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What is SCID?

SCID is a congenital disorder of the defense system. The term SCID stands for „severe combined immunodeficiency“. „Severe“ refers to the fact that the illness is life-threatening. In SCID, the defense system is so weak that it can barely provide protection from infections.

SCID is a „combined“ immunodeficiency, meaning that various parts of the immune system are affected. Among these is the part of the immune response predominantly necessary for controlling bacterial infections, and the part of the immune response predominantly needed to fight viral or fungal infections.

The essential characteristic in SCID is the absence or the lacking function of lymphocytes, which have crucial tasks in fighting infections. Not all forms of SCID are the same, but all forms result in severe dysfunction of the immune system, and afflicted children urgently need immediate treatment to protect them from infections.

The illness has been known since 1950. Before the introduction of modern treatment methods such as bone marrow transplantation, most children with SCID died from infections already within their first year of life. Between then and now, medicine has taken a big step forward: Reducing the risk of life-threatening infections has been successful, and in the majority of cases, even curative treatment of SCID is possible.

What causes SCID?

Severe combined immunodeficiency is a congenital disease and is caused by an error in the child’s genetic code (DNA). This means that the illness is, in most cases, passed from the parents to the child.

Each person carries a very large quantity of genetic information with which his or her partner is then passed down in equal parts to their descendants. Except for those DNA sections that determine the gender as well, every piece of genetic information is present
in duplicate. At the same time, every person has some genes in his or her genetic code that contain small changes. Usually, these changes do not lead to health consequences, since they can be compensated for by the healthy second gene.

Each gene in our genetic code contains the construction plan for a protein that is responsible for certain functions in our body. Some genes are necessary for the normal development of the immune system. Here, a defect can lead to the protein being formed with defects or not at all, which then leads to dysfunctional development of the immune system.

In SCID, above all, the development of so-called T-cells is disrupted. T-cells are crucial for fighting viral and fungal infections. Moreover, they help the B-cells to form antibodies and to thus fight bacterial infections. Finally, they also play a role in the control of immune responses. If these key cells of the immune system cannot develop or do not function properly, the consequences are a disruption of all these processes and a „combined“ immunodeficiency.

There are at least 20 different genes controlling the development and activation of T-cells. Therefore, there is also a corresponding number of SCID subtypes. They all share the dysfunction of T-cells and the resulting susceptibility to all kinds of infectious diseases. The individual subtypes of SCID are named and classified according to the underlying gene defects.

If the genetic code contains an error in the construction plan for a protein that is responsible for the body’s defense system, then also the defensive cells formed (here, the red T-lymphocytes) will contain errors and cannot provide sufficient protection from viruses, fungi and bacteria.
What does SCID mean for my child?

In most cases, the children are born „healthy“ at first and develop completely normally during the first weeks of life. This is because the illness only shows after contact with pathogens, and during the first months of life, the children are protected at least in part by maternal antibodies, which have been passed from the mother to the child through the umbilical cord.

The first problems usually arise between the 3rd and 6th months of life. The maternal antibodies have been used up, and the child’s immune system cannot work properly. This leads to the child becoming susceptible to infections. Compared to other children, your child falls ill more frequently, needs more time to recover, and infections take a more serious course. Repeated and prolonged treatments with antibiotics are frequently necessary. „Normal“ germs, which do not endanger people with a healthy immune system, can lead to severe infections in children with SCID. Compared to other children, your child falls ill more frequently, needs more time to recover, and infections take a more serious course. Repeated and prolonged treatments with antibiotics are frequently necessary. „Normal“ germs, which do not endanger people with a healthy immune system, can lead to severe infections in children with SCID.

As a consequence, the children do not properly gain weight. Many suffer from chronic diarrhea, in part also without detectable infection, which leads to further impairment of thriving. Skin rashes are observed relatively frequently, which are sometimes due to an infection but are sometimes also a sign of a misdirected immune response. Occasionally, skin rash, liver and lung disease are also a consequence of the transmission of maternal blood cells, which respond to the child’s organs. The prenatal transmission of maternal cells is of no consequence in healthy children, since they are destroyed by the child’s immune system. However, these cells may cause severe damage in children with SCID.

The frequently occurring, prolonged and severe infections are life-threatening for SCID patients. Many children die within the first year of life unless steps are taken to replace the defective immune system.
How common is the illness?

SCID is a rare disease. It occurs in approximately 1 of 25,000 newborns.

How is it diagnosed?

As a rule, afflicted children attract attention already during infancy due to constantly recurring infections (especially of the respiratory and intestinal tract), lack of weight gain and nutritional problems. These problems lead to frequent visits to the doctor. Sometimes, the first indication of SCID may be a serious, and often life-threatening infection, which leads directly to hospitalization. These infections can be so severe that a stay in intensive care unit and an intensive therapy may be necessary. Frequently, there is a delay in diagnosis, as the children seem healthy in the first months and as infections and lack of weight gain are common in infants; whereas, severe immune defects are rare. If the suspicion exists, the children must be transferred to a center specializing in immunodeficiencies as soon as possible.

If SCID is suspected, first and foremost a detailed medical history with concomitant evaluation of the family history (e.g., blood relationship or known immunodeficiency in family history) will be collected and a careful physical examination will be performed.

Special attention is paid during the physical examination to the condition of the skin (some patients show skin rashes resembling neurodermatitis), the lungs (bronchitis and pneumonia are common in SCID), liver and spleen (which may be enlarged in SCID) as well as the lymph nodes and tonsils, which may, though to a lesser extent, also be larger than normal. Weight, height and head circumference are measured to determine whether the child has developed appropriately for his or her age.

In addition to the patient history and physical examination, several blood tests are necessary as well. The first laboratory diagnostic is the careful evaluation of the blood count, whereby the number of lymphocytes (a subgroup of white blood cells) is of great importance. A low lymphocyte count is an important indicator of SCID. In addition, the levels of antibodies are measured, which are usually decreased. If
the child was already inoculated, it may further be examined whether the child is able is to form antibodies specific to the vaccines. This is usually not possible for children with SCID. If the lymphocytes are decreased, the different subgroups are determined (T-cells, B-cells and NK-cells), and their function is examined in the test tube. The pattern of dysfunctions in the different cell types then allows for conclusions on the type of SCID. In some cases, immune cells may be present that were transferred from the mother. However, these cells usually cannot contribute much to the immune response and may even harm the child under certain circumstances.

In addition to the blood tests, frequently a skin biopsy (taking a tiny piece of skin as a sample) or the examination of lymph node tissue, intestinal mucosa or bone marrow may be required for more accurate classification of the disease. Using imaging techniques such as X-ray and ultrasound can determine whether the thymus is present. The thymus gland is important for the development of lymphocytes, and it is usually noticeably too small in SCID.

Depending upon the actual situation, further tests such as urine and stool examinations and possibly, even imaging of the lungs (bronchoscopy) are performed in order to detect current infections. Bronchoscopy may be necessary in order to have a closer look at the bronchi with the help of special equipment and to sample secretions, which then can be tested for potentially present germs.

If special examinations are required for your child, you will receive in-depth information and will have enough time to ask questions.

In most cases of SCID, the suspected clinical diagnosis can later be confirmed by a gene test. However, this test usually takes several weeks, meaning that the decision for treatment cannot wait for this result.

SCID is an immunological emergency and requires rapid treatment, which should be performed at a specialized center.
What is done to my child?

First, the child is admitted to the hospital. Here, it is important that your child is protected from environmental infections and this protection is a focus of treatment.

In order to prevent infections, your child is isolated from the other children in a single room. The number of visitors should be limited at first, and a visit to the play room is not possible. Often, this is a new and difficult situation at first. As a rule, however, you are admitted as well and will continue to have the opportunity of feeding your child yourself, as well as caring for and playing with your child. Your child needs you and your family exactly the same way as before.

In order to avoid infections, you will be instructed in the various hygiene procedures (e.g. hand disinfection, gown, and mask). During the inpatient stay, necessary examinations are performed, and treatment is initiated. Likewise, the time is utilized to give you important information about the disease and to answer questions.

Special hygiene rules apply for children with immunodeficiency in general and for bone marrow transplantation (BMT) in particular. Photo: Ritterbusch
What kind of treatment does my child need at the time of diagnosis:

Most children with SCID show similar symptoms at first, regardless of the specific SCID subtype, and therefore, they also receive the same treatment to start with. Usually, your child needs many examinations and therapies, and sometimes supplemental nutrition as well. For this, it is necessary to introduce a central access, i.e. a central venous catheter. During a brief period under anesthesia this catheter is inserted into a large blood vessel and is fastened to the skin surface. This facilitates treatment and protects your child from getting poked and prodded repeatedly for every single blood sample. Likewise, medicines can be administered well over this system.

**Medicines:**
Due to the weak immune system, the child needs preventive administration of certain medicines to fight off infections. This includes medicines that are specifically attuned to certain risks of infection.

Administration of antibiotics helps to prevent bacterial infection, antiviral medications protect against some viruses; even antifungal medications are used as a precaution.

Many of the medicines are available as juices, but sometimes it is also necessary for your child to receive the medications as an infusion or via the central venous catheter. Unfortunately, these medicines are frequently not sufficient in order to stave off infections completely.

**Immunoglobulins:**
Due to the defective defense cells, children with SCID cannot build enough or not the right type of antibodies (immunoglobulins) to be able to fight infections. Therefore, these antibodies must be supplied in form of an infusion. It is also possible to give the antibodies via a vein or (with longer-term treatment) even subcutaneously into the fat tissue under the skin. The antibody therapy will be given starting from the time of diagnosis up to a certain time after bone marrow transplantation (see information leaflet immunoglobulins).

**PEG ADA:**
One specific form of SCID is caused by the absence of the ADA (adenosine deaminase) protein. If this enzyme is missing, a toxic metabolite is formed, which in turn leads to lymphocyte damage. By substituting the missing enzyme with the help of injections (PEG-ADA), this process can be stopped, and the immune system can recover.

As a rule, this treatment is used only
temporarily, since the results are not quite as good as bone marrow transplantation. With other forms of SCID, this enzyme substitution therapy is without effect.

**Blood transfusions:**
It is possible that your child needs a blood transfusion. If your child needs blood, these blood samples are specially treated (irradiated) in order to remove all immune cells and to thus reduce the risk of reactions. Before the infusion, the blood preparations are specially tested for pathogens once more, in order to avoid any risk.

**Bone marrow transplantation:**
Bone marrow transplantation (BMT) is presently the only curative therapy option for children with SCID. The goal of this therapy is to replace the diseased defense system (immune system) with the immune system of a healthy donor. Healthy bone marrow is rich in stem cells, which are cells exhibiting no or only little differentiation and thus, are not yet dedicated to their later function in the organism. Therefore, stem cells have the ability to develop into different cell types, and among other things, into cells of the immune system. If a suitable healthy donor is found, it is possible to transfer healthy bone marrow to the afflicted child by means of an infusion. Bone marrow transplantation is not a transplantation in the way as we know it from other organs, but the stem cells contained in the bone marrow can find their way via the blood into the bone marrow and can then start there to build healthy blood cells.

However, BMT harbors many risks, and complications may occur. Usually, the complications are easy to treat, but some may take a life-threatening course.

Before a therapy is decided on, a team of specialists (immunologists, hematologists) will discuss the exact procedure, risks and benefits with you in detail and will give you enough time to ask questions and to clarify uncertainties.

In order to perform BMT, it is important to find a suitable donor. Therefore, blood samples are taken from parents and siblings (sometimes even from other family members) in order to be able to determine those characteristics that need to match for a transplanta-
If a suitable donor for the afflicted child is found within the family (usually, a healthy sibling), this person is eligible as a donor. If a suitable donor cannot be found within the family, a world-wide search for a suitable donor is arranged via a register, which at present offers a very good chance to find a donor for most patients.

Once a suitable donor is found, therapy preparations for BMT begin. Usually, it is necessary to perform chemotherapy before BMT in order to "downregulate" the child's immune system and thus, reduce the risk of rejection of the transplanted stem cells. If a donor close enough to a perfect match is found within the family, an initial chemotherapy is not always necessary. The hematology team will also discuss the risks and adverse effects of chemotherapy with you in detail.

**Gene therapy:**

Gene therapy is a novel form of treatment, which is currently being tested. Here, stem cells are taken from the sick child, the healthy form of the defective gene is inserted into these isolated stem cells, which are then returned to the child. This treatment has the advantage that the child receives his or her own cells and not those of a stranger. Thus, the risks of rejection or incompatibility are clearly smaller. On the other hand, transferring a new gene into stem cells is a procedure harboring risks of its own. The procedure may lead to the altered cells changing their properties, possibly even turning malignant (triggering cancer). Over 50 patients worldwide have been treated with gene therapy so far. Most treatments were successful, meaning a real alternative to BMT exists in the future, particularly if no suitable donor is found. However, some patients in the early studies developed leukemia. Intense research is currently in progress in order to develop safe procedures for gene transfer.
How is SCID passed on?

Every human possesses two copies of each gene, one from the father and one from the mother. For most hereditary diseases, the manifestation of the disease requires both genes to be defective, given that one healthy gene is usually sufficient for building enough healthy proteins. However, different modes of inheritance may be the cause of the manifestation of SCID.

In the autosomal recessive form of heritable SCID, both parents are clinically healthy carriers of the defective gene. This means that both have a healthy gene aside from the defective one, which is sufficient to protect them from the disease. For the descendants, this results in a 25 percent probability of inheriting the disease. Half of the children, like their parents, become clinically healthy gene carriers and may pass the gene down to their children. One quarter of the children inherits two healthy genes and is completely healthy. Here, the heredity is not linked to sex, i.e. both boys and girls can be affected.

A different mode of inheritance is present in the X-linked, i.e. sex-linked mode of inheritance. Here, the gene in question is located on the X-chromosome determining the gender. In this mode of inheritance, the disease is usually passed down by the mothers. However, they are clinically healthy, since they can make up for the defective X-chromosome with their second, healthy X-chromosome. Sons of affected mothers can now inherit either the defective or the healthy X-chromosome. Because men possess only one X-chromosome, so that a son who inherits the defective X-chromosome is not able to compensate for the defect. This means that there is a 50% chance the sons from a mother with a defective gene will get sick from SCID. All daughters are healthy, but 50% could inherit a defective gene and in turn pass down the disease to their sons. In some cases, the mother of an afflicted son may have two healthy genes; in this case, the genetic defect occurred during the development of the child, and further children of this mother will not be affected.

In any case, the diagnosis of SCID should be followed by genetic examination and counseling of the extended family in order to be able to assess the risk of another case of disease and to provide the appropriate advice.
In the autosomal recessive mode of inheritance, both parents are healthy. The normal gene (Gene An, green) dominates the defective gene (Gene Ad, orange). Each child receives one gene copy from each parent. The descendants inheriting the defective gene from both parents fall ill. Healthy brothers and sisters, who carry a defective gene, can pass this down to their children.

In the X-linked mode of inheritance, the defect is located on the sex chromosome X. Since girls have two X-chromosomes, they do not fall ill, as the healthy chromosome makes up for the defect. Boys fall ill if they inherit the defective gene from the mother.
Are genetic counseling of the families and prenatal diagnostics possible?

Yes. In those cases of SCID in which the genetic defect is identified, it can be examined whether the parents are carriers of the same mutation and whether there is a risk of passing down the disease to further children. Such an analysis and genetic counseling should be offered to all families. With further pregnancies, prenatal diagnostics are possible, in order to see whether the fetus is affected by the gene defect identified in this family or not.

Further support for your child - nutrition

If you want to nurse your child, we are happy to support you and also encourage you to do so. However, it may happen that pathogens will pass into the breast milk. As a rule, this is not a problem for children with a healthy immune system but may pose a danger for children with SCID. Therefore, after SCID has been diagnosed, tests for these pathogens (above all, cytomegalovirus CMV) should be performed first before the breastmilk is fed.

There is the option, if necessary, to pump off the milk and to store it as well. Despite all efforts, however, it is possible that with this nutrition, your child does not get enough calories, and that vitamins and minerals have to be substituted as well. If there are difficulties with food intake, it might make sense to feed your child additionally and temporarily over a feeding tube, in order to ensure a sufficient supply of energy. A feeding tube is a thin tube inserted via the nose into the stomach, with which your child can then be fed. If this form of nutrition is also insufficient or if your child does not tolerate it, TNP nutrition (parenteral nutrition = nutrition through the vein) may become necessary. The composition of TNP food is optimized for your child, and the requirements have been calculated exactly. It contains all essential nutrients and the optimal number of calories.
What does SCID mean to the family?

As any other child, your child needs all of your love, care and attention. Repeated inpatient hospital stays will be necessary, which also means repeated separations from relatives and the rest of the family. Repeated blood tests and further examinations frequently lead to stress, anxiety and feelings of guilt. Many parents reach the limits of their strength and resilience with the illness of the child. During the entire phase of disease, the entire treatment team will be at your side and will try to help you find a wholesome way of dealing with this difficult time.

Brothers and sisters may feel neglected during the time in which the afflicted child requires your undivided attention. Here, it is frequently a good idea to get other family members or close friends involved in the care, so that you can take a “time-out” on occasion, with the peace of mind that the sick child is not alone.

You will also need the time and energy for the relationship with your partner. In such a difficult phase, most partners feel really close, share decisions and help each other with the overwhelming emotions they are confronted with. However, at times it may still become hard to deal with all those different demands. In those times, it may be good to know that there are possibilities for help even here, e.g. with the support of self-help groups or social services. Even the best relationships are put to the test during such a phase; therefore, do not hesitate to ask for support and professional help.

Part of our team consists of psychologists and social workers, who can help you with various questions and problems or may inform you about further possibilities of support.
CCI is an interdisciplinary center for research and treatment at the University Medical Center Freiburg, sponsored by BMBF [Federal Ministry for Education, Science, Research and Technology]. CCI diagnoses and treats patients with immunodeficiency at any age.

CCI closely collaborates with the Arbeitsgemeinschaft Pädiatrische Immunologie (API; Association for Pediatric Immunology), a federal network for the care of children with immunodeficiency (www.kinderimmunologie.de).

Further information on innate immunodeficiencies can be found over the Deutsche Selbsthilfegruppe für angeborene Immundefekte (German self-help group for innate immunodeficiencies, www.dsai.de).

In co-operation with

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