Severe Combined Immune Deficiency and Combined Immune Deficiency

Chapter 9

Severe Combined Immune Deficiency (SCID, pronounced "skid") is a potentially fatal primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. There are at least 13 different genetic defects that can cause SCID. 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 stem cell transplantation, exist that can cure the disorder. The future holds the promise of gene therapy for several more types of SCID.

Definition of Severe Combined Immune Deficiency

SCID is a rare, potentially fatal syndrome of diverse genetic causes in which there is combined absence of T-lymphocyte and B-lymphocyte function (and in many cases also natural killer, or NK, lymphocyte function). The different genetic causes of SCID vary with respect to laboratory findings and patterns of inheritance.

Deficiency of the Common Gamma Chain of the T-Cell Receptor (X-SCID)

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 γc, for common gamma chain. Mutations in this gene result in very low T-lymphocyte 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 B-cells have abnormal receptors for growth factors on their cell surfaces. *(See chapter titled "The Immune System and Primary Immunodeficiency Diseases.")*

This deficiency is inherited as an X-linked recessive trait. *(See chapter titled "Inheritance.")* 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 as well as a 1 in 2 chance of passing the carrier state on to each daughter.

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. *(See chapter titled "Inheritance.")* Both boys and girls can be affected. Lack of the ADA enzyme also leads to neurological problems such as cognitive impairment, hearing and visual impairment, low muscle tone and movement disorders. The neurological problems are not fully curable by bone marrow transplantation.

Deficiency of the Alpha Chain of the IL-7 Receptor

Another form of SCID is due to mutations in a gene 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 do not work because of the lack of T-cells. IL-7Rα deficiency is

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the third most common cause of SCID accounting for 11% of SCID cases. It is inherited as an autosomal recessive trait. *(See chapter titled "Inheritance.")* Both boys and girls can be affected.

Deficiency of Janus Kinase 3

Another type of SCID is caused by a mutation in a gene that encodes an enzyme found in lymphocytes called Janus kinase 3 (Jak3). This enzyme is necessary for function of the above-mentioned γc. Thus, when T, B and NK-lymphocyte counts are done, infants with this type look very similar to those with X-linked SCID, they are T-, B+, NK-. Since this form of SCID is inherited as an autosomal recessive trait both boys and girls can be affected. *(See chapter titled "Inheritance.")* 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 a group of molecules on the surface of T-lymphocytes, 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

Five 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 mutations in these genes also cause Omenn's Syndrome), Artemis deficiency, Cernunnos deficiency, and Ligase 4 deficiency. Infants with these types of SCID lack T- and B-lymphocytes but have NK-lymphocytes, that is they have a T-B-NK+ phenotype. These deficiencies are all inherited as autosomal recessive traits. *(See chapter titled "Inheritance.")*

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

Less Severe Combined Immunodeficiencies

There is another group of rare genetic disorders of the immune system that results in combined immunodeficiencies that usually do not reach the level of clinical severity that would qualify them as severe combined immunodeficiency. Unfortunately, this distinction and thus the prognosis is not always easy to determine at the level of the individual child. This becomes important when considering the relative potential risks vs. the potential benefits of a particular treatment strategy. Fortunately, the success rate of stem cell transplantation, particularly for patients without an HLA-matched sibling donor, has improved substantially over the past few years so that the risk of this treatment has become much more acceptable for less severely affected individuals.

A list of several of these disorders follows, although there may be additional syndromes that qualify for

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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; Coronin 1A deficiency and MHC class I deficiency. Sometimes a child with clinical CID is found to have a mutation in a gene (listed previously under Other Causes of SCID) that would be expected to result in SCID, but does not have the typically severe disease as anticipated. This situation is often called "leaky" SCID.

Clinical Presentation of Severe Combined Immune Deficiency

Severe infection is the most common presenting symptom of patients with SCID. These infections are not usually the same infections that normal children have. The infections of the patient 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 patient must have a high index of suspicion in order to detect this condition.

Children with SCID may develop infections 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 dangerous organism is the chicken pox virus (varicella). Although chicken pox is annoying and causes much discomfort in healthy children, its effects are usually limited to the skin and mucous membranes and the disease resolves in a matter of days. In the patient with SCID, chicken pox can be fatal because it does not resolve and can progress to cause infection in the lungs, liver and brain. Cytomegalovirus (CMV), which nearly all people carry in their salivary glands, may cause fatal pneumonia in patients with SCID.

Other dangerous viruses for patients with SCID are the cold sore virus (Herpes simplex), adenovirus, parainfluenza 3, Epstein-Barr virus (EBV, the infectious mononucleosis virus), polioviruses, measles virus (rubeola) and rotavirus.

Since vaccines for chicken pox, measles, mumps, rubella and rotavirus are live virus vaccines, children with SCID can contract infections from those vaccine viruses if they receive these 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 it has been determined that the new infant does not have SCID. This is especially a problem with the rotavirus vaccine, which is routinely given when babies are 6-8 weeks old. The baby with SCID may not have been diagnosed by this time unless the disease has been discovered in the infant's newborn screening. Note that newborn screening for SCID is not yet universal in the United States although the number of states that screen is increasing each year. *(See chapter titled "Newborn Screening.")*

Fungal (yeast) infections in patients with SCID 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, in the child with SCID, oral thrush does not spontaneously resolve. When antifungal medicines are given it may improve, but it does not go completely away and usually recurs as soon as the medication is stopped. The diaper area may also

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be an area where candidal infections can occur. Occasionally, candida pneumonia, abscesses, esophageal infection or even meningitis may develop in patients with SCID.

Persistent diarrhea, resulting in growth failure or malabsorption, is a common problem in children with SCID. The diarrhea may be caused by the same bacteria, viruses or parasites, which affect normal children. However, in the case of patients with SCID, the organisms are difficult to get rid of once established. Often, the intestines in patients with SCID function poorly even in the absence of infection.

The skin may also be involved in children with SCID. The skin may become chronically infected with the same fungus (candida) that causes thrush. Patients with SCID 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). Sometimes a small number of T-cells develop in the infant and attack the GI tract (causing diarrhea) and the skin causing a similar rash. This is called Omenn's syndrome.

Diagnosis of Severe Combined Immune Deficiency

The diagnosis of SCID is usually first suspected in children because of the clinical features discussed previously. However, in some instances, there has been a previous child with SCID in the family, and this positive family history may prompt diagnostic screening for SCID before the child develops any symptoms. In some states, screening for SCID is done on every newborn via routine newborn screening. *(See chapter titled "Newborn Screening.")*

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 healthcare provider can calculate the absolute lymphocyte count (or total number of lymphocytes in the blood). There are usually more than 4,000 lymphocytes (per cubic millimeter) in normal infant blood in the first few months of life, 70% of which are T-cells. Since infants with SCID have no T-cells, they usually have many fewer lymphocytes than this.

The average lymphocyte count for patients with all types of SCID is 1,500 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 and counted. In this way, the number of total T-lymphocytes (including new T-cells that have markers indicating they are made in the baby's thymus), 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

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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 (IgG, IgA, IgM and IgE). Since IgG from the mother passes into the baby's blood through the placenta, it is often present in the newborn's and young infant's blood at nearly normal levels. Therefore, IgG deficiency may not be present in babies with SCID until the transferred maternal IgG is metabolized away. This may take a few months.

The diagnosis of SCID can also be made before the baby is born if there has been a previously affected infant in the family and if the gene defect has been identified. If genetic analysis had been completed on the previously affected infant, a diagnosis can be determined during subsequent pregnancies. This can be done by molecular testing of cells from a chorionic villous sampling (CVS) or from an amniocentesis, where a small amount of amniotic 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 fetus 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 the baby 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 three months of life have a 94% success rate. In fact, screening newborns to detect SCID soon after birth has been made possible because of recent scientific advances. Approximately half of the babies born in the U.S. are now being screened for SCID. If routine screening were extended to infants born in all states, nearly every infant with SCID could be diagnosed within days of birth. The search for a donor could then begin, and most of these babies that do not require "conditioning" should be able to undergo stem cell transplantation or gene therapy within the three month window of time after birth that has the highest chance for a successful outcome.

Inheritance of Severe Combined Immune Deficiency

All types of SCID are 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. *(See chapter on "Inheritance.")*

Parents of children with SCID should seek genetic counseling so that they are aware of the risks of future pregnancies and can make informed decisions about childbearing.

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 of Severe Combined Immune Deficiency

Children with this life-threatening condition need all the support and love that parents can provide. 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. In addition to medical care, patients and families will require psychosocial support and care.

Until definitive treatment such as stem cell transplantation, the infant with SCID needs to be isolated from children outside the family, especially from young children. If there are siblings who attend daycare, religious school, kindergarten or grade school, the possibility of bringing infectious illnesses into the home represents the greatest danger.

Nevertheless, the parents need to alert the school authorities as to this danger, so that they can be notified, particularly 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 (11-21 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 or immunoglobulin replacement therapy immediately. If, despite this, the infant with SCID breaks out with pox, the infant should be given intravenous acyclovir in the hospital for 5-7 days.

Usually the child 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. *(See chapter titled "General Care.")*

Death from infection with *Pneumocystis jiroveci*, a widespread organism which rarely causes infection in normal individuals, but causes pneumonia in patients with SCID, is 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, chicken pox, mumps, rubella, 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 the new rotavirus vaccine. There is usually not a problem if the patients' siblings receive the other live viral vaccines. The exception to this could be the chickenpox vaccine. If the sibling develops a rash with blisters, chicken pox could be transmitted to the child with SCID.

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If your baby with SCID needs to have a blood or platelet transfusion, the product should be irradiated (to kill T-lymphocytes in the blood that could attack the infant), it should test negative for the CMV virus (to prevent possible infection with this virus) and it should be depleted of leukocytes (white blood cells), in order to prevent possible interference with future bone marrow transplant.

Specific Therapy of Severe Combined Immune Deficiency

Immunoglobulin therapy should be given to all infants with SCID. 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 of 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 with PEG-ADA is not as good as with a transplant and is not a permanent cure; it requires two intramuscular injections weekly for the rest of the child's life. Simultaneous PEG-ADA treatment is not recommended if the patient has the opportunity for a stem cell transplant or gene therapy because it may interfere with engraftment of the donor or gene-corrected cells. In this case, the PEG-ADA treatment can be stopped for a few days before those treatments so as to not interfere with their success.

The most successful therapy for SCID is immune reconstitution via stem cell transplantation. Stem cell transplantation for SCID is best performed at medical centers that have had experience with SCID and where there are pediatric immunologists overseeing the transplant. Stem cells for the transplant can be obtained from the bone marrow, peripheral blood or even from cord blood from related or unrelated donors that at least partially match the tissue type of the patient.

The ideal donor for an infant with SCID 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 matched unrelated donors and even half-matched related donors (such as a mother or a father). Several hundred marrow transplants have been performed in infants with SCID 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 at 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 been used successfully to treat SCID, and the immune reconstitution after these types of transplants is often better than when a half-matched parent is a donor.

There does not appear to be any advantage to in utero marrow stem cell transplantation over transplantation performed immediately after birth. For in utero transplantation, the mother would probably not be able to be used as the donor since anesthesia required for the bone marrow harvesting procedure would cause some risk to the fetus. In addition to potential risk for the mother and baby, there is no way to detect GVHD in the infant who has undergone an in utero transplant.

Finally, another type of treatment that has been explored over the past two decades is gene therapy. Gene therapy has been used successfully in patients with both X-linked and ADA SCID and research in this area is ongoing. One cannot perform gene therapy unless the abnormal gene is known, hence the importance of making a molecular diagnosis.

Expectations for Patients with Severe Combined Immune Deficiency

SCID is generally considered to be the most serious of the primary immunodeficiencies. Without a successful stem cell transplant, enzyme replacement therapy or gene therapy, the patient is at constant risk for severe or fatal infections. With a successful transplant, the patient's own defective immune system is replaced with a normal immune system, and normal T-lymphocyte function is restored. Usually, but not always, there is correction of the B-cell defect so the transplanted infant makes their own immune globulin and no longer needs immunoglobulin replacement therapy. The first bone marrow transplantation for SCID was performed in 1968. That patient is alive and well today.