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The Management of SCID

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

ADA	Adenosine deaminase-deficient
CMV	Cytomegalovirus
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
IEI	Inborn errors of immunity
Ig	Immunoglobulin
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
RAG	Recombination activating gene
SCID	Severe combined immunodeficiency

Severe Combined Immunodeficiency (2nd edition)

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SUMMARY

Severe combined immunodeficiency (SCID) comprises a group of rare, inherited disorders that represent one of the most important paediatric emergencies. SCID is usually present at birth and manifests as an absence of T-cells and severe deficiencies of B-cell functions. These defects in the immune system lead to extreme susceptibility to serious infections that can be life-threatening.

Most newborns or infants with SCID have no outward physical findings to distinguish them from normal newborns or infants and they are usually clinically well until the onset of infections. In addition to the usual infections, infants with SCID are at increased risk of infections such as pneumonia, pneumocystosis, meningitis, chickenpox, cytomegalovirus and/or bloodstream infections. Newborn screening can detect SCID prior to the onset of an infection and can be performed on dried blood spot samples that are currently collected in a standardised fashion from all newborn babies almost worldwide.

Initial treatment requires patients to be placed in a clean environment to lower the risk of infection and receive as a minimum antimicrobial (antibiotic, antiviral and/or antifungal) therapies and immunoglobulin replacement therapy while waiting for curative treatment. Curative treatment involving haematopoietic stem cell transplantation (HSCT; previously known as bone marrow transplantation) before the occurrence of infection, given during the first 3 months of life after newborn screening has a 5-year overall survival of 92.5%.[1] Curative therapies may also include gene therapy or thymus transplant. Without successful treatment, patients are at constant risk of a fatal infection and usually eventually die within the first year of life. Hence the importance of early diagnosis.

Jakob, Canada

INTRODUCTION

This booklet explains what SCID is, the manifestations of SCID, how it is diagnosed, treated and managed and the role of newborn screening in achieving an early diagnosis.

Primary immunodeficiencies (PIDs), which are now also referred to as inborn errors of immunity (IEI), are rare diseases that occur when components of the immune system are either not present or not functioning normally. People without the protection of a properly functioning immune system can be prone to infections and/or other complications (e.g., autoimmunity, malignancy).

[1] Thakar MS, et al. Lancet June 20, 2023. doi.org/10.1016/S0140-6736(23)00731-6.

Within PIDs, severe combined immunodeficiency (SCID) comprises a group of rare, life-threatening inherited disorders that represent a paediatric emergency. These disorders are usually present at birth and manifest as an absence of T-cell and B-cell function leading mainly to extreme susceptibility to serious infections. Early diagnosis is essential to enable early intervention before infections occur since it has been demonstrated that the outcome is excellent if the patient receives a haematopoietic stem cell transplantation (HSCT; previously known as bone marrow transplantation) or a gene therapy before the occurrence of infection. HSCT given during the first 3 months of life after newborn screening has a 5-year overall survival of 92.5%.1 Without a successful HSCT or gene therapy, patients are at constant risk of a fatal infection and usually eventually die within the first year of life.

WHAT IS SCID?

SCID is a rare and life-threatening group of diverse genetic disorders defined by an absence of autologous T-cell development (and sometimes an absence of B cells and/or natural killer [NK] cells). This leads to a very profound immunodeficiency. More than twenty genes have been found to be causing SCID. Defects in these genes can cause a variety of abnormalities that affect T-cell development. Infants with typical SCID have an absence of T cells and severe deficiencies in both T-cell and B-cell function. These defects in the immune system lead to extreme susceptibility to serious infections.

Recently, atypical (hypomorphic) SCID has been described in which patients have 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.

As SCID comprises a group of inherited disorders, newborn babies and infants are affected. SCID represents a paediatric diagnostic and therapeutic emergency. Without early diagnosis and treatment these infants might not survive and will succumb to a serious infection, usually within the first year of life. Children born with SCID are partially protected from infection in the first few weeks of life because of the presence of maternal antibodies in their blood; those that are breastfed will continue to receive some antibodies through breast milk (although it can also lead to cytomegalovirus [CMV] infection). Once these antibodies disappear from the child's system, they become prone to severe, life-threatening infections.

INHERITANCE

SCID can be inherited from the parents either as an X-linked (sex-linked) recessive 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. Family history can be helpful in establishing the possible role of genes or chromosomes in a particular PID and in identifying a pattern of inheritance.

For X-linked recessive SCID, the gene causing disease is present on the X chromosome. Males have only one X chromosome that is inherited from their mother so if a male inherits an X chromosome that contains a defective gene, he will develop the disease (**Figure 1**). Females have two X chromosomes, so those that have a defective gene present on one of their X chromosomes are "carriers" for that disorder (**Figure 1**).

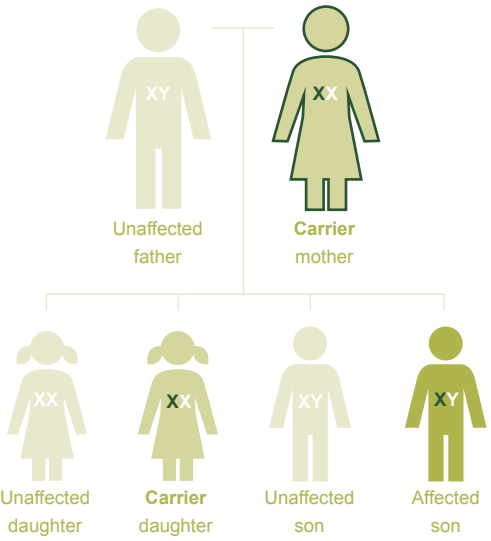

FIGURE 1. Inheritance pattern of X-linked SCID with a carrier mother

As can be seen from Figure 1, women who are carriers of an X-linked disorder, such as X-linked SCID, have a 25% chance with each pregnancy of having a non-carrier daughter, a 25% chance of having a carrier daughter like themselves, a 25% chance of having an unaffected son and a 25% chance of having a son affected with the disease (**Figure 1**).

A man with X-linked SCID will pass the defective gene to all of his daughters, who will be carriers, while none of his sons will be affected as he cannot pass an X-linked gene to his sons because males always pass their Y chromosome to male offspring (**Figure 2**).

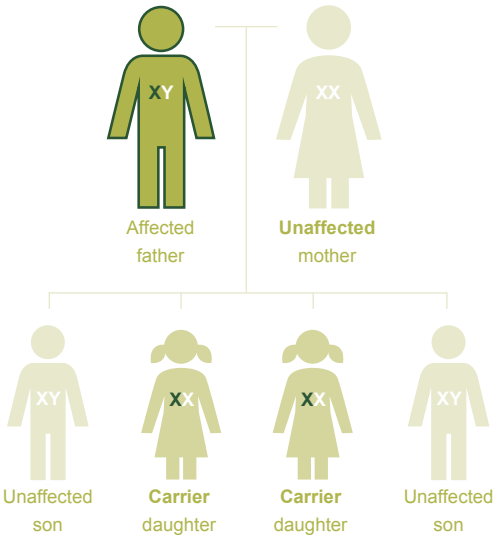

FIGURE 2. Inheritance pattern of X-linked SCID with an affected father

However, occasionally, female carriers can present with symptoms similar to males with X-linked SCID due to a process called X-inactivation. In this situation, as before, mothers who are carriers can pass on the disease to their sons if the sons inherit the affected gene while daughters will become carriers if they inherit the affected gene.

For autosomal recessive SCID, two abnormal copies of the gene, typically one from each parent, must be inherited to cause symptoms of the condition. Usually, parents of the affected child each carry one copy of an abnormal gene and are unaffected themselves because of the normal functioning of the other gene. If both parents are carriers of an abnormal autosomal recessive gene, this leads to a 25% chance (1 in 4) that any offspring, irrespective of gender, will be affected by the disorder. There is a 50% chance (1 in 2) that the offspring will be a carrier (have one abnormal gene), and a 25% (1 in 4) that the baby will not inherit the faulty gene from either parent, and therefore will not be affected by the condition or be able to pass it on to their children (**Figure 3**). The chances remain the same for all future pregnancies, and the outcome of each pregnancy is not affected by previous pregnancies.

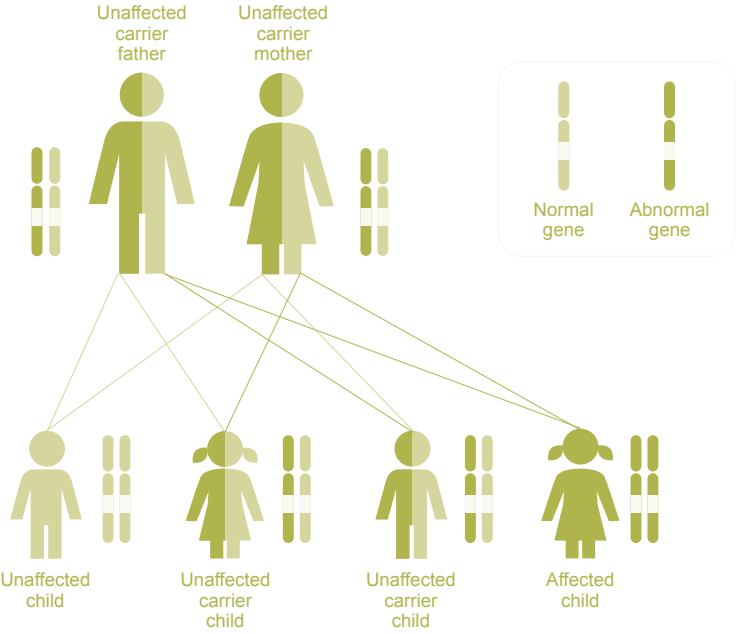

FIGURE 3. Inheritance pattern of autosomal recessive SCID with a carrier mother and a carrier father

SIGNS AND SYMPTOMS – CLINICAL PRESENTATION OF SCID

Importantly, before the occurrence of infection or of failure to thrive, most newborns or infants with SCID have no outward physical findings to distinguish them from normal newborns or infants 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. In addition to the usual infections experienced by normal infants, such as frequent colds, infants with SCID are at increased risk of infections caused by organisms that are not usually harmful in infants with normal immunity but can be life-threatening for them – these can include pneumonia, pneumocystosis, meningitis, chickenpox virus (varicella), cytomegalovirus (CMV), and/or bloodstream infections.

Since most vaccines that infants receive (for example: for tuberculosis [BCG vaccine], chickenpox, measles and rotavirus) are live virus vaccines, infants with SCID can contract infections from those vaccine strains through immunisation. 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 newborn babies born into the family until SCID has been ruled out in those babies.

Fungal (yeast) infections may be very difficult to treat in infants with SCID and the skin may become chronically infected by 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 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.

Persistent diarrhoea resulting in failure to thrive is a common symptom in children with SCID. It can lead to severe weight loss and malnutrition. Diarrhoea may be caused by the same bacteria, viruses or parasites that affect normal children but, in infants with SCID, the organisms are very difficult to get rid of once they become established.

HOW IS SCID DIAGNOSED?

In addition to the clinical presentation described above, a family history of SCID may prompt a diagnosis even before a child develops symptoms. One of the easiest ways to diagnose SCID is to count the peripheral (or cord) blood lymphocytes. Infants usually have around 4000 lymphocytes/mm3 of blood in the first year of life, 70% of which are T cells. As infants with SCID have very low T cell counts, their lymphocyte count can be much lower (on average around 1500 lymphocytes/mm3) in certain types of SCID; however, this is not the case in all types of SCID so it is necessary to perform a lymphocyte subset count (T cells, B cells and NK cells). A low T-cell count should prompt referral to a clinical centre with expertise in managing infants with PID.

In some circumstances, the number of T cells can be normal, either because maternal T cells have proliferated in the baby's system or because some T cells of the patient have developed and proliferated abnormally. More sophisticated tests, such as the detection of maternal T cells and lymphocyte sub-population with enumeration of naïve T cells, can help diagnose SCID in such cases.

Immunoglobulin (Ig) levels are usually very low in patients with SCID but may be near normal levels in the blood of newborns as a result of the presence of IgG from the mother that the infant has received prior to birth through the placenta; this is in contrast to very low/absent IgA and IgM levels.

Newborn screening for SCID is a life-saving tool allowing for a crucial early diagnosis to be made, but is only available in certain countries (see specific section below). Implementation of this screening tool in regions where it is not yet available should be encouraged.

NEWBORN SCREENING FOR SCID

SCID is a paediatric emergency. Without early diagnosis and treatment these infants might not survive and will succumb to a serious infection, usually within the first year of life.

Newborn screening can detect SCID prior to the onset of an infection (in cases without a positive family history of SCID) and can be performed on dried blood spot samples that are currently collected in a standardised fashion from all newborn babies almost worldwide. A delay in the diagnosis of SCID reduces the success of a curative option and impairs survival or quality of immune reconstitution and quality of life because of sequelae. It has been shown that newborn screening is associated with a better outcome after early curative treatment with HSCT.

WHAT TREATMENT IS SUGGESTED FOR SCID

INITIAL TREATMENT

Infants with SCID are unable to fight off bacterial, viral, parasitic or fungal infections as effectively as those with fully functioning immune systems. This is a result of the absence of T cells and, as a consequence of, dysfunctional B cells and NK cells. Patients must be placed in a clean environment to lower the risk of infection and receive antimicrobial (antibiotic and antifungal and/or antiviral) medications and Ig replacement therapy as a minimal mainstay therapy while waiting for curative treatment.

For patients with SCID due to adenosine deaminase (ADA1) deficiency, replacement therapy with a modified form of the enzyme has been used with some success but is not a curative approach.

CURATIVE TREATMENT

Haematopoietic stem cell transplantation

HSCT is a curative therapy for SCID. Haematopoietic stem cells (HSC) from a suitable healthy donor with a good human leucocyte antigen (HLA) match are administered to replace the HSC of the recipient that will ultimately produce normal immune cells (i.e. T cells).

The ideal donor for an infant with SCID and requiring HSCT is a perfect HLA-type matched normal sibling (success rate above 95%). In the absence of an HLA identical sibling, the use of either an HLA-matched unrelated donor (either cord blood or bone marrow) or half-matched related donor (usually one of the parents) are used with a survival rate above 90% if the HSCT is performed before the infant is 3.5 months old and in the absence of infection. This highlights the importance of fast diagnosis.

Gene therapy

A less common but promising treatment option for SCID is gene therapy, which is currently being evaluated and developed in clinical trials. In gene therapy, the aim is to extract a child's defective blood-forming cells, correct the underlying genetic defect (X-linked SCID due to gamma-c mutation, ADA SCID, RAG1 SCID, or ARTEMIS SCID), and put the corrected cells back into the child. The repaired cells provide the child with a working immune system.

LIVING WITH SCID – EXPECTATIONS FOR PATIENTS/CARING FOR INFANTS

CMV can be serious for infants with SCID as it can be transmitted in the breast milk of a breastfeeding mother. Hence, if a child has SCID and the mother wishes to breastfeed, she should be tested for CMV. If the result is positive, it is advised to stop breastfeeding, owing to the risk of transmitting CMV to the baby, and formula milk feeds are recommended. Recently, data from a large single-centre cohort from 1997 to 2016 suggest a 5% rate of breast milk transmission of CMV to infants with severe combined immunodeficiency.[2]

An infant with suspected SCID should be isolated from children outside the family, especially from young children. In addition, older siblings attending daycare or school can bring home infections that might potentially be life-threatening for the infant with SCID, such as chicken pox. An infant with SCID should not be taken to public places and contact with relatives should be limited, especially for those with young children. Home hygiene is essential and although nutrition is important, no special diets have been shown to be helpful.

Once SCID has been diagnosed, patients must be placed in a clean environment to lower the risk of infection and receive antifungal and Ig replacement therapy as a minimal mainstay therapy while waiting for curative treatment.

[2] Kelty WJ, et al. J Allergy Clin Immunol Pract. 2019;7(8):2863-2865.e3. doi: 10.1016/j.jaip.2019.05.041.

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

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