Immunodeficiency

Immunodeficiency is the failure of the immune system to protect against disease or malignancy. Primary immunodeficiency is caused by genetic or developmental defects in the immune system. These defects are present at birth but may show up later on in life. Secondary or acquired immunodeficiency is the loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging.

SPECIFIC IMMUNE SYSTEM

There are variety of immunodeficiencies which result from defects in stem cell differentiation and may involve T-cells, B-cells, and/or immunoglobulins. A defect in the early hematopoiesis which involves stem cells results in reticular dysgenesis that leads to general immune defects and subsequent susceptibility to infections. This condition is often fatal but very rare. It can be treated successfully by bone marrow transplantation.

Lymphoid lineage immunodeficiency

If the lymphoid progenitor cells are defective, then both the T and B cell lineages are affected and result in the severe combined immunodeficiency (SCID). This makes infants to be susceptible to opportunistic microorganisms (bacterial, viral, fungal and protozoan infections).

In about 50% of SCID patients, the immunodeficiency is X-linked whereas in the other half the deficiency is autosomal. Both are characterized by an absence of T cell and B cell immunity and absence (or very low numbers) of circulating T and B lymphocytes. Thymic shadows are absent on X-rays.

Other genetic defects leading to SCID include those for Recombinase activating genes RAG1, RAG2 and IL-7-alpha

SCID includes several disorders

RAG

Patients having both T and B cell deficiency lack recombinase activating genes (RAG1 and 2) that are responsible for the T cell receptor and immunoglobulin gene rearrangements. These patients are athymic and are diagnosed by examining the T
Defects in B cells are not observed in early infant life because of passive antibodies obtained from the mother. NK cells are normal in these patients. This is an autosomal recessive trait.

**CD3 chain**

In some SCID patients, T cells may be present but functionally defective because of deficiency in signaling mediated by the CD3 chain that is associated with the TCR.

**Interleukin-2 receptor**

Interleukin-2 receptor common gamma chain (IL-2Rγc) may be lacking in patients thereby preventing signaling by IL-2 and other cytokines which act as growth factors. This leads to a defect in the proliferation of T cells, B cells and NK cells. This is an autosomal recessive trait.

**Adenosine deaminase**

Adenosine deaminase (ADA) is an enzyme responsible for converting adenosine to inosine. ADA deficiency leads to accumulation of adenosine which results in the production of toxic metabolites that interfere with DNA synthesis. The patients have defects in T, B and NK cells.

SCIDs are autosomal recessive traits and can be treated by gene therapy or stem cell transplantation.

**Disorders of T cells**

T cell disorders affect both cell-mediated and humoral immunity making the patient susceptible to viral, protozoal and fungal infections. Viral infections such as those by cytomegalovirus and attenuated measles in the vaccine can be fatal in these patients.

**DiGeorge's Syndrome (Deletion 22 Syndrome)**

This the most clearly defined T-cell immunodeficiency and is also known as congenital thymic aplasia/hypoplasia, or immunodeficiency with hypoparathyroidism. These defects results from abnormal development of the fetus (3rd and 4th pharyngeal pouch) during the 6th to 10th week of gestation when parathyroid, thymus, lips, ears and aortic arch are being formed. No genetic predisposition is clear. A thymic graft taken from an early fetus (13 - 14 weeks of gestation) can be used for treatment. Older grafts may result in GVH reaction. In severely immunodeficient DiGeorge patients, live vaccines may cause progressive infections.
T cell deficiencies with variable degrees of B cell deficiency

Ataxia-telangiectasia
T-cells and their functions are reduced to various degrees. B cell numbers and IgM concentrations are normal to low. IgG is often reduced and IgA is considerably reduced (in 70% of the cases). There is a high incidence of malignancy, particularly leukemias, in these patients. The defects arise from a breakage in chromosome 14 at the site of TCR and immunoglobulin heavy chain genes.

Wiskott-Aldrich syndrome
Wiskott-Aldrich syndrome is associated with normal T cell numbers with reduced functions. IgM concentrations are reduced but IgG levels are normal. Both IgA and IgE levels are elevated. Patients with this syndrome develop severe eczema, petechia (due to platelet defect and thrombocytopenia). They respond poorly to polysaccharide antigens and are susceptible to pyogenic infection. Wiskott-Aldrich syndrome is an X-linked disorder.

MHC deficiency (Bare leukocyte syndrome)
A number of cases of immunodeficiency have been described in which there is a defect in the MHC class II protein gene, which results in a lack of class II MHC molecules on their APC. Since the positive selection of CD4 cells in the thymus depends on the presence of these MHC molecules, these patients have fewer CD4 cells and are infection prone. There are also individuals who have a defect in their transport associated protein (TAP) gene and hence do not express the class I MHC molecules and consequently are deficient in CD8+ T cell.

Disorders of B lymphocytes
There are a number of diseases in which T cell numbers and functions are normal: B cell numbers may be low or normal but immunoglobulin levels are low.

X-linked infantile hypogammaglobulinemia
X-linked hypogammaglobulinemia, is the most severe hypogammaglobulinemia in which B cell numbers and all immunoglobulin levels are very low. The patients have failure of B-cell maturation associated with a defective B cell tyrosine kinase (btk) gene. Thus, B cells exist as pre-B cells with H chains but not L chains rearranged. Diagnosis is based on enumeration of B cells and immunoglobulin measurement. Patients have no immunoglobulins and suffer from recurrent bacterial infections.

Transient hypogammaglobulinemia
Children, at birth, have IgG levels comparable to that of the mother. Because the half life of IgG is about 30 days, its level
gradually declines, but by three months of age normal infants begin to synthesize their own IgG. In some infants, however, IgG synthesis may not begin until they are 2 to 3 years old. This delay has been attributed to poor T cell help. This results in a transient deficiency of IgG which can be treated with gamma-globulin.

**IgA deficiency**

IgA deficiency is the commonest of all immunodeficiencies and results from a defect in class switching. About 20% of individuals with IgA deficiency also have low IgG. IgA-deficient patients are very susceptible to gastrointestinal, eye and nasopharyngeal infections.

**X-linked Hyper-IgM immunodeficiency**

Individuals with this type of immunodeficiency have low IgA and IgG concentrations with abnormally high levels of IgM. These patients cannot make a switch from IgM to other classes which is attributed to a defect in CD40Ligand on their CD4 cells. They are very susceptible to pyogenic infection and should be treated with intravenous gamma-globulin.

**NON-SPECIFIC IMMUNE SYSTEM - DEFECTS IN THE MYELOID LINEAGE**

Primary immunodeficiencies of the non-specific immune system include defects in phagocytic and NK cells and the complement system.

**Congenital Agranulomatosis**

Patients have a decrease in the neutrophil count. This is due to a defect in the myeloid progenitor cell differentiation into neutrophils. These patients are treated with granulocyte-macrophage colony stimulating factor (GM-CSF) or G-CSF.

**Defects of the phagocytic system**

Defects of phagocytic cells (numbers and/or functions) can lead to increased susceptibility to a variety of infections.

**Chronic granulomatous disease (CGD)**

CGD is characterized by marked lymphadenopathy, hepato- splenomegaly and chronic draining lymph nodes. Leukocytes
have poor intracellular killing and low respiratory burst. In majority of these patients, the deficiency is due to a defect in NADPH oxidase that participate in phagocytic respiratory burst.

**Leukocyte Adhesion Deficiency**

In this disease, T cells and macrophages lack the complement receptor CR3 and consequently they cannot respond to C3b opsonin. Alternatively there may a defect in integrin molecules. These molecules are involved in diapedesis and hence defective neutrophils cannot respond effectively to chemotactic signals.

**DISORDERS OF COMPLEMENT SYSTEM**

Complement abnormalities also lead to increased susceptibility to infections. There are genetic deficiencies of various components of complement system, the most serious of which is the C3 deficiency which may arise from low C3 synthesis or deficiency in factor I or factor H.

**SECONDARY (ACQUIRED) IMMUNODEFICIENCIES**

**Immunodeficiencies associated with infections**

Bacterial, viral, protozoan, helminthic and fungal infections may lead to B cell, T cell, PMN and macrophage deficiencies. Most prominent among these is acquired immunodeficiency syndrome (AIDS). Secondary immunodeficiencies are also seen in malignancies.

**Immunologic abnormalities in the AIDS**

AIDS is caused by Human Immunodeficiency Virus (HIV)-1. the patients exhibited fungal infections with opportunistic organisms such as Pneumocystis carinii and in other cases, with a skin tumor known as Kaposi's sarcoma. HIV is spread through sexual intercourse, infected blood and body fluids as well as from mother to offspring. The HIV-1 virion consists of a viral envelope made up of the outer lipid bilayer of the host cell in which are embedded glycoproteins composed of the transmembrane gp41 along with the associated gp120. The gp120 binds the CD4 expressed on host T cells.

The virus replicates rapidly and within about two weeks the patient may develop fever. The viral load in the blood increases significantly and peaks in two months, after which there is a sudden decline because of the latent virus found in germinal centers of the lymph nodes. CTL develop very early whereas antibodies can be detected between 3 - 8 weeks. The CTL killing of Th cells around 4 - 8 weeks leads to a decrease in CD4+T cells. When the CD4+ T cell count decreases
below 200 per cubic mm, full blown AIDS develops.

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<th>Disease</th>
<th>T-cells No.</th>
<th>T-cells Fx</th>
<th>B-cells No.</th>
<th>B-cells Fx</th>
<th>Immunoglobulins</th>
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<td>N</td>
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</tbody>
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A: absent; a: autosomal; H: high; L: low; N: normal; U: unknown; V: variable; x: x-linked

**Table 1. Summary of T cell and B cell immunodeficiency diseases (ID)**