded as the earliest

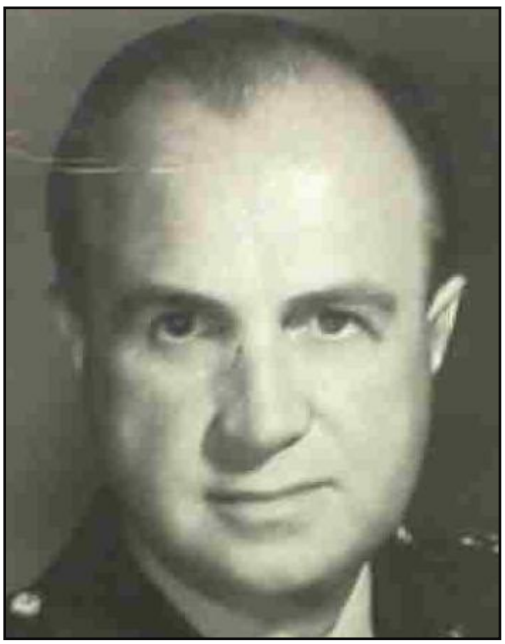

Fig.1: Ogden Carr Bruton
https://commons.wikimedia.org/w/index.php?curid=5908582

breakthrough of immunodeficiency disorders **(Fig.1)**. In fact the disorder has been named after him as "Bruton-type agammaglobulinemia". Not only was Dr Bruton responsible for the discovery, he is also credited for finding a specific immunotherapy for this X-linked disorder in the form of intramuscular injections of IgG immunoglobulin. After the first report of X-linked agammaglobulinemia in 1952, nearly 150 different types of Immunodeficiency disorders have been identified (Geha *et al* 2007). The discovery of Immunodeficiency disorders and the molecular characterization of these diseases paved

the way for better understanding of organization of immune system. This further led to better immunological diagnostic methods or techniques which led to early detection and better treatment.

4. Classification of Immunodeficiency Disorders

Immunodeficiency could be due to certain inherited factors, drugs, or certain medical or physiological conditions like infections, pregnancy, ageing or due to numerous other factors. Based on different criteria, these diseases have been variously classified. The most common classification deals with the origin of the cause of immunodeficiency that could either are in the immune system or there is involvement of some extrinsic factor causing the disease. Accordingly, they have been categorized as

4.1Primary Immunodeficiencies- They are the inherited defects of the immune system. They result from genetic or developmental defects of the immune system. Mostly the defect is present at birth, though it may not manifest itself at the time of birth. Primary immunodeficiencies are also called congenital immunodeficiencies.

4.2 Secondary Immunodeficiencies- They are the defects that arise due to certain extrinsic factors like drugs or minerals, malnutrition or certain infections. The most common being AIDs or acquired immunodeficiency syndrome due to infection with the human immunodeficiency virus 1 (HIV-1).

Alternatively the Immunodeficiency disorders are also classified as –

4.3Specific Immunodeficiency disorders- These are those disorders in which the specific component of the immune system responsible for the condition is known for e.g. abnormalities of B and T cells

4.4 Non-Specific Immunodeficiency disorders- The abnormalities of non-specific components of immune system are responsible for these disorders

It has been seen that in primary immunodeficiency disorders, defects may perhaps be specific or nonspecific type. Sometimes the immunodeficiency disorders are also characterized based on the component that is affected as given in **Table 1.**

TYPE	AFFECTED COMPONENTS	EXAMPLE
Humoral immune deficiency	B-lymphocytes, plasma cells or antibodies mostly accompanied with hypogammaglobulinemia	chronic lymphoid leukemia, multiple myeloma
T cell deficiency	T-lymphocytes	secondary disorders such as acquired immune deficiency syndrome (AIDS)
Neutropenia	Neutrophils	chronic granulomatous disease
Asplenia	Impaired or no function of spleen	splenectomy, sickle cell anemia
Complement deficiency	deficiency of complement components	congenital deficiencies

Table 1: Classification of Immunodeficiency disorders based on affected components

Here, we have classified immunodeficiencies as Primary and Secondary immunodeficiencies as that covers almost all types.

5. Primary Immunodeficiency Diseases (PID)

Primary Immunodeficiencies involve abnormal development of immune system. It can be due to impaired innate or adaptive immune system. Deficiencies involving adaptive immunity could be due to deficient B cell system or deficient T cell system or both as there is considerable overlapping between the two as any deficiency of T-helper cell or T-suppressor cell will directly affect antibody synthesis.

In most cases primary immunodeficiency disorders are found to be inherited single-gene disorders occurring in infancy or early childhood (Stiehm 2007). However, they can also be present in grown-up children, pubescent and adults. At times, they can be associated with relatively mild clinical manifestations in some patients. With 70% of patients being male, PID shows a clear gender bias! This is due to X-linked inheritance in many syndromes (Lim *et al* 2004).

Also, 50% of defects are those related to B-cells; T-cell defects account for 30%, 18% belong to deficiencies in phagocytes and 2% belong to complement deficiencies (LeBien *et al* 2008). The frequency of PIDs has been found to be around 1:10,000 individuals (Boyle *et al* 2007).

Primary immunodeficiencies are further classified as under-

1 Humoral immunodeficiencies (B cell defects)

2 Cellular Immunodeficiencies (T cell defects)

3 Combined Immunodeficiencies (B and T cell defects)

4 Disorders of Complement

5 Disorders of Phagocytosis

In this chapter, we will be discussing the first three types of Primary immunodeficiencies while disorders of complement system and disorders of phagocytosis along with secondary immunodeficiencies would be discussed in the next chapter.

5.1 Humoral immunodeficiencies (B cell defects)- B cell immunodeficiencies could involve complete deficiency of mature recirculating B cells, plasma cells, and immunoglobulin or absence of a particular class of immunoglobulin. Some of the common diseases of the type are-

5.1.1 X-linked agammaglobulinemia

5.1.2 Transient hypogammaglobulinemia of infancy

5.1.3 Common variable immunodeficiency or late onset hypogammaglobulinemia

5.1.4 Selective immunoglobulin deficiency (IgA, IgM or IgG subclasses)

5.1.5 Immunodeficiencies with hyper-IgM

5.1.6 Transcobalamin II deficiency

5.1.1 X-linked agammaglobulinemia-(also called X-linked hypogammaglobulinemia,XLA, Bruton type agammaglobulinemia, Sex-linked agammaglobulinemia, or Bruton syndrome) - The disease was first elucidated by Ogden CarrBruton in 1952. It is a rare X-linked genetic disorder that involves mutations in the gene coding for Bruton tyrosine kinase (BTK). BTK is very important for the maturation of pre–B cells to differentiating mature B cells. All classes of immunoglobulins are depleted in the serum of the patient. BTK gene is present on X chromosome and therefore the defect is inherited as X-linked recessive and is almost always limited to the sons of female carriers, latter being asymptomatic all their lives (**Fig.2**). The symptoms of XLA include repeated and often severe infections accompanied with ear infections, sinusitis, diarrhea due to Giardia and pneumonia. The most common pyogenic bacteria responsible for infection in XLA are *Streptococcus, Staphylococcus* and *Haemophilus*. The treatment involves Immunoglobulin replacement therapy or intravenous introduction of mixture of immunoglobulin (IVIg, human IgG antibodies) on a regular basis, for life.

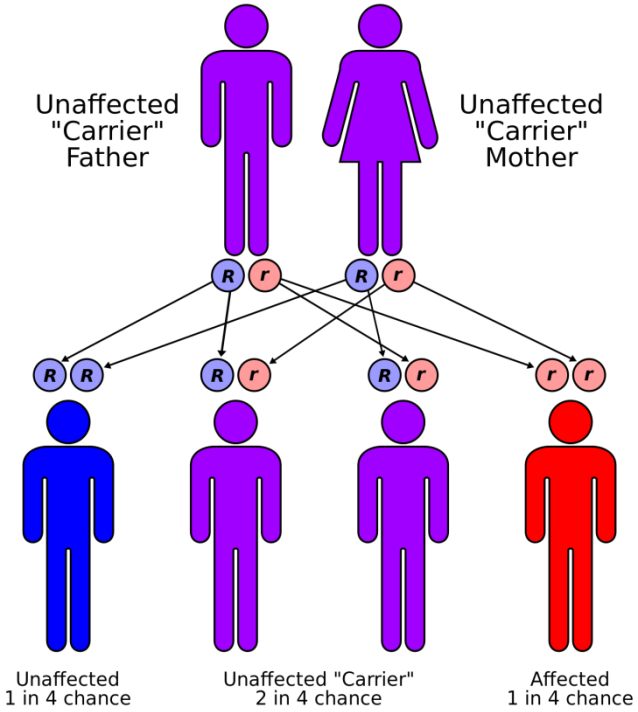

Fig. 2: Inheritance Pattern in XLA
Source-en.wikipedia.org

5.1.2 Transient hypogammaglobulinemia of infancy (THI)-The immune system in a newborn is not fully developed. Most of the immunoglobulins in neonates are those that were produced by the mother and transferred by the placenta before birth. These Immunoglobulins provide protection to the neonates till they start producing their own, usually by age 6 months. Meanwhile the levels of immunoglobulins from the mother also start decreasing. In infants with transient hypogammaglobulinemia of infancy, there is a delay in the production of normal amounts of immunoglobulins. This results in low levels of immunoglobulins at age 3 to 6 months and back to normal levels at about age 12 to 36 months. The disease may be present in infants of both the sexes. Although the condition rarely leads to serious infections but few infants develop respiratory or digestive tract infections. This disorder may last for few months to few years but get resolved without treatment. Antibiotics are often prescribed to combat infections. Certain studies have however suggested that THI may be an intrinsic B-cell defect with abnormal antibody responses (Dorsey *et al.* 2006)

5.1.3 Common variable immunodeficiency (late onset hypogammaglobulinemia) - CVID is one of the most common symptomatic primary immunodeficiency wherein the symptoms develop around 15-35 years of age. It is generally characterized by recurrent pyogenic infections, accompanied by

malabsorption and giardiasis. The level of immunoglobulins is less than 300mg/mL. It has been seen that B cells are present at normal levels however there is defect in their ability to differentiate into plasma cells and secrete immunoglobulins. This is accompanied with decreased T-helper cells activity and increased activity of T-suppressor cells. Individuals with CVID are more prone to developing certain forms of cancer (lymphoma). The genetic causes of CVID are largely unknown though mutations in at least five genes have been associated with CVID. These include inducible T cell co-stimulator (ICOS) along with some other proteins on B-cells. The treatment involves intravenous infusion of immunoglobulin.

5.1.4 Selective immunoglobulin deficiency (IgA, IgM or IgG subclasses)-SIgD is an inherited disorder wherein there is selective deficiency of a class of immunoglobulin, while the others remain normal or may be elevated in some cases. The most common form of selective deficiency is that of IgA. Most of the IgA in the body is in the sero-mucus secretions including tears, saliva, colostrum, genital, respiratory and gastrointestinal secretions. It is a dimeric antibody that plays a major role in protecting us from infections in these areas (**Fig. 3**). Though most of the patients do not show any symptoms, however in some there is increased susceptibility to respiratory and gastrointestinal infections. In some patients, anti-IgA has also been detected. Allergies may also be common in these patients.It has been seen that some patients with IgA deficiency are also found to have IgG2 and/or IgG4 subclass deficiency. In these patients, the common finding is a maturation defect in B cells to produce IgA. It is not currently possible to substituteIgA in patients suffering from IgA deficiency, although scientists are currently working on purification of human IgA. The condition gets further aggravated with knowledge that IgA in the serum, unlike IgG, does not remain stable in the circulation for very long. Therefore, there is no effective treatment for this disorder, though antibiotics can be prescribed to combat infections.

Selective IgM deficiency has also been found in some patients and is generally associated with septicemia.

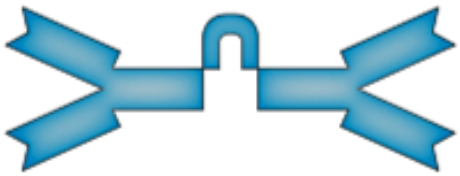

Fig. 3 **Dimeric IgA antibody**
By Martin Brändli (brandlee86) - Own work, CC BY-SA 2.5,
https://commons.wikimedia.org/w/index.php?curid=560511

5.1.5 Immunodeficiencies with hyper-IgM (HIGM syndrome) – In this disorder, there are an elevated levels of IgM and decreased levels of IgA, IgG and IgE. The IgM are normal and have antibody activity. IgM is the form of pentameric antibody that all B cells produce initially, before B cells go through class switching due to exposure to an antigen (**Fig. 4**). HIGM is X-linked or autosomal recessive and is accompanied with impaired antibody class switching mechanism. Patients show enhanced susceptibility to infections along with thrombocytopenia, neutropenia, hemolytic anemia and renal lesions.

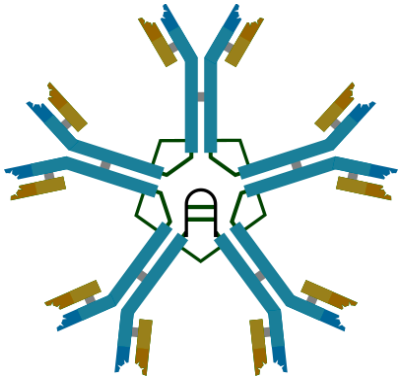

Fig.4 Pentameric IgM
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Five types of HIGM have been characterized:

- Hyper-IgM syndrome type 1 (X-linked), involves mutations of the CD40L gene. Signal from T cells to B cells for class switching is lacking.
- Hyper-IgM syndrome type 2 (autosomal recessive), involves mutations of the AICDA gene. Defection heavy chain production hindering class switching.
- Hyper-IgM syndrome type 3, involves mutations of the CD40 gene. B cell not able to receive signal from T cells for class switching.
- Hyper-IgM syndrome type 4, involves defect in class switch recombination downstream of the AICDA gene.
- Hyper-IgM syndrome type 5, involves mutations of the UNG gene.

Patients with all forms of HIGM syndrome have a severe IgG deficiency and they require immunoglobulin replacement therapy.

5.1.6 Transcobalamin II deficiency- It is inherited as autosomal recessive disorder where there is deficiency of Vitamin B12, along with megaloblastic anemia (scarcity of red blood cells and abnormally large sized red blood cells that are remaining) and intestinal villus atrophy.

Transcobalamin II is a protein that is actually responsible for transporting vitamin B12 to tissues from GI tract. Cobalamin or Vitamin B12 is obtained from the diet and is found in animal products such as meat, eggs, and shellfish. The absence of cobalamin leads to impaired growth, a shortage of blood cells hypogammaglobulinemia, and other symptoms those become apparent within the first weeks or months of life. Neurological function is compromised in such individuals, and they suffer from progressive inflexibility and weakness in their legs (paraparesis), muscle twitches (myoclonus), or intellectual disability. Treatment with Vitamin B12 can help in restoration of hematopoietic, gastrointestinal and B cell functions.

5.2 Cellular Immunodeficiencies (T cell defects)- T cells play a very vital role in immune system therefore any deficiency in T cell would directly affect both humoral as well as cell mediated immunity. This further leads to increased susceptibility to viral, protozoan, and fungal infections. Most common intracellular pathogens such as *Mycobacteria*, *Pneumocystis carinii*, and *Candida albicans* have been found to be thriving in such cases hence showing the importance of T cells in eliminating these pathogens. Some of the most common T cell immunodeficiency defects are as below-

1 Thymic hypoplasia

2 Chronic mucocutaneous candidiasis

3 Purine nucleoside phosphorylase deficiency

5.2.1 Thymic hypoplasia (Digeorge syndrome, 22q11.2 deletion syndrome, Shprintzen syndrome, velocardiofacial syndrome (VCFS), Takao syndrome, conotruncal anomaly face syndrome (CTAF) or Sedlackova syndrome, Cayler cardiofacial syndrome, congenital thymic aplasia, thymic hypoplasia, Strong syndrome, DGS)- It is a microdeletion syndrome involving removal/deletion of a small segment on one copy of chromosome 22. The inheritance pattern is autosomal dominant and the ratio at which it is prevalent is about 1:4000 persons in a general population (Oskarsdóttir 2004, Kobrynski *et al* 2007). About 90% are *de novo* (the deletion of genes from chromosome 22 usually occurs as a random event in the father's sperm or in the mother's egg, or it may occur early during fetal development). Rest are inherited from a parent. The syndrome was described by an endocrinologist Angelo DiGeorge in 1968 (**Fig. 5**).

Fig. 5: Angelo DiGeorge

The exact mechanism that is responsible for different features of the disease are unknown. Of all the deleted genes (about 30-50), some have been identified as possibly playing a pivotal role in the development of some of the signs and symptoms of the disease.

TBX1 is part of the T-box family of genes that play an important role in tissue and organ formation during embryonic development (**Fig.6**). In DGS, point mutation in this gene has multiple effects including abnormal development of endodermal derivatives of third and fourth pharyngeal pouches, leading to aplasia or hypoplasia of thymus and parathyroid glands. Since thymus is involved in the development of T-cell/cellular immunity, patients with DGS are highly susceptible to intracellular pathogens. They also seem to be more prone to get Parkinson's diseases.

The syndrome is also known as CATCH 22 where 22 stands for abnormality in chromosome 22 and CATCH for the following features-

Cardiac abnormality (interrupted aortic arch, truncus arteriosus and tetralogy of Fallot)

Abnormal face

Thymic aplasia

Cleft palate

Hypocalcemia/Hypoparathyroidism

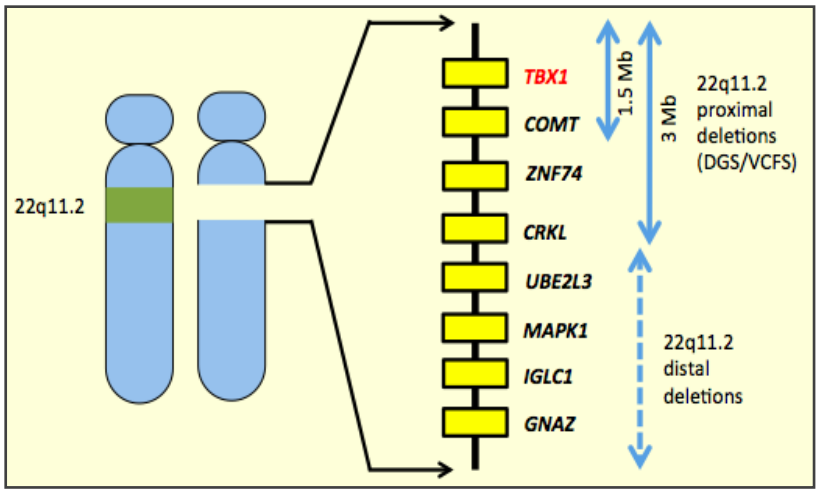

Fig. 6: Diagram depicting 22q11.2 deletions and associated genes
www.genetics4medics.com/digeorge-syndrome.html

The FISH (Fluorescent In Situ Hybridization) test has made the diagnosis of DGS more precise and more common. No effective cure has been found for this syndrome. Though transplantation of thymus can be done in case of a rare case where there is complete lack of thymic tissue called "complete" DiGeorge syndrome. Repeated bacterial infections are treated with antibiotics while cardiac surgery can be done to correct congenital heart abnormalities. Hypocalcaemia due to Hypoparathyroidism can be treated with lifelong vitamin D and calcium supplements**.**

5.2.2 Chronic mucocutaneous candidiasis- It is a heterogeneous disorder with impaired cell-mediated immunity against *Candida* species. Inheritance in this case has been found to be autosomal dominant wherein there is a mutation in the signal transducer and activator of transcription 1 gene *(STAT1)* or it is recessive in some cases involving a mutation in the autoimmune regulator gene *(AIRE).* In many cases T cells completely fail to recognize the antigen. Patients develop candidiasis of mucosa, nail and skin **(Fig.7**). Antifungal are useful to control the disease.

Fig. 7: Candidiasis of the nail
https://en.wikipedia.org

5.2.3 Purine nucleoside phosphorylase deficiency- It is also called PNP-deficiency and is a rare autosomal recessive disorder that causes decreased cell mediated immunity along with recurrent or chronic infections (Sasaki*et al* 1998). The disorder is due to a mutation in the purine nucleoside phosphorylase (PNP) gene that is located at chromosome 14q13.1(Snyder*et al* 1997). Enzyme PNP is involved in sequential degradation of purines to hypoxanthine and then to uric acid. Absence of PNP leads to building up of such metabolites in the cell which are particularly toxic to immature lymphoid cells, leading to lymphopenia and impaired cell-mediated immunity. Diagnosis can therefore be done by checking the uric acid levels in the patients.

5.3 Combined Immunodeficiencies (B and T cell defects)- The combined immunodeficiencies of both humoral and cell-mediated branches are the worst of all the immunodeficiency disorders, involving multiple components of the immune system. Some important disorders that belong to this category are-

1 Nezelof Syndrome
2 Ataxia telangiectasia (Louis–Bar syndrome)
3 Wiskott-Aldrich syndrome
4 Severe combined immunodeficiencies (SCID)

5.3.1 Nezelof Syndrome (Cellular immunodeficiency with abnormal immunoglobulin synthesis) - It is an autosomal recessive genetic disorder affecting both males and females. The condition is characterized by absent T cell function, and varying degree of deficiency of B cell mediated immunity. Patients generally have progressively severe, recurrent, and eventually fatal infections. It is generally accompanied with thymic dysplasia. Despite the normal presence of immunoglobulins, an antigenic stimulus doesn't induce antibody formation. Treatment includes monthly injections of gamma globulin or combinations of fresh frozen plasma and heavy use of antibiotics to fight infection.

5.3.2 Ataxia telangiectasia (Louis–Bar syndrome) - It is an autosomal recessive genetic disorder i.e. both parents must provide a copy of a nonworking gene to the child to develop this disorder.The combined immunodeficiency in this case is accompanied with cerebellar ataxia (ataxia means poor coordination), telangiectasia (stands for small dilated blood vessels), ovarian dysgenesis and chromosomal abnormalities. Generally the survival rate is very low. Cell mediated immunity is defective along with low levels of IgA and IgE. The disease is found to be progressive with symptoms of immunodeficiency along with neurological defects getting worse with time. Thymus transplants in

foetus and transfer factor therapy are used to treat or control the symptoms. Some of the symptoms include decreased coordination of movements (ataxia), decreasing mental development, discoloration of skin areas on exposure to sunlight, blood vessels are enlarged or dilated in skin of nose, ears, inside of the elbow and knee and also in the whites of the eyes (**Fig. 8**), jerky or abnormal eye movements (nystagmus) late in the disease, sensitivity to radiation, including x-rays and severe and persistent respiratory infections.

Fig. 8 Ocular telangiectasia in a person with Ataxia telangiectasia
https://en.wikipedia.org

5.3.3 Wiskott-Aldrich syndrome- It is an X-linked recessive disorder characterized by eczema, thrombocytopenia (low platelet count), bloody diarrhoea (secondary to the thrombocytopenia) and overall immune deficiency. The syndrome is also called the eczema-thrombocytopenia-immunodeficiency syndrome as eczema occurs in the first month of birth. Affected boys very rarely survive beyond 10 years due to recurrent infections, hemorrhage or lymphoreticular malignancy. The female carriers are usually asymptomatic. The levels of serum IgM is very low along with progressively deteriorating cell mediated immunity. Treatment involves bone marrow transplant or transfer factor therapy. The syndrome is named after Dr. Robert Anderson Aldrich, who was an American pediatrician. He described the disease in a family of Dutch-Americans in 1954 (Aldrich*et al* 1954).

5.3.4 Severe combined immunodeficiencies also called **alymphocytosis**, **Glanzmann–Riniker syndrome, severe mixed immunodeficiency syndrome**, and **thymic alymphoplasia-** The deficiency leads to numerous syndromes involving both cellular and humoral immune responses. SCID is considered to be most severe form of PIDs. Also known as **bubble baby disease** and **bubble boy disease** (well-known case of David Vetter) because its victims are extremely vulnerable to infectious

diseases. Infants with SCID have severe recurrent respiratory infections. Infections are generally serious and at times life threatening. Other symptoms include poor growth, eczema, chronic diarrhea etc.Bone marrow transplant is the only cure currently and routinely available for SCID which provides a new immune system to the patient.

In many cases of SCID, it has been found to be associated with X chromosome (X-linked recessive) while in others it is transmitted by an autosomal, or non-sex–linked, recessive gene (autosomal recessive). Scientists have found at least nine different known genes in which mutations lead to a form of SCID(Buckley 2003). More recently around 15 defective genes have been found to be responsible for SCID (Schwartz *et al*. 2011). The classification of different types of SCID is given in **Table 2**.

Type	Description
X-linked severe combined immunodeficiency	This is the most common form of SCID involving mutations in the gene IL-2Rγ, which is located on the X-chromosome encoding the common gamma chain (γ_c) that is shared by the receptors for interleukins IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. These interleukins and their receptors are involved in the development and differentiation of T and B cells. This leads to nonfunctional gamma chain and defective interleukin signaling, causing complete failure of immune system. The condition is inherited in an X-linked recessive pattern.
Adenosine deaminase deficiency	It is second most common form of SCID, caused by a defective enzyme, adenosine deaminase (ADA). ADA is essential for the breakdown of purines. Deficiency of ADA leads to accumulation of dATP. This metabolite will inhibit the activity of ribonucleotide reductase, the enzyme that is involved in reduction of ribonucleotides to deoxyribonucleotides. The efficiency of the immune system depends upon proliferation of lymphocytes and hence dNTP synthesis which gets hampered by non-functional ribonucleotide reductase. The immune system is hence compromised.
Purine nucleoside phosphorylase deficiency	It is an autosomal recessive disorder that involves mutation of the purine nucleoside phosphorylase (PNP) gene. PNP is an important enzyme of purine salvage pathway. Deficiency of functional enzyme causes an elevated dGTP level that leads to T-cell toxicity and deficiency.
Reticular dysgenesis	Impaired mitochondrial adenylate kinase 2 that leads to inability of granulocyte precursors to form granules
Omenn syndrome	Mutations of the RAG-1 or RAG-2 genes that prevent V(D)J recombination, causing SCID. (RAG-1 and RAG-2 are involved in synthesis of recombinase enzymes that are involved in the manufacture of immunoglobulins.)
Bare lymphocyte syndrome	Inherited as autosomal recessive. MHC class II is not expressed on the cell surface of all antigen presenting cells due to defective MHC-II gene regulatory proteins.
JAK3	Mutation in Janus kinase-3 (JAK3) causing SCID. This enzyme mediates transduction downstream of the γ_c signal.
Artemis/DCLRE1C	Defective gene called Artemis primarily in Navajo and Apache populations. The deficiency causes severe form of SCID where bodies of children are unable to repair DNA.

Table 2: Classification of different types of SCID

6. Prognosis and Prevention of Primary Immunodeficiency Diseases (PID)

Most of the PIDs discussed above are genetic and generally lifelong. In many types of PIDs, the patients can lead a normal life if the condition is diagnosed early and effective treatment is given.It is known that delay in diagnosis leads to many complications and sometimes death in the patients with PIDs. In certain disorders however, the prognosis is less optimistic and may require intensive care. Genetic counseling of prospective parents who also happens to be carriers can be an effective strategy of prevention of PIDs. Sex determinations can also prevent incidence of X linked disorders. Development of better screening tests for identification of PIDs is very important. Screening at genetic laboratories as part of prenatal, neonatal and carrier screening programs could be made mandatory especially for families with a positive history.Also,specific programs may be designed for those who are planning marriages within relatives as this increases the frequency of PIDs.

7. Management of Primary Immunodeficiency Diseases (PID)

- Healthy life style must be ensured for the patients of PIDs. They must be kept in infection-free environment and away from all sources of infections.
- Regular dental checkup is a must
- Live vaccines are never given to patients suffering from PIDs. Killed vaccines may be used when required.
- All kinds of bacterial and fungal infections must be treated at the earliest.
- In some cases continuous use of prophylactic antibiotics may be appropriate.
- Antiviral therapies such as amantidine and ramantadine can be life-saving for the management of viral infections.
- Treatment may include monthly injections of gamma globulin or combinations of fresh frozen plasma and heavy use of antibiotics to fight infection. However, Immunoglobulin replacement is contra-indicated in selective IgAD, as serious anaphylactic reactions can be caused.
- The best treatment for T-cell deficiency conditions is bone marrow transplant, if a suitable donor can be found.
- Other treatment options may include treatment with cytokines or stem cell transplantation or gene therapy or thymic transplants.

8. Summary

Immunodeficiency disorders weaken the immune system's ability to provide an effective defense to the body against pathogens or abnormal cells that attack it (such as bacteria, viruses, fungi, parasites and cancer cells etc). Primary immunodeficiencies (PIDs) are those disorders in which body's immune system is either missing or does not have normal function.Almost all types of PIDs are genetic or congenital in nature. It has also been seen that men are more prone to get immunodeficiency disorders. In most cases skin, respiratory system, the ears, the brain or spinal cord, or the urinary or gastrointestinal tractsget affected. Heart defects are also seen in many patients. Many a times, autoimmunity and malignancy are also associated with immunodeficiency.

Depending on the type, some PIDs are so mild that they go unnoticed; however, some can be so severe that bone marrow transplant or stem cell transplant is the only cure. Patients suffering from SCID, generally die in infancy. However, research in PID is making great strides and with efficient diagnosis and new treatment options the life quality of affected individuals is greatly enhanced.