BUBBLE BOY DISEASE AN OVERVIEW

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Summary

The review is directed towards find out the extensive study of SCID and its preventive measures as it occurs mostly in pediatrics and may prove as fatal sometimes. SCID severe combined immunodeficiency disease named as bubble boy disease mainly occurs in pediatrics considered as a pediatric emergency require immediate diagnosis and treatment. There are several forms of SCID. The most common type is linked to the X chromosome, making this form affect only males. Other forms of SCID usually follow an autosomal recessive inheritance pattern or are the result of spontaneous mutations. One of these other forms is linked to a deficiency of the enzyme adenosine deaminase (ADA). Other Immunodeficiency is a primary immune deficiency. The defining characteristic is usually a severe defect in both the T- & B-lymphocyte systems. This usually results in the onset of one or more serious infections within the first few months of life. These infections are usually serious, and may even be life threatening, meningitis or bloodstream infections. SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients. All forms of SCID are inherited, with as many as half of SCID cases linked to the X chromosome, passed on by the mother. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene which produces the common gamma chain subunit, a component of several IL receptors. Now a day's gene therapy finds its way in the treatment of SCID.

Key-words: Bubble boy disease, severe combined immunodeficiency diseases.

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Introduction

SCID, Severe Combined when the world Lear" This once-fatal disease should be now seen as a pediatric emergency, a condition that needs immediate diagnosis and treatment. "Early diagnosis of SCID is rare because doctors do not routinely perform a test in newborns to count white blood cells. Such a blood test could pick up children with SCID as well as those with they may include pneumonia other serious immune deficiencies that would not be apparent until the child developed an infection. A simple blood test could allow us to treat, and most likely cure, SCID in an infant at a reasonable cost.[1,2,3] If found later, less effective treatment can run into the millions." "What we're saying is that essentially every baby with SCID could be cured if diagnosed early enough. SCID should be considered a pediatric emergency." SCID is often called "bubble boy disease". SCID became widely known during the 1970's and 80's, need of David Vetter, a boy with X-linked SCID, who lived for 12 years in a plastic, germ-free bubble. There are several forms of SCID. The most common type is linked to the X chromosome, making this form affect only males. Other forms of SCID usually follow an autosomal recessive inheritance pattern or are the result of spontaneous mutations. One of these other forms is linked to a deficiency of the enzyme adenosine deaminase (ADA). Other Immunodeficiency, is a primary immune deficiency. The defining characteristic is usually a severe defect in both the T- & B-lymphocyte systems. This usually results in the onset of one or more serious infections within the first few months of life. These infections are usually serious, and may even be life threatening,, meningitis or bloodstream infections.[4,5]

"This once-fatal disease should be now seen as a pediatric emergency, a condition that needs immediate diagnosis and treatment. "Early diagnosis of SCID is rare because doctors do not routinely perform a test in newborns to count white blood cells. Such a blood test could pick up children with SCID as well as those with other serious immune deficiencies that would not be apparent until the child developed an infection. A simple blood test could allow us to treat, and most likely cure, SCID in an infant at a reasonable cost. If found later, less effective treatment can run into the millions." Buckley states, "What we're saying is that essentially every baby with SCID could be cured if diagnosed early enough. SCID should be considered a pediatric emergency." [6,7]

Severe combined immunodeficiency: [9-11]

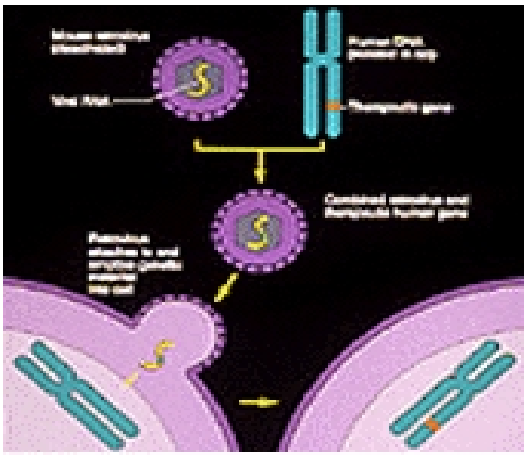

Fig:1: Gene therapy in treatment of SCID

Severe combined immunodeficiency (SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infection by viruses, bacteria and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients. All forms of SCID are inherited, with as many as half of SCID cases linked to the X chromosome, passed on by the mother. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene which produces the common gamma chain subunit, a component of several IL receptors. IL2RG activates an important signaling molecule, JAK3. A mutation in JAK3, located on chromosome 19, can also result in SCID. Defective IL receptors and IL receptor pathways prevent the proper development of T-lymphocytes that play a key role in identifying invading agents as well as activating and regulating other cells of the immune system. In another form of SCID, there is a lack of the enzyme adenosine deaminase (ADA), coded for by a gene on chromosome 20. This means that the substrates for this enzyme accumulate in cells. Immature lymphoid cells of the immune system are particularly sensitive to the toxic effects of these unused substrates, so fail to reach maturity. As a result, the immune system of the afflicted individual is severely compromised or completely lacking. Some of the most promising developments in the search for new therapies for SCID center on 'SCID mice', which can be bred deficient in various genes including ADA, JAK3, and IL2RG. It is now possible to reconstitute the impaired mouse immune system by using human components, so these animals provide a very useful model for studying both normal and pathological immune systems in biomedical research.

SCID is actually a group of inherited disorders that cause severe abnormalities of the immune system. These disorders lead to reduced or malfunctioning T- and B-lymphocytes, the specialized white blood cells made in the bone marrow to fight infection. When the immune system doesn't function properly, it can be difficult or impossible for it to battle viruses, bacteria, and fungi that cause infections. SCID is called "combined" immunodeficiency because it affects the function of two kinds of infection-fighting cells where other immune system diseases involve only one. There are several forms of SCID. The most common type is caused by a problem in a gene found on the X chromosome and affects only males. Females may be carriers of the condition, but because they also inherit a normal X chromosome, their immune systems usually can fight infections normally. Males, on the other hand, only have one X chromosome. Another form is caused by a deficiency of the enzyme adenosine deaminase (ADA). Other cases of SCID are caused by a variety of other genetic defects. [12-14]

Type of SCID:

1 .X-linked serve combined immunodeficiency (X-SCID) 15

2. Adenosine deaminase [16-18]

Adenosine deaminase (also known as ADA) is an enzyme (EC 3.5.4.4) involved in purine metabolism. It is needed for the breakdown of adenosine from food and for the turnover of nucleic acids in tissues.

Reactions: ADA irreversibly deaminates adenosine, converting it to the related nucleoside inosine by the removal of an amino group. Inosine can then be deribosylated (removed from ribose) by another enzyme called purine nucleoside phosphorylase (PNP), converting it to hypoxanthine.

Pathology: Some mutations in the gene for adenosine deaminase cause it to be not expressed. The resulting deficiency is one cause of severe combined immunodeficiency (SCID). Conversely, mutations causing this enzyme to be overexpressed are one cause of hemolytic anemia. There is some evidence that a different allele (ADA2) may lead to autism.

Pathophysiology: When defects occur in the recombination process certain types of severe combined immunodeficiency (SCID) conditions occur, where T and B cells are defective. NK cells are left intact, as NK receptors do not undergo V (D) J recombination. Severe combined immunodeficiency (SCID) can be caused by a variety of distinct genetic defects that interfere with lymphocyte development and function. These defects lead to loss of function of both B and T cells. A defect that affects early lymphocyte development, such as progenitor cells, can lead to an inability to produce both B cells and T cells. Also, a defect of T cells alone can lead to combined immune defects because B cells are dependent on T-cell help for a response to antigen and immunoglobulin class-switching. Although novel causes of SCID continued to be revealed, the pathogenesis can be grouped into mechanisms that are related to lymphocyte development and function. A defect in lymphoid stem cell development can lead to profound deficiency of both B cells and T cells, such as reticular digenesis. An early block may occur within the T-cell differentiation pathway. The most common form, occurring in 40-60% of patients with SCID, is the X-linked form, SCID-X1, which arises from defects in the common g chain of interleukin receptors. This molecular defect results in absent T- and natural killer (NK)–cell maturation, although recent evidence suggests that the g chain is also involved in B-cell development. The g chain is a member of the hematopoietic cytokine receptor family. Interleukin 2Ra (IL-2Ra) and interleukin 2Rb (IL-2Rb), in combination with the g chain, recruits interleukin 2 (IL-2), resulting in signal transduction by means of activation of its tyrosine kinase Janus kinase 3 (JAK3). Phosphorylation of signal transducers and activators of transcription 5 (STAT-5) proceeds, enabling its translocation to the nucleus for transcription of genes involved in cell division. Mutation of JAK3 results in the absence of T- and NK-cell function as in SCID-X1. In addition, the g chain is a member of the interleukin 4 (IL-4), interleukin 7 (IL-7), interleukin 9 (IL-9), interleukin 15 (IL-15) and interleukin 21 (IL-21) receptors, which also function to increase cytokine binding affinity and signal transduction.[4,5] In addition, defects in signaling molecules that associate with the T-cell receptor can lead to SCID; examples include mutations in the *Lck* and *Zap70* genes. Other cytokine receptor–associated genes include *JAK1* and *JAK3,* which, when defective, can lead to SCID. Defects in the CD45 molecule, the common leukocyte antigen that functions as a protein phosphatase, can lead to SCID. CD45 is essential in regulating the transmission of cell surface signals in B cells and T cells. Defects in the expression of the major histocompatibility complex (MHC) lead to bare lymphocyte syndrome, which then results in an inability of the T cells to function. Patients with this condition can have defects in the regulatory region of the MHC class II gene or a defect in a transcription regulator, CTIIA, which is responsible for controlling the expression of MHC class II genes. Abnormal purine metabolism may be involved. Adenosine deaminase (ADA) deficiency accounts for 20% of all SCID cases. The enzyme deficiency results in the accumulation of intermediates, such as adenosine diphosphate, guanosine triphosphate, and deoxyadenosine triphosphate (dATP), which results in lymphocyte toxicity, particularly with immature thymic lymphocytes. Purine nucleoside

phosphorylase (PNP) deficiency is mechanistically similar to ADA deficiency in that the accumulation of deoxyguanosine triphosphate (d GTP) exerts a lymphotoxic effect. In both conditions, T-cell function is most severely affected. Abnormal recombination of genes may occur. Both B-cell maturation and T-cell maturation involve a process of recombination in which various combinations of variable, diversity, and joining (VDJ) genes are assembled to create unique and specific antigen receptors. Two recombination activating genes, recombinase activating gene 1 (*RAG1*) and recombinase activating gene 2 (*RAG2*), which mediate initial DNA double-strand breaking at specific sequences, enable subsequent joining of the various gene segments. Both *RAG1* and *RAG2* mutations result in a T-B-NK+ SCID phenotype and Omenn syndrome, in which residual VDJ recombination activity occurs. The gene *DNA-PK* is a DNA-dependent serine-threonine protein kinase that is required for correct recombination. Mutations in this gene are autosomal recessive and can also lead to combined deficiency. DNA from the cells of these patients is associated with an increased radio sensitivity. The *ARTEMIS* gene, located on chromosome 10, encodes a product that plays a role in VDJ recombination and is associated with SCID that develops from an early block in B- and T-cell development. Reticular dysgenesis is a rare form of SCID that arises from the lack of appropriate stem cell development. Patients with this disease have agranulocytosis in addition to a lack of both B cells and T cells in the adaptive immune system. [19-21]

Microscopic Lesions: There is a generalized lymphopenia, rudimentary thymic medulla without a cortex, lymph nodes without follicles (Fig. 1) and a small spleen lacking white pulp. Lymphoid aggregates in the lung and gastrointestinal tract are rudimentary, consisting of reticuloendothelial cells (Fig. 2; Custer, et al., 1985). Figure 1 Lymph node of a +/? control has numerous, prominent follicles with germinal centers (A,B) while the *SCID/SCID* littermate has only a small, rudimentary lymph node consisting of reticuloendothelial cells (C,D). [22]

Immunologic and Biochemical Lesions: Severe combined immunodeficiency (*SCID*) mice have been found to lack functional T and B cells as well as Thy-1^+ dendritic epidermal cells, but they exhibit normal differentiation and function of myeloid cells, antigen presenting cells, and natural killer cells (Nixon-Fulton, et al., 1987; Shultz, 1991; Dorshkind, et al., 1984; 1985; Czitrom, et al., 1985). This mutation appears to cause an abnormal recombinase system for the assemblage of antigen receptor genes in developing lymphocytes (Review:Shultz, 1991). [23-25]

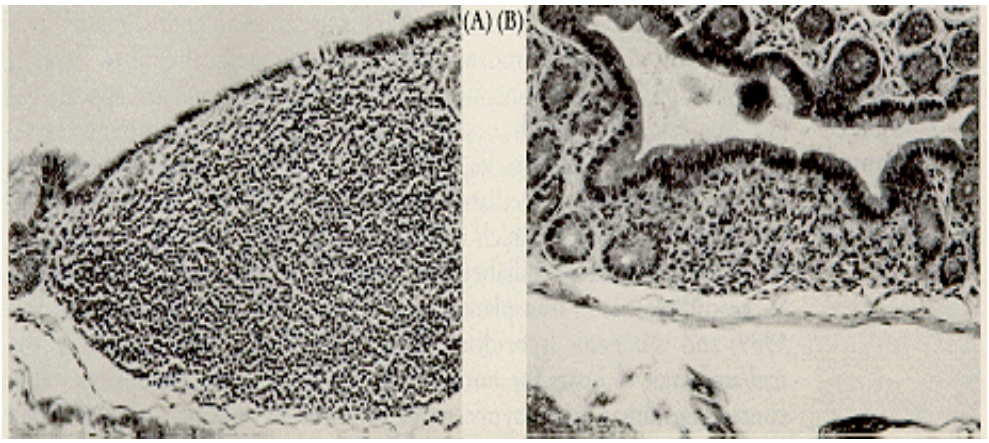

Fig:2: Immunologic and Biochemical Lesions

Diagnosis

Diagnosis is generally made clinically because most SCID infants suffer recurrent overwhelming infections within 1 year of birth. Some infants are diagnosed after a severe reaction to vaccination. Defective humoral immunity is difficult to detect before age 5 months. Before then, even normal infants have very small amounts of serum immunoglobulin (Ig) M and IgA. [26, 27] Normal IgG levels merely reflect maternal IgG. Confirming diagnosis Severely diminished or absent T-cell number and function, as well as lymph node biopsy showing absence of lymphocytes, can confirm diagnosis of SCID. SCID is diagnosed by the typing of T and B cells in the child's blood. B cells can be detected by immunofluorescence tests for surface markers (unique proteins) on the cells. T cells can be identified in tissue sections (samples) using enzyme-labeled antibodies. [28, 29]

Treatment

1. Treatment aims to restore the immune response and prevent infection. Histocompatible bone marrow transplantation is the only satisfactory treatment available to correct immunodeficiency. Because bone marrow cells must be human leukocyte antigen and mixed leukocyte culture matched, the most common donors are histocompatible siblings. However, because bone marrow transplant can produce a potentially fatal graft-versus-host (GVH) reaction, newer methods of bone marrow transplant that eliminate GVH reaction (such as lectin separation and the use of monoclonal antibodies) are being evaluated. Fetal thymus and liver transplants have achieved limited success. Immune globulin administration may also play a role in treatment. Some SCID infants have received long-term protection by being isolated in a completely sterile environment. However, this approach isn't effective if the infant already has had recurring infections. Gene therapy is being used to treat ADA deficiency. [30, 31]

2. Patients with SCID can be treated with antibiotics and immune serum to protect them from infections, but these treatments cannot cure the disorder. Bone marrow transplants are currently regarded as one of the few effective standard treatments for SCID.

Investigational treatments: In 1990, the Food and Drug Administration (FDA) approved PEG-ADA, an orphan drug (not available in US but available elsewhere), for the treatment of SCID. PEG-ADA, which is also called pegademase bovine, works by replacing the ADA deficiency in children with this form of SCID. Children who receive weekly injections of PEG-ADA appear to have normal immune functions restored. Another treatment that is still in the experimental stage is gene therapy. In gene therapy, the children receive periodic infusions of their own T cells corrected with a gene for ADA that has been implant ed in an activated virus. [32-34]

Causes and symptoms: SCID is an inherited disorder. There are two ways in which a developing fetus' immune system can fail to develop normally. In the first type of genetic problem, both B and T cells are defective. In the second type, only the T cells are abnormal, but their defect affects the functioning of the B cells. For the first few months of life, a child with SCID is protected by antibodies in the mother's blood. As early as three months of age, however, the SCID child begins to suffer from mouth infections (thrush), chronic diarrhea, otitis media and pulmonary infections, including pneumocystis pneumonia. The child loses weight, becomes very weak, and eventually dies from an opportunistic infection. [35]

Conclusion

severe combined immunodeficiency (SCID) is a genetic disorder, there is currently no known method of prevention. However, individuals can be tested to determine whether they are carriers of the disease. Preventative treatment against *Pneumocystis jiroveci* pneumonia (previously called *Pneumocystis carinii* pneumonia) is recommended for patients who are older than two months, until their T-cell function returns to normal after a bone marrow transplant. Trimethoprim-Sulfamethoxazole (Bactrim®, Bactrim DS®, Septra®, Septra DS®) is the standard drug of choice. Patients receive intravenous (IV) injections into their bloodstream three times a week. The treatment is also directed towards the gene therapy which may prove fruitful recently in treatment of SCID.

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