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KLINIKUM** FREIBURG

CID

Combined
Immunodeficiency

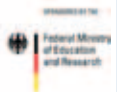
understand

recognise

treat



Center for Chronic
Immunodeficiency





CID

Combined
Immunodeficiency

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Combined Immunodeficiency (CID) - what is that?

Children with combined immunodeficiency (= CID) suffer from rare congenital diseases of the defense system (immune system). In contrast to SCID (severe combined immunodeficiency), however, remaining functions of the immune system are preserved and thus, also a partial protection from pathogens and parasites.

The term „combined“ is used since both the immune cells and the formation of so-called antibodies against pathogens may be affected.

As with the combined immunodeficiencies, both parts of the immune system are impaired, the clinical picture is variable and differs from case to case. „Normal“ germs, which do not endanger people with a healthy immune system, can lead to severe infections in children with CID.

Moreover, infections occur from germs that otherwise only very rarely lead to disease. Thus, pathogens like *Pneumocystis jirovecii*, *Aspergillus*, Cytomegaloviruses or *Cryptosporidia* may lead to serious liver disease, pneumonia and severe diarrhea in children with CID.

Childhood illnesses such as chickenpox, German measles, herpes infections or

otherwise uncomplicated fungal diseases (diaper candidiasis) may turn life-threatening in children with CID.

The immune defect may also manifest itself by lack of immune regulation, directing the defense system against the own body. In this case, autoimmune diseases occur, which are directed predominantly against blood cells, sometimes also against skin, joints, eyes or the thyroid gland. In some patients, lymph nodes, liver or spleen swell. Eczemas, chronic intestinal inflammation, unclear bouts of fever, formation of granulomas (formation of little nodules within the skin or internal organs) can be an expression of impaired control of the immune system. In addition, inflammatory processes and an increased risk of cancer are part of this as well.

Compared to other children, children with combined immunodeficiency fall ill more frequently, infections take a more serious course and the children affected need more time to recover. At the forefront are bacterial infections, especially of the respiratory tract (middle ear infections, infections of the sinuses, the bronchi and the lungs). Diarrhea is common as well. Repeated and prolonged treatments with antibiotics are often necessary.

The formation of antibodies against own blood cells may lead to a significant shortage of blood cells in the body (autoimmune cytopenia). This leads to pallor, headaches and decreased performance due to lack of blood (anemia), impaired bleeding control due to a shortage in blood platelets (thrombopenia) and/ or susceptibility to infections due to a decrease in white blood cells (neutropenia).

Due to its variable genetic causes, CID affects every patient differently. The extent of susceptibility to infections or autoimmune symptoms can differ widely. Also the course of the disease is very different from patient to patient. Symptoms of the disease may start in childhood or even as late as the early adult years.

The term CID is to be distinguished from CVID (common variable immunodeficiency) and from SCID (severe combined immunodeficiency).

In CVID, the lack of antibodies predominates, the immune cells themselves are usually but little impaired. However, many physicians do not use these terms precisely and patients with CID are frequently given a diagnosis of "severe" CVID or CVID with T cell deficiency.

In SCID, the dysfunction of the immune cells is in the foreground. Since cellular functions are also necessary for sufficient antibody formation, SCID is always

accompanied by a secondary lack of antibodies. The course of SCID is so severe that serious infections already occur during infancy, and without bone marrow transplantation, afflicted children die before reaching the second year of life (see patient brochure SCID).

In CID, some functions of the defense system remain and protect the patient at least in a part. Likewise, the disruption of the cellular defense is at the forefront, however, not as severe as in SCID. Antibody formation is also affected to a variable extent. Patients with CID can be relatively healthy and show only later in life (sometimes even only in adult age) symptoms indicating an immunodeficiency.



The variety of symptoms includes eczemas, which may appear in combined immunodeficiency (CID).

Photo: ZKJ Freiburg

How common is the illness?

CID is a rare disease. Taking all subtypes together, combined immunodeficiencies affect approximately 1 of 10,000 persons in Germany.

What are the causes of the disease?

The healthy defense system enables the body to recognize and fight off pathogens.

Cells of the defense system (lymphoid progenitor cells) mature just like the other blood cells in the bone marrow first and then go through different stages in order to develop into functional defense cells of the immune system.

One important stage of cell maturation after the bone marrow is the thymus gland, an organ behind the breastbone. In the thymus, part of the lymphocytes called T-cells after the place of their differentiation, are then „trained“ for their later function in the defense system. In addition to multiplying within the thymus, on the other hand, they also „learn“ to distinguish between the body's own components („self“ antigens) and pathogens („non-self“ antigens). Only when the T-cells have gone through „thymus training“ are they able to take over their specific tasks in the immune system.

When the T-cells leave the thymus, they move through the body via the blood and the lymphatic system. After infection with a pathogen, they become activated and form important inflammation and messenger substances that not only affect the pathogens but also have a regulatory effect on other defense cells on the other hand. At the end of a successful immune response, T-cells enter a resting state again but form a „memory“, i.e. they can react much more quickly and effectively upon a renewed encounter with the same pathogen.

Combined immunodeficiencies are hereditary diseases that primarily lead to disruptions in the development, maturation and activation of T-cells. The term combined immunodeficiency summarizes a multitude of different illnesses. The severity of the combined defect depends on which process exactly is disrupted in the life cycle of the T-cells. A complete disruption of T-cell

maturation leads to severe combined immunodeficiency (SCID). However, if the disruption is incomplete and still permits some maturation of T-cells, the clinical picture is more moderate, and the symptoms begin later. A decrease in T-cells is characteristic of combined immunodeficiencies, but sometimes the patients may have normal numbers of T-cells, which, however, cannot be activated properly. Other immune cells are impaired in their number and function to a very variable extent.

The cause of the impaired development or function of T-cells are gene defects. The clinical picture of a combined immunodeficiency can be caused by a multitude of different gene defects (more than 40 genes).

Is it a hereditary disease?

Gene defects are hereditary diseases. If a hereditary disease is present, that means that the patient has inherited the defective gene from the mother and/or father. Every person possesses two copies of each gene, one from the father and one from the mother. For most hereditary diseases, it is necessary for both genes to be defective, since one healthy gene is usually sufficient.

There are several modes of inheritance for combined immunodeficiencies.

Moreover, not all genes of importance for the complicated development and function of T-cells are known to date. This leads to the fact that with today's methods, a causative gene defect cannot be detected in all patients with CID. With the help of the symptoms and a set of examinations of the immune system, however, it is possible in many cases to more accurately characterize the disease and to develop a clear concept of therapy even in the absence of a genetic diagnosis.

Autosomal recessive

This means that both parents are clinically healthy carriers of the defective gene, i.e. both parents have a healthy gene aside from the defective one, which is sufficient to protect them from the disease.

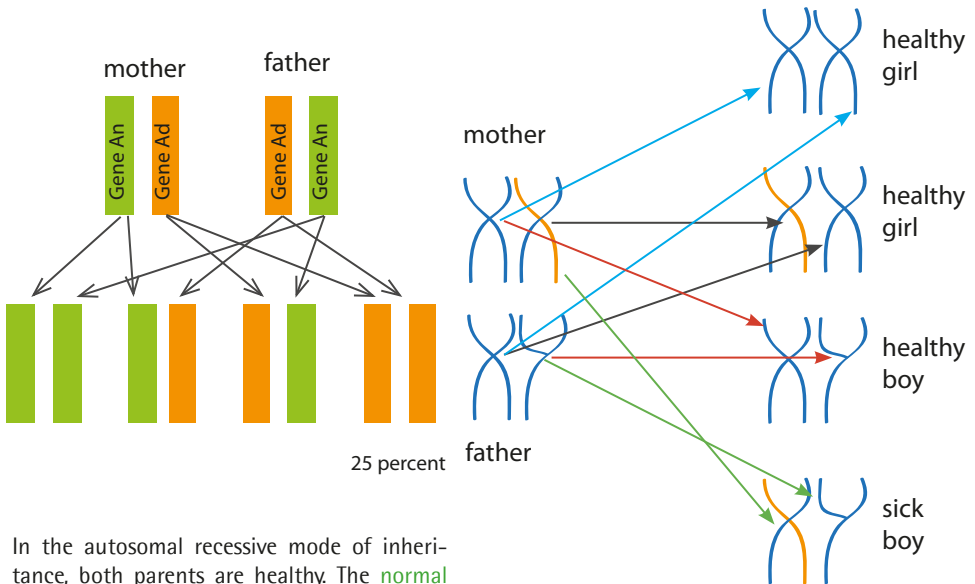
For the descendants, there is a 25 percent probability to fall ill. Half of the children, like their parents, become clinically healthy gene carriers but may pass the gene down to their children,

and 25 percent are completely healthy. Here, the mode of inheritance is independent of gender.

X-linked

Here, usually the mother is the clinically healthy carrier of the defective gene but can compensate for this with the healthy gene on her other X-chromosome. Boys have only one X-chromosome, which they inherit as one of the

two maternal X-chromosomes. If they inherit the X-chromosome with the defective gene, the disease will break out since it cannot be compensated for with a second healthy gene. In this mode of inheritance, half the boys are affected by the disease while the girls are all healthy. Half of the girls, however, can pass down the disease to their own male children.



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.

How is the disease diagnosed?



A careful physical examination is important.
Photo: Ritterbusch

As a rule, patients with combined immunodeficiency attract attention during childhood already with constantly recurring infections, autoimmune diseases (e.g. by antibody-caused anemia or bleeding tendency), unclear eczemas or chronic intestinal inflammation. These problems lead to frequent visits to the doctor. Sometimes, the first indication of CID may be a serious infection that leads to hospitalization. These in-

fections can be so severe that a stay in an intensive care unit and an intensive therapy may be necessary. Frequently, the recurring infections also impair growth and development.

If a combined immunodeficiency is suspected, the children should be transferred to a center specializing in immunodeficiencies as soon as possible, since a speedy diagnosis is important for starting the appropriate treatment.

If an immunodeficiency is suspected, a detailed medical history with concomitant evaluation of the family history (e.g., blood relationship or known immunodeficiency in family history) as well as a careful physical examination are of first importance.

Special attention is paid in the physical examination to the skin (some patients show skin rashes resembling neurodermatitis), the lungs (bronchitis and pneumonia are common in CID), liver and spleen (which may be enlarged in CID) as well as the lymph nodes and tonsils, which may also be enlarged. Some combined immunodeficiencies are syndromes, in which minor malformations (shape of the face, outer ears, tooth enamel or shape of teeth) may indicate the exact disease. Weight, height and head circumference are measured

to determine whether the child has developed appropriately for his/ her age.

In addition to medical history and physical examination, several blood tests are necessary as well.

The first important piece of laboratory diagnostics here is the careful evaluation of the blood count, whereby the number of lymphocytes (a subgroup of the white blood cells) is of great importance. A low number of lymphocytes is an important indicator of combined immunodeficiencies. In addition, the levels of antibodies are measured, which are frequently decreased.

If the child was already vaccinated, it may further be examined whether the child is able to form antibodies specific to the vaccines.

If the lymphocytes are decreased, the different subgroups are isolated (T-cells, B-cells and NK-cells), and their functions are examined. The pattern of dysfunctions in the various cell types then allows for conclusions as to the type of CID.

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

the more accurate classification of the disease. Imaging procedures such as X-ray and ultrasound help determine the presence of enlargements or changes in organs, e.g. nodules in the lungs or in the liver.

Depending on the clinical situation, various further examinations such as urine and stool examinations and possibly, even imaging of the lungs (bronchoscopy) are performed. With bronchoscopy, the lungs may be viewed directly with the help of special equipment and secretion can be sampled, which then can be tested for potentially present germs. Colonoscopies may be required as well in order to allow for better assessment of chronic diarrheas and intestinal inflammations. If such examinations are necessary, you will receive in-depth information and will have enough time to ask questions.

In some CID cases, the clinically suspected diagnosis can be confirmed by a genetic test during the further course of the disease. However, these examinations sometimes take several months, so that the decision for treatment should not always wait for this. Patients with CID should always be treated in a specialized center.

What are the options for treatment?

The treatment of the CID depends on the form and severity of the disease. The principles of treatment are: treatment of already existing infections, prophylaxis and prevention of new infections, treatment of impairments in immunoregulation, strengthening the immune system by antibody infusions and in many cases, also the replacement of the immune system by bone marrow transplantation.

Due to the impaired immune system, the child sometimes needs preventive administration of certain medications to fight off infections. Preventive administration of antibiotics helps to prevent bacterial infection, antiviral medications protect against some viruses, and even antifungal medications are used as a precaution. Many of the medicines are available as juices, but sometimes it is also necessary for your



Subcutaneous therapy with immunoglobulins can be learned for the use at home.

Photo: Ritterbusch

child to receive the medications as an infusion or over the central venous catheter. Unfortunately, these medicines are frequently not sufficient in order to stave off infections completely. Inoculations usually do not make sense for patients with combined immunodeficiency. The missing response to inactivated vaccines is utilized in diagnostics. Live vaccines (e.g. measles, chickenpox, rotavirus) should not be administered.

Immunoglobulins

Due to the defective immune defense cells, children with CID usually cannot build enough or not the right antibodies (immunoglobulins) to be able to fight infections. Therefore, these antibodies must be supplied in form of an infusion. It is possible to give the antibodies via a vein (every 4 weeks) or even subcutaneously into the fat tissue under the skin (1x/week). Since antibodies are degraded after a certain time in the body, the infusions must be repeated on a regular basis. The handling of the pump can be learned for use at home. More information on antibody substitution therapy is available in a separate information leaflet.

Immunosuppressives

With children showing an impairment of immunoregulation (e.g. eczemas, diarrheas, spleen enlargement, autoimmune disorders) sometimes medica-

tions must be used that suppress the badly controlled, excessive immune response. The so-called immunosuppressives are part of this group of medications. The most frequently used drug is cortisone, which has a very good anti-inflammatory effect with rapid onset of action. With longer administration, usually unwanted side effects occur, so that additional drugs are used that decrease the need for cortisone. These additional drugs usually need some more time to show an effect. These immunosuppressives must be used with caution in CID, and some experience is required to obtain the proper extent of immunosuppression without substantially increasing the susceptibility to infections. Sometimes medicines are also used that kill dysregulated immune cells (e.g. rituximab, a medicine that destroys antibody-forming B-cells). This medicine stops the formation of disease-causing auto-antibodies.

Spleen removal

Some patients with CID develop severe cytopenia caused by auto-antibodies, i.e. a destruction of blood cells or blood platelets by antibodies. Frequently, this destruction can be successfully stopped by administration of antibodies, cortisone or immunosuppressives. In some cases, however, in particular in patients with a significantly enlarged spleen, this is not always sufficient. In such cases, removal of the spleen may

be necessary. Since spleen removal poses a risk of susceptibility to infections, a permanent prophylaxis with antibiotics needs to be started after the surgery, which is usually well tolerated.

Blood transfusion

It may happen that your child needs a transfusion of blood products. This includes red blood cells or maybe blood platelets. If your child needs blood, these blood samples are specially treated (irradiated) in order to remove all immune cells from the stored blood and to thus reduce the risk of reactions. Likewise, only blood products are given that were meticulously tested for pathogens, since otherwise harmless viruses may pose a risk for children with immunodeficiencies.



Bluttransfusionen können zur Therapie bei CID gehören. Foto: Ritterbusch

Bone marrow transplantation

Bone marrow transplantation (BMT) is an important therapy option for children with CID, which can completely cure the disease after successful trans-

plantation. 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. Stem cells 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, among other things, into cells of the immune system.

If a suitable 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 over the blood into the bone marrow and can then start there to build healthy blood cells.

However, BMT harbors risks as well, 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 it 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 have to match in a transplantation. 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, through which presently there is 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 with CID. The hematology team will also discuss the risks and adverse effects of chemotherapy with you in detail.

This treatment is not for all patients with CID. In each case, a careful risk-benefit analysis must take place that includes the current state of health, the specific kind of CID and experiences available to date, availability of a suitable donor and other factors. Finally, a decision on the right course of action is made together with the family.

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, and then, the cells are returned to the child. This treatment has the advantage that the child receives his/her own



Large registers such as the Deutsche Knochenmarkspenderdatei (German bone marrow donor file) help to find suitable donors for the ill. Logo: DKMS

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 world-wide have been treated with gene therapy so far. Most treatments were successful mean-

ing 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 to develop safe procedures for gene transfer.

What's the long-term perspective (prognosis)?

Ultimately, the prognosis of CID depends on the form and the extent of the dysfunction. Without treatment, there will be recurring infections that will in part take a serious course, and many patients will suffer from impaired immunoregulation. With the help of immunoglobulines, preventive medication against bacteria, viruses and fungi as well as immunosuppressives, these signs of disease can be reduced

but usually, they cannot be prevented completely. Chronic lung disease is a common problem. Here, good lung hygiene with intensive physiotherapy is a very important element of therapy. In the long run, the only cures for CID are bone marrow transplantation or gene therapy.

Are vaccinations permitted?

Vaccines work by stimulating the production of antibodies. In patients with CID, however, the T-cell defect frequently results in an impairment of B-cells and thus, to decreased antibody formation. Here, vaccinations are of limited use and may even cause harm to the weakened immune system. Therefore, live vaccines (measles, mumps, German measles, BCG, rotavirus) should be used only after detailed examination of the lymphocytes. There is no harm to be expected from inactivated vaccines.

Sometimes, vaccination with an inactivated vaccine can provide important information for the assessment of CID. Whether further vaccinations with inactivated vaccines make sense has to be discussed with the treating physician in the individual case. Annual vaccination of close contact persons with the influenza vaccine does make sense.

Can the child attend kindergarten or school?

Children with CID can usually attend kindergarten and school. In some cases, however, special precautions are necessary, such as avoiding contact with infections. It is therefore impor-

tant that you discuss with your treating physician what to watch out for in your individual case.



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CCI is an interdisciplinary center for research and treatment at the Medical Center - University of 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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