Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 8

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Chapter 8

Classic Severe Combined Immunodeficiency

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Overview

Severe Combined Immunodeficiency (SCID, pronounced "skid") is a serious primary immunodeficiency disease (PI) in which there is combined absence of T lymphocyte and B lymphocyte function. SCID is fatal without a stem cell transplant or corrective gene therapy. 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 one of the most serious forms of PI. Fortunately, effective treatments, such as hematopoietic stem cell transplantation (bone marrow transplant), exist that can treat the disorder, and the future holds the promise of gene therapy for some types.

Definition

SCID is a rare and 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 (NK) lymphocyte function. These defects lead to extreme susceptibility to serious infections. There are currently at least thirteen different genes that, when mutated (changed), cause SCID. Although they vary with respect to the genetic type that causes the immunodeficiency, some of their laboratory findings and their pattern of inheritance, these infants all have an absence of T cells and severe deficiencies in both T cell and B cell function. Recently, leaky or atypical (hypomorphic) SCID was described. In these patients, there are low numbers of T cells with reduced but not absent function. While these patients can be diagnosed in infancy, particularly if SCID newborn screening is available, many are diagnosed later in life.

Deficiency of the Common Gamma Chain of the T Cell Receptor

The most common form of SCID, affecting nearly 30% of all cases, is due to a mutation in a gene on the X chromosome that encodes a component (or chain) called IL2RG shared by the T cell growth factor receptor and other growth factor receptors. This component is referred to as the common gamma chain (γc). Changes in this gene result in very low T lymphocyte and NK lymphocyte numbers, but the B lymphocyte count is normal or high (a so-called T-, B+, NK- phenotype). Despite the presence of B lymphocytes, there is no B lymphocyte function, since the B cells have abnormal receptors for growth factors on their cell surfaces. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) This deficiency is inherited as an X-linked recessive trait. (See Inheritance Chapter.) 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.

Deficiency of Recombinase Activating Gene 1 and 2

With the advent of newborn screening, improved access to genetic testing and recognition of leaky SCID as a clinical entity, there has been increased diagnosis of SCID caused by autosomal recessive mutations in Recombinase Activating Gene 1 and 2 (RAG1 and RAG2). RAG1 and RAG2 are enzymes critical to development of T and B cells, but not NK cells. Babies with this type of SCID will present with low or absent T and B cells, but typically have normal or high NK cells. RAG1 and RAG2 mutations are seen in 40% of those with leaky SCID and about 19% of those with SCID overall. Both boys and girls can be affected.

Adenosine Deaminase Deficiency

Another common 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 about 15% of cases. Babies with this type of SCID can have the lowest total lymphocyte counts of all because T, B, and NK lymphocyte counts are all very low. This form of SCID is inherited as an autosomal recessive trait. (See Inheritance Chapter.) 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). Infants with this type of SCID have B and NK cells, but no T cells. However, the B cells don't work because of the lack of T cells. The B cells and NK cells are intrinsically normal; however, so after T cell reconstitution through transplantation, the function of all cell lineages is normal. IL-7Rα deficiency accounts for less than 10% of SCID cases. It is inherited as an autosomal recessive trait. (See Inheritance Chapter.) 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 common gamma chain (γc). Infants with this type look very similar to those with X-linked SCID, so they are T-, B+, NK-. However, since this form of SCID is inherited as an autosomal recessive trait, both boys and girls can be affected. (See Inheritance Chapter.) 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 CD3Aσ, ε or ζ chains (CD3 delta, epsilon or zeta). These deficiencies are also inherited as autosomal recessive traits and account for less than 5% of individuals with SCID. Both boys and girls can be affected.

Deficiency of Artemis and Other Radiosensitive Forms of SCID

There are a group of other autosomal recessively inherited forms of SCID associated with a lack of T and B cells, but presence of NK cells as well as sensitivity to ionizing radiation. These are due to mutations in genes necessary for DNA repair, including DCLRE1C (encoding the ARTEMIS protein), PRKEDC, NHEJ1, and LIG4. In addition to radio sensitivity and absence of T and B cells, individuals with PRKEDC, NHEJ1, and LIG4 commonly exhibit microcephaly, when the brain does not develop properly resulting in a smaller than normal head. The radiosensitive forms of SCID comprise less than 5% of those with SCID, but they require special consideration in selection of conditioning agents to minimize the risk of late effects.

Other Causes of SCID

There are several other genetic defects associated with autosomal recessive inheritance of SCID, including mutations in the genes that encode CD45, Coronin 1A, and LAT. In a recent study, in about 6-10% of individuals with SCID, there was not an identifiable genetic defect to explain their clinical and laboratory features.

Clinical Presentation

The presentation of SCID is changing rapidly in the U.S. because of the introduction of nationwide newborn screening for SCID using the detection of T cell receptor excision circles (TREC) to identify infants at risk before the onset of infections. This allows for earlier intervention and improved survival. Infants with SCID have no outward physical findings to distinguish them from normal newborns and are usually clinically well until the onset of infections. For those not detected by newborn screening, an excessive number of infections is the most common presenting symptom of infants with typical SCID. These infections are not usually the same sorts of infections that normal children have, such as frequent colds. The infections of the infant with SCID can be much more serious and even life threatening, and they may include pneumonia, severe viral respiratory

infections, meningitis, and/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.

Infants with SCID are susceptible to routine infections seen in healthy babies, but they are also at increased risk for infections caused by organisms or live vaccines which are usually not harmful in children with normal immunity. Among the most dangerous is an organism called *Pneumocystis jiroveci* that can cause a rapidly fatal pneumonia (PJP) 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, chickenpox can be fatal because it doesn't resolve and can then infect the lungs, liver, and 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 infants with SCID are the cold sore virus (Herpes simplex), adenovirus, respiratory syncytial virus, rhinovirus, 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 these immunizations. If the newborn screen for SCID is abnormal or 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. This is especially a problem for the rotavirus vaccine, which is routinely given when babies are 6 to 8 weeks old, and the baby with SCID may not have had any infections by that time, so would not be diagnosed except by newborn screening.

Fungal (yeast) infections may be very difficult to treat. As an example, candida infections of the mouth (thrush) are common in most babies but usually disappear spontaneously or with oral medication. In contrast, for the child with SCID, oral thrush may improve, but it either 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 infants with SCID.

Persistent diarrhea resulting in failure to thrive is a common problem in children with SCID. It can lead to severe weight loss and malnutrition. Diarrhea may be caused by the same bacteria, viruses or parasites that 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. Infants with SCID may also have a rash that is mistakenly diagnosed as eczema, but it 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) due to maternal engraftment.

In individuals with leaky SCID, the clinical presentation may be later in life, if they are not diagnosed due to an abnormal newborn screen. In these individuals, the symptoms can be highly variable signs and symptoms of combined immunodeficiency, with autoimmunity and invasive granulomatous lesions being common as the individual ages.

Diagnosis

The diagnosis of SCID currently and in the future is most likely going to be made after an abnormal newborn screen and while the newborn is clinically well. If newborn screening is not available, SCID is usually first suspected because of the above clinical features. 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 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 for all types of SCID is around 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 with special stains and counted in a technique called flow cytometry. 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 that detect new T cells that have just come out of the baby's thymus and tests of T cell function. The most definitive test to examine the function of the 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 individuals with SCID do not react to these stimuli.

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, IgG deficiency may not be present for several months until the transferred maternal IgG has been metabolized away. However, other immunoglobulin levels (IgA and IgM) are usually very low in SCID. IgE may be elevated, particularly in those with leaky SCID.

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 genetic 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 (that 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.

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 and a half months of life have a 96% success rate prior to the onset of infection. As noted earlier, screening of all newborns to detect SCID soon after birth is possible through the use of TREC based newborn screening. As of 2018, all babies born in the U.S. are now being screened for this condition.

Inheritance

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 (see previous section on the causes SCID) where both parents carry a defective gene. See Inheritance Chapter to more fully understand how autosomal recessive and sex-linked recessive diseases are inherited, the risks for having other children with the disease, and how these patterns of inheritance affect other family members. Parents of children with SCID should seek genetic counseling so that they are aware of the risks for 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 that, 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 someone 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. Family counseling may be necessary to keep relationships together, even with a successful therapeutic outcome for the child with SCID.

The infant with SCID needs to be isolated, especially from young children. If there are siblings who attend daycare, religious school, kindergarten, or grade school, the possibility of bringing infections, particularly those of viral origin, into the home represents the greatest danger. Cytomegalovirus (CMV), is currently the most common viral illness seen in newborns with SCID. This infection can lead to devastating long-term complications such as chronic lung disease and neurologic impairment, particularly blindness. It is for this reason that screening of mothers for serologic positivity to CMV is commonly done prior to allowing the child to breastfeed by many but not all immunology and transplant centers.

The infant with SCID should not be taken to public places, such as group child care settings, stores, 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 General Care Chapter.)

Death from infection with *Pneumocystis jiroveci*, a widespread organism which rarely causes infection in normal individuals but causes pneumonia in individuals with SCID, used to be a common occurrence in this syndrome. This type of infection has become less common with early diagnosis and 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 healthcare provider 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 child's siblings should not receive the rotavirus vaccine. If viruses in the other live virus vaccines are given to the child'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 around the vaccine site.

If your infant with SCID 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 from contracting an infection with CMV.

Specific Therapy

Immunoglobulin (Ig) replacement therapy, given either intravenously or subcutaneously, should be given to infants with SCID when they are diagnosed and continued on an ongoing basis until they have been transplanted and demonstrate recovery of B cell function. Even after transplantation, individuals with SCID who do not develop B cell function will need to continue to receive this indefinitely. Although Ig replacement 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 benefit.

For individuals with SCID due to ADA deficiency, enzyme replacement therapy (elapegademase-lvlr) has been used with some success, particularly as a bridge or temporary treatment before transplant or gene therapy. The immune reconstitution effected by enzyme replacement therapy is not as good as with a transplant or gene therapy and is not a permanent cure; it requires regular injections for the rest of the child’s life.

Currently, the most successful therapy for SCID is immune reconstitution by hematopoietic stem cell transplantation (HSCT). HSCT 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 HSCT, bone marrow cells, peripheral stem cells, or umbilical cord stem cells from a normal healthy donor are given to the individual with SCID to replace the defective lymphocytes of their 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 people with cancer, 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 an infant with SCID is a perfectly HLA-type matched normal brother or sister. Lacking that, techniques have been developed over the past four decades that permit good success with matched unrelated donors or 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 70% at 10 years from HSCT. However, the outcomes are better if the donor is a matched sibling (>94% success rate) and if the transplant can be performed soon after birth or less than three and a half months of life. There is controversy in the field regarding the use of pre-transplant chemotherapy based conditioning, and there does not appear to be an impact on survival with the use of conditioning. However, the use of conditioning does appear to be associated with improved immune function, particularly recovery of B cell function in certain genetic forms of SCID. The decisions regarding donor source and conditioning regimen choices should be discussed with the immunologist and the transplant team at the center to decide the best available treatment option for a particular person with SCID.

There does not appear to be any advantage to *in utero* marrow stem cell transplantation over transplantation performed immediately after birth.

Finally, another type of treatment that has been explored over the past three decades is gene therapy. There have been successful cases of gene therapy in both X-linked and ADA-deficient SCID leading to correction of the immunodeficiency. Unfortunately, in one of the clinical trials for X-linked SCID, there was a high rate of later development of blood born cancers in the treated individuals. This has led to the development of safer ways to administer gene therapy. Gene therapy for ADA SCID has been commercially available in Europe as Strimvelis since 2016. This gene therapy product has demonstrated similar efficacy to non-sibling donor HSCT. There are currently clinical trials underway to explore new gene therapy options for x-linked (IL2RG) and ARTEMIS forms of SCID. One cannot perform gene therapy, however, unless the abnormal gene is known; hence the importance of making a specific molecular diagnosis.

Expectations

SCID is generally considered to be one of the most serious forms of PI. Without a successful HSCT, enzyme replacement therapy, and/or gene therapy, the individual with SCID is at constant risk for a severe or fatal infection. With a successful HSCT, the individual'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!

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