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IPOPI

INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

SEVERE COMBINED IMMUNODEFICIENCY

Biotherapies for Life™ CSL Behring

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SEVERE COMBINED IMMUNODEFICIENCY

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SEVERE COMBINED IMMUNODEFICIENCY

Severe Combined Immunodeficiency is an uncommon primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. There are a number of different genetic defects that can cause Severe Combined Immunodeficiency. These defects lead to extreme susceptibility to very serious infections. This condition is generally considered to be the most serious of the primary immunodeficiencies. Fortunately, effective treatments, such as bone marrow transplantation, exist that can cure the disorder and the future holds the promise of gene therapy.

DEFINITION

Severe combined immunodeficiency (SCID, pronounced "skid") is a rare, fatal syndrome of diverse genetic cause in which there is combined absence of T-lymphocyte and B-lymphocyte function (and in many cases also natural killer, or NK lymphocyte function). These defects lead to extreme susceptibility to serious infections. There are currently twelve known genetic causes of SCID. Although they vary with respect to the specific defect that causes the immunodeficiency, some of their laboratory findings and their pattern of inheritance, these all have severe deficiencies in both T cell and B cell function.

Deficiency of the Common Gamma Chain of 6 different Cytokine Receptors

The most common form of SCID, affecting nearly 45% of all cases, is due to a mutation in a gene on the X chromosome that encodes a component (or chain) shared by the T cell growth factor receptor and other growth factor receptors. This component is referred to as $c\gamma$, for common gamma chain. Mutations in this gene result in very low T-ymphocyte and NK-lymphocyte counts, but the B-lymphocyte count is high (a so-called T-, B+, NK- phenotype). Despite the high number of B-lymphocytes, there is no B-lymphocyte function since the T cells are not able to "help" the B cells to function normally. This deficiency

is inherited as an X-linked recessive trait. Only males have this type of SCID, but females may carry the gene and have a 1 in 2 chance (50%) of passing it on to each son.

Adenosine Deaminase Deficiency

Another type of SCID is caused by mutations in a gene that encodes an enzyme called adenosine deaminase (ADA). ADA is essential for the metabolic function of a variety of body cells, but especially T cells. The absence of this enzyme leads to an accumulation of toxic metabolic by-products within lymphocytes that cause the cells to die. ADA deficiency is the second most common cause of SCID, accounting for 15% of cases. Babies with this type of SCID have the lowest total lymphocyte counts of all, and T, B and NK-lymphocyte counts are all very low. This form of SCID is inherited as an autosomal recessive trait. Both boys and girls can be affected.

Deficiency of the Alpha Chain of the IL-7 Receptor

Another form of SCID is due to mutations in a gene on chromosome 5 that encodes another growth factor receptor component, the alpha chain of the IL-7 receptor (IL-7Rα). When T, B and NK cell counts are done, infants with this type have B and NK cells, but no T cells. However, the B cells don't work because of the lack of T cells. IL-7Rα deficiency is the third most common cause of SCID accounting for 11% of SCID cases. It is inherited as an autosomal recessive trait. Both boys and girls can be affected.

Deficiency of Janus Kinase 3

Another type of SCID is caused by a mutation in a gene on chromosome 19 that encodes an enzyme found in lymphocytes called Janus kinase 3 (Jak3). This enzyme is necessary for function of the above-mentioned cγ. Thus, when T, B and NK-lymphocyte counts are done, infants with this type look very similar to those with X-linked SCID, i.e. they are T-, B+, NK-. Since this form of SCID is inherited as an autosomal recessive trait both boys and girls can be affected. Jak3 deficiency accounts for less than 10% of cases of SCID.

Deficiencies of CD3 Chains

Three other forms of SCID are due to mutations in the genes that encode three of the individual protein chains that make up another component of the T cell receptor complex, CD3. These SCID-causing gene mutations result in deficiencies of CD3δ, ε or ζ chains. These deficiencies are also inherited as autosomal recessive traits.

Deficiency of CD45:

Another type of SCID is due to mutations in the gene encoding CD45, a protein found on the surface of all white cells that is necessary for T cell function. This deficiency is also inherited as an autosomal recessive trait.

Other Causes of SCID

Four more types of SCID for which the molecular cause is known are those due to mutations in genes that encode proteins necessary for the development of the immune recognition receptors on T and B-lymphocytes. These are: recombinase activating genes 1 and 2 (RAG1 and RAG2) deficiency (in some instances also known as Ommen's Syndrome), Artemis deficiency and Ligase 4 deficiency. Infants with these types of SCID lack T and B-lymphocytes but have NK lymphocytes, i.e. they have a T- B- NK+ phenotype. These deficiencies are all inherited as autosomal recessive traits.

Finally, there are probably other SCID-causing mutations that have not yet been identified.

Less Severe Combined Immunodeficiencies

There is another group of genetic disorders of the immune system that results in combined immunodeficiencies that usually do not reach the level of clinical severity to qualify as ***severe*** combined immunodeficiency. A list of several of these disorders follows, although there may be additional syndromes that qualify for inclusion as combined immunodeficiency (CID) that are not listed. These disorders include Bare Lymphocyte syndrome (MHC class-II deficiency); purine nucleoside phosphorylase (PNP) deficiency; ZAP70 deficiency; CD25 deficiency; Cartilage-Hair Hypoplasia; and MHC class I deficiency.

CLINICAL PRESENTATION

An excessive number of infections is the most common presenting symptom of infants with SCID. These infections are not usually the same sorts of infections that normal children have, e.g., frequent colds. The infections of the infant with SCID can be much more serious and even life threatening and may include pneumonia, meningitis or bloodstream infections. The widespread use of antibiotics even for minimal infections has changed the pattern of presentation of SCID, so the doctor seeing the infant must have a high index of suspicion in order to detect this condition.

Organisms that cause infections in normal children may cause infections in infants with SCID, or they may be caused by organisms or vaccines which are usually not harmful in children who have normal immunity. Among the most dangerous is an organism called Pneumocystis jiroveci which can cause a rapidly fatal pneumonia (PCP) if not diagnosed and treated promptly. Another very dangerous organism is the chickenpox virus (varicella). Although chickenpox is annoying and causes much discomfort in healthy children, it usually is limited to the skin and mucous membranes and resolves in a matter of days. In the infant with SCID, it can be fatal because it doesn't resolve and can then infect the lung, liver and the brain. Cytomegalovirus (CMV), which nearly all of us carry in our salivary glands, may cause fatal pneumonia in infants with SCID. Other dangerous viruses for SCID infants are the cold sore virus (Herpes simplex), adenovirus, parainfluenza 3, Epstein-Barr virus (EBV or the infectious mononucleosis virus), polioviruses, the measles virus (rubeola) and rotavirus.

Since vaccines that infants receive for chickenpox, measles and rotavirus are live virus vaccines, infants with SCID can contract infections from those viruses through the immunizations. If it is known that someone in the family has had SCID in the past, or currently has SCID, these vaccines should not be given to new babies born into the family until SCID has been ruled out in those babies.

Fungal (yeast) infections may be very difficult to treat. As an example, candida fungal infections of the mouth (thrush), are common in most babies but

usually disappear spontaneously or with simple oral medication. In contrast, for the child with SCID, oral thrush usually persists despite all medication; it may improve but it doesn't go completely away or recurs as soon as the medication is stopped. The diaper area may also be involved. Occasionally, candida pneumonia, abscesses, esophageal infection or even meningitis may develop in SCID infants.

Persistent diarrhea resulting in failure to thrive is a common problem in children with SCID. It may lead to severe weight loss and malnutrition. The diarrhea may be caused by the same bacteria, viruses or parasites which affect normal children. However, in the case of SCID, the organisms are very difficult to get rid of once they become established.

The skin may be involved in children with SCID. The skin may become chronically infected with the same fungus (candida) that infects the mouth and causes thrush. SCID infants may also have a rash that is mistakenly diagnosed as eczema, but is actually caused by a reaction of the mother's T cells (that entered the SCID baby's circulation before birth) against the baby's tissues. This reaction is called graft-versus-host disease (GVHD).

DIAGNOSIS

The diagnosis is usually first suspected in children because of the above clinical features. However, in some instances there has been a previous child with SCID in the family and this positive family history may prompt the diagnosis even before the child develops any symptoms. One of the easiest ways to diagnose this condition is to count the peripheral blood lymphocytes in the child (or those in the cord blood). This is done by two tests; the complete blood count and the manual differential (or a count of the percentage of each different type of white cell in the blood), from which the doctor can calculate the absolute lymphocyte count (or total number of lymphocytes in the blood). There are usually more than 4000 lymphocytes (per cubic millimeter) in normal infant blood in the first year of life, 70% of which are T cells. Since SCID infants have no T cells, they usually have many fewer lymphocytes than this. The average for all types of SCID is 1500 lymphocytes

(per cubic millimeter). If a low lymphocyte count is found, this should be confirmed by repeating the test once more. If the count is still low, then tests that count T cells and measure T cell function should be done promptly to confirm or exclude the diagnosis.

The different types of lymphocytes can be identified with special stains and counted. In this way, the number of total T-lymphocytes, helper T-lymphocytes, killer T-lymphocytes, B-lymphocytes and NK-lymphocytes can be counted. Since there are other conditions that can result in lower than normal numbers of the different types of lymphocytes, the most important tests are those of T cell function. The most definitive test to examine the function of the T-lymphocytes is to place blood lymphocytes in culture tubes, treat them with various stimulants and then, incubate them for several days. Normal T lymphocytes react to these stimulants by undergoing cell division. In contrast, lymphocytes from patients with SCID usually do not react to these stimuli.

Immunoglobulin levels are usually very low in SCID. Most commonly (but not always), all immunoglobulin classes are depressed (i.e. IgG, IgA, IgM and IgE). Since IgG from the mother passes into the baby's blood through the placenta, it will be present in the newborn's and young infant's blood at nearly normal levels. Therefore, the immunoglobulin deficiency may not be recognized for several months until the transferred maternal IgG has been metabolized away.
The diagnosis of SCID can also be made in utero (before the baby is born) if there has been a previously affected infant in the family and if the molecular defect has been identified. If mutational analysis had been completed on the previously affected infant, a diagnosis can be determined for the conceptus (an embryo or fetus with surrounding tissues).This can be done by molecular testing of cells from a chorionic villous sampling (CVS) or from an amniocentesis, where a small amount of fluid (which contains fetal cells) is removed from the uterine cavity. Even if the molecular abnormality has not been fully characterized in the family, there are tests that can rule out certain defects. For example, adenosine deaminase deficiency can be ruled in or out by enzyme analyses on the above-mentioned CVS or amnion cells.

If there is documentation that the form of SCID is inherited as an X-linked recessive trait and the conceptus is a female, she would not be affected.
In a majority of cases, unless termination of the pregnancy is a consideration if the fetus is affected, the diagnosis is best made at birth on cord blood lymphocytes, since there is some risk to the fetus by the above procedures or if blood is collected for lymphocyte studies while he or she is in utero.

Early diagnosis, before the infant has had a chance to develop any infections, is extremely valuable since bone marrow transplants given in the first 3 months of life have a 96% success rate. In fact, screening all newborns to detect SCID soon after birth is technically possible because of recent scientific advances.

INHERITANCE

All types of SCID are probably due to genetic defects. These defects can be inherited from the parents or can be due to new mutations that arise in the affected infant. As already noted, the defect can be inherited either as an X-linked (sex-linked) defect where the gene is inherited from the mother or as one of multiple types of autosomal recessive defects where both parents carry a defective gene. Parents should seek genetic counseling so that they are aware of the risks of future pregnancies.

It should be emphasized that there is no right or wrong decision about having more children. The decision must be made in light of the special factors involved in the family structure; the basic philosophy of the parents; their religious beliefs and background; their perception of the impact of the illness upon their lives; and the lives of all the members of the family. There are countless factors that may be different for each family.

GENERAL TREATMENT

Infants with this life-threatening condition need all the support and love that parents can provide. They may have to tolerate repeated hospitalizations which, in turn, may be associated with painful procedures. Parents need to call upon all of their inner resources to learn to handle the anxiety and stress of this devastating problem. They must have well-defined and useful coping

mechanisms and support groups. The demands on the time and energies of the parents caring for a patient with SCID can be overwhelming. If there are siblings, parents must remember that they need to share their love and care with them. Parents also need to spend energy in maintaining their own relationship with each other. If the stress of the child's illness and treatment destroys the family structure, a successful therapeutic outcome for the patient is a hollow victory indeed.

The infant with SCID needs to be isolated from children outside the family, especially from young children. If there are siblings who attend daycare, Sunday school, kindergarten or grade school, the possibility of bringing chickenpox into the home represents the greatest danger. Fortunately, this threat is being diminished by the widespread use of the chickenpox vaccine (Varivax). Nevertheless, the parents need to alert the school authorities as to this danger, so that they can be notified if and when chickenpox is in the school. If the siblings have been vaccinated or have had chickenpox, there is no danger. If the siblings have a close exposure and they have not been vaccinated nor had chickenpox themselves, they should live in another house during the incubation period (11 to 21 days). Examples of close contacts for the sibling would be sitting at the same reading table, eating together or playing with a child who breaks out in the "pox" anytime within 72 hours of that exposure. If the sibling breaks out with "pox" at home and exposes the patient, the patient should receive varicella immunoglobulin (VZIG) or immunoglobulin replacement therapy immediately. If, despite this, the SCID infant breaks out with "pox", he or she should be given intravenous acyclovir in the hospital for 5-7 days. Children who have been vaccinated with live polio vaccine may excrete live virus which could be dangerous to the SCID infant. Therefore, children who come in contact with the patient (such as siblings) should receive the killed polio vaccine.

Usually the infant with SCID should not be taken to public places (day care nurseries, church nurseries, doctors' offices, etc.) where they are likely to be exposed to other young children who could be harboring infectious agents. Contact with relatives should also be limited, especially those with young children. Neither elaborate isolation procedures nor the wearing of masks

or gowns by the parents is necessary at home. Frequent hand-washing is essential, however.
Although no special diets are helpful, nutrition is nevertheless very important. In some instances, the child with SCID cannot absorb food normally, which in turn can lead to poor nutrition. As a result, in some instances the child may need continuous intravenous feedings to maintain normal nutrition. Sick children generally have poor appetites, so maintaining good nutrition may not be possible in the usual fashion.

Death from infection with Pneumocystis jiroveci, a widespread organism which rarely causes infection in normal individuals, but causes pneumonia in SCID patients, used to be a common occurrence in this syndrome. Pneumonia from this organism can be prevented by prophylactic treatment with trimethoprim-sulfamethoxazole. All infants with SCID should receive this preventive treatment until their T cell defect has been corrected.

LIVE VIRUS VACCINES AND NON-IRRADIATED BLOOD OR PLATELET TRANSFUSIONS ARE DANGEROUS.

If you or your doctor suspect that your child has a serious immunodeficiency, you should not allow rotavirus, chickenpox, mumps, measles, ***live*** virus polio or BCG vaccinations to be given to your child until their immune status has been evaluated. As mentioned above, the patient's siblings should not receive live poliovirus vaccine or the new rotavirus vaccine. If viruses in the other live virus vaccines are given to the patient's siblings, they are not likely to be shed or transmitted from the sibling to the patient. The exception to this could be the chickenpox vaccine if the sibling develops a rash with blisters.

If your SCID infant needs to have a blood or platelet transfusion, your infant should always get irradiated (CMV-negative, leukocyte-depleted) blood or platelets. This precaution is necessary in order to prevent fatal GVHD from T cells in blood products and to prevent your infant contracting an infection with CMV.

SPECIFIC THERAPY

Immunoglobulin (IVIG) replacement therapy should be given to SCID infants who are more than 3 months of age and/or who have already had infections. Although immunoglobulin therapy will not restore the function of the deficient T-cells, it does replace the missing antibodies resulting from the B-cell defect and is, therefore, of some benefit.

For patients with SCID due to ADA deficiency, replacement therapy with a modified form of the enzyme (from a cow, called PEG-ADA) has been used with some success. The immune reconstitution effected by PEG-ADA is not a permanent cure and requires 2 subcutaneous injections weekly for the rest of the child's life. PEG-ADA treatment is not recommended if the patient has an HLA-matched sibling available as a donor for a marrow transplant.

The most successful therapy for SCID is immune reconstitution by bone marrow transplantation. Bone marrow transplantation for SCID is best performed at medical centers that have had experience with SCID and its optimal treatment and where there are pediatric immunologists overseeing the transplant. In a bone marrow transplant, bone marrow cells from a normal donor are given to the immunodeficient patient to replace the defective lymphocytes of the patient's immune system with the normal cells of the donor's immune system. The goal of transplantation in SCID is to correct the immune dysfunction. This contrasts with transplantation in cancer patients, where the goal is to eradicate the cancer cells and drugs suppressing the immune system are used heavily in that type of transplant.

The ideal donor for a SCID infant is a perfectly HLA-type matched normal brother or sister. Lacking that, techniques have been developed over the past three decades that permit good success with half-matched related donors (such as a mother or a father). Pre-transplant chemotherapy is usually not necessary. Several hundred marrow transplants have been performed in SCID infants over the past 30 years, with an overall survival rate of 60-70%. However, the outcomes are better if the donor is a matched sibling (>85% success rate)and if the transplant can be performed soon after birth or less than 3.5 months of life (>96% survival even if only half-matched). HLA-

matched bone marrow or cord blood transplantation from unrelated donors has also be used successfully to treat SCID.
There does not appear to be any advantage to in utero marrow stem cell transplantation over transplantaion performed immediately after birth. Moreover, the mother would probably not be able to be used as the donor since anesthesia would cause some risk to the fetus, the procedures carry risk to both mother and fetus, and there would be no way to detect GVHD.
Finally, another type of treatment that has been explored over the past two decades is gene therapy. There have been successful cases of gene therapy in both X-linked and ADA-deficient SCID. However, research in this area is still being conducted to make this treatment safer. One cannot perform gene therapy unless the abnormal gene is known, hence the importance of making a molecular diagnosis.

EXPECTATIONS

Severe combined immunodeficiency syndrome is generally considered to be the most serious of the primary immunodeficiencies. Without a successful bone marrow transplant or gene therapy, the patient is at constant risk for a severe or fatal infection. With a successful bone marrow transplant, the patient's own defective immune system is replaced with a normal immune system, and normal T-lymphocyte function is restored. The first bone marrow transplantation for SCID was performed in 1968. That patient is alive and well today!

NOTES