Combined immunodeficiency (CID) in children
information for families

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What is combined immunodeficiency (CID)?

Combined immunodeficiency (CID) is the name given to a group of rare, inherited disorders of the immune system. The major problem in CID is that specialised white blood cells, known as T cells, do not function properly or there are not enough of them. Antibody production is usually also impaired, which is why the term ‘combined’ is used.

T cells are essential for protection against many infections: viruses, bacteria and fungi. They are also important in controlling inflammation and preventing cancer. If T cells are completely missing then severe CID (SCID) results, producing a characteristic pattern of illness in babies – a separate leaflet is available about SCID available at www.piduk.org/static/media/up/SCID.pdf. This leaflet describes some of the common clinical features of CID in children.

Not all patients are affected in the same way and sometimes the diagnosis is not made until adulthood. Treatment is now available that can reduce the risk of serious infection, manage autoimmunity or overgrowth of white blood cells and, in some cases, cure the disorder.

What causes it?

CID is usually an inherited condition, passed on in families in a similar way to physical characteristics, such as eye colour. It is caused by a mistake (or ‘mutation’) in a child’s genetic make-up. PID UK has a separate information leaflet devoted to the genetics of primary immunodeficiency, available on its website at www.piduk.org/whatarepids/geneticaspectsofpid. Specialists in genetics and genetic counselling are also on hand to talk through the inheritance of CID with you if needed.

The immune system relies on a large number of genes for its normal development. In children affected by CID, a defect in one or more of these genes results in the absence or malfunction of a protein necessary for normal functioning of the immune system. Different types of CID are named based on the particular protein or gene that is affected or sometimes the doctor(s) who first described it. Some of the better-known types include Wiskott-Aldrich syndrome, DOCK8 deficiency and recombination activating gene (RAG) deficiency. It is helpful to know the exact cause: (a) because in some conditions there may be specific treatments available, and (b) to allow accurate genetic counselling for future pregnancies.
What are the signs and symptoms of CID?

Children with CID may seem well at birth and for the first few months or years of life. This is because they are partly protected by antibodies passed from mother to baby across the placenta during the last few months of pregnancy. They also have partially functional immunity of their own and may be able to respond to some extent to vaccinations and germs they encounter.

CID can affect children in many different ways. They are likely to suffer infections more frequently than other infants. Ordinary problems, such as coughs and colds, may seem more severe and last longer than would be expected, requiring repeated and prolonged courses of treatment. Skin rashes (such as eczema), a wheezy chest or breathlessness and even food allergies may be present. Sometimes children with CID may have a poor appetite, have chronic diarrhoea and fail to grow and gain weight normally, even if no definite infection is found.

Apart from infections, some children with CID cannot regulate their immune system correctly. They may not be able to ‘turn down’ an immune response triggered by infection, so ending up with a vicious cycle of fever and inflammation called haemophagocytic lymphohistiocytosis (HLH). The immune system might also get turned against the child’s own body, resulting in autoimmune diseases, such as arthritis, bowel problems or a low blood count.

How is it diagnosed?

The most important clue is often the family history. If there is another member of the family who has had unusual infections, autoimmune disease or cancers at a young age, then this can highlight an inherited problem. If parents are blood relatives, the risk of inherited diseases, including CID, is increased in their offspring.

CID may show up in the form of repeated and/or severe infections, especially when accompanied by poor growth or an autoimmune condition (such as anaemia or a bleeding tendency caused by antibodies against blood cells). Occasionally there may be clues to a certain type of CID outside the immune system; for example, problems with the skin, bones, teeth or heart. As a result, children with CID are often in contact with child health services from a young age.

If immunodeficiency is suspected, an immunologist will be consulted and referral made to the regional or national specialist immunology centre. Special investigations will be arranged. Some of the tests will have to be sent away and the results may take a long time to come back. Accurate diagnosis of infection and other complications is all part of building up a full picture. Often, genetic testing is needed to be sure of the diagnosis.

How is it treated?

In the UK there are several specialist paediatric immunology centres that can diagnose and often treat CID. Care is usually shared between the specialist centre and paediatricians in the local centre and other specialties, such as gastroenterologists or lung specialists, as well as the child’s family doctor (GP).

Initial management

The immediate priorities are to treat any current infection, to prevent new infections and to perform appropriate tests and assessments. Other complications, such as autoimmunity, may require specific treatment. Depending on the severity and type of condition, it may be appropriate to think about treatments designed to fix the faulty immune system permanently.

Simple measures to prevent infection in more severely affected children include drinking cooled, boiled water instead of water straight from the tap. If a child with CID is exposed to chickenpox or shingles, especially for the first time, they may need an urgent injection and/or medicine to protect them, so contact your healthcare team straight away.

Vaccination

In many cases, vaccines will already have been given before the diagnosis of CID is made. Most of these are completely safe and do not cause problems. Some live vaccines might need to be avoided, particularly BCG, rotavirus, measles/mumps/rubella (MMR) and chickenpox (VZV, not in the routine immunisation schedule in the UK, but routinely given in other countries).
**Immunoglobulin (antibody) therapy**

Children affected by CID often have problems producing antibodies, leaving them vulnerable to infection. This can be corrected by immunoglobulin therapy, made from a solution of human antibodies. Further information about immunoglobulin treatment can be found in a range of leaflets from PID UK.

**Other issues**

Repeated chest infections, often before the diagnosis of CID is made, can lead to scarring and widening of the airways (bronchiectasis). In this situation children usually benefit from regular physiotherapy. This helps to clear secretions and prevent infection from taking hold. Expert physiotherapists can often teach parents to do this and older children can do physiotherapy for themselves.

Depending on the particular problems in individual children, other treatments may also be needed. These will be discussed in detail with your immunology doctors and nurses.

A new diagnosis of CID can be worrying. Anxiety about catching or passing on an infection can make life very stressful. The hospital team, nurses and support groups will provide families with guidance on protecting the child from infection, keeping the house clean and coping with diet and medication. Parents are always able to ring the hospital and speak to an immunologist or a nurse if they are worried at any time.

**Corrective treatment of CID**

**Haematopoietic stem cell transplantation**

In some cases, haematopoietic stem cell transplant (HSCT) (including bone marrow transplant, BMT) offers the potential for long-term cure of CID. This treatment is most well-established for defined types of CID that are known to be life-limiting because of predictably severe complications. HSCT aims to replace the faulty immune system with an immune system from a healthy donor. Stem cells, from which all the cells of the immune system develop, can be obtained from healthy bone marrow, or in some cases from umbilical cord blood or donor blood. The healthy stem cells can be given by transfusion into a vein to a child with CID.

**HSCT is not an operation like a heart or kidney transplant.** Stem cells contained in the donor bone marrow are able to find their way from the bloodstream to the child’s bone marrow, where they start to produce healthy blood cells. HSCT does involve a number of risks, and complications can arise afterwards – some of which are temporary, others of which can be life-threatening. Further information about HSCT/BMT will be provided by the BMT centre, and families will have the opportunity to discuss their concerns in detail with an immunologist and BMT consultant on several occasions.

**Gene therapy**

Gene therapy aims to correct the underlying genetic abnormality by replacing the faulty gene in immune cells with a normal copy. It is currently undergoing clinical trials in selected patients who have certain specific conditions.

**Thymic transplantation**

Rarely, CID happens not because of a problem with the T cells themselves but because of missing or faulty tissue in an organ called the thymus, where T cells develop. The commonest condition affecting thymus development is called 22q11 deletion syndrome (also known as DiGeorge syndrome). In the small fraction (<1%) of DiGeorge patients whose thymus is completely missing, thymic transplant may need to be considered. This is still an experimental treatment that is only available at a few centres (GOSH in the UK). Further information about 22q11 deletion syndrome is available from the support organisation Max Appeal! – details at the end of this leaflet.

**What does this mean for the future?**

Continuing developments and improvements are transforming the lives of children with CID. Better diagnostic techniques and genetic technology, better treatments and better medications enable many children with CID to live healthy lives pending curative therapy, such as stem cell transplant. It is likely that new treatments, such as gene therapy, will continue to develop and become applicable to more types of CID.

**Genetic counselling**

In many cases, the genetic cause of CID can now be identified. This means that accurate genetic counselling is available for the immediate and extended family, and that prenatal diagnosis, or even pre-implantation diagnosis in highly selected cases, is possible for future pregnancies.
Is there a support group?

PID UK is the main support organisation in the UK for anyone affected by a primary immunodeficiency disease. Call our helpline on 0800 987 8986 or visit our website at www.piduk.org

Max Appeal! is the name of the UK support group for families affected by 22q11 deletion syndrome. Its website is at www.maxappeal.org.uk

The leaflet How to become a bone marrow donor can be obtained from the Anthony Nolan Bone Marrow Trust by ringing 0303 3030303 or visiting their website at www.anthonynolan.org

Glossary of terms

**antibody** a type of protein (immunoglobulin) that is produced by certain types of white blood cells. Antibodies fight bacteria, viruses, toxins and other substances foreign to the body.

**arthritis** inflammation of a joint, with pain and swelling.

**Aspergillus** a type of fungus that can cause severe infection in people with immune deficiency.

**autoimmune** immune reaction against the body’s own tissues. This can cause disease of organs (such as the thyroid gland), tissues (such as arthritis) or the blood. Autoimmune disease of the blood can lead to destruction of one or more types of blood cells - called haemolytic anaemia (red blood cells destroyed), thrombocytopenia (destruction of platelets causing bleeding and bruising) or autoimmune neutropenia (destruction of neutrophils). These disorders can require urgent treatment. Many autoimmune diseases need treatments that suppress the immune system because of the damage they are causing, even though the immune system is weaker at fighting infections.

**BCG** the live vaccine against tuberculosis.

**bone marrow** soft, spongy tissue located in the hollow centres of most bones that contains developing blood cells and cells of the immune system.

**bone marrow transplantation (BMT)** transfer of bone marrow, obtained by aspiration usually from the hip bones, from a donor - either related or unrelated - to a recipient. The donor bone marrow replaces the recipient bone marrow, giving the recipient a new immune system and curing the immunodeficiency (See also Haematopoietic stem cell transplantation).

**combined immune deficiency (CID)** a disorder of T and B cell function that results in susceptibility to infection and failure of the immune system to regulate itself properly.

**cryptosporidium** a parasite that causes the unusual infection cryptosporidiosis that affects the gastro-intestinal tract and bile ducts. It causes diarrhoea and may be difficult to get rid of in certain types of immunodeficiency. Infection can be caused through water contamination, uncooked or unwashed food, handling farm animals or household pets, and through touch by contaminated hands.
Cytomegalovirus (CMV)  a virus that causes a mild illness in healthy individuals, but can cause severe and life-threatening disease in people with primary immune deficiency.

deficiency  a lack of or shortage.

diGeorge syndrome  a complex condition usually caused by a tiny missing piece of chromosome 22 – known as 22q11 deletion syndrome. Affected children may have serious heart abnormalities, a particular facial appearance, problems regulating calcium levels in the blood, and sometimes immune deficiency, as well as many other possible problems. In a minority of cases where the immune deficiency is severe, treatment by thymic transplantation may be needed.

DOCK8 deficiency  a specific form of CID caused by faults (mutations) in the DOCK8 gene.

donor  an individual who could donate bone marrow or stem cells for transplantation. Donors may be family members, or unrelated, but need to be well matched with the potential recipient by tissue-typing.

Epstein-Barr Virus (EBV)  virus that causes glandular fever in healthy people, which can cause severe problems in patients affected by some forms of combined immunodeficiency.

fungus  member of a class of relatively primitive microorganisms, including mushrooms, yeasts and moulds. Fungal infections can be particularly serious in people with primary immune deficiency.

gene  section of DNA on a chromosome that codes for a functional RNA molecule and thus a protein. Put another way, a word rather than a letter in the genetic code. Genes are the fundamental units of inheritance that carry the instructions for how the body grows and develops.

gene therapy  attempting to cure genetic diseases by placing a normal ‘healthy’ gene into cells that have a faulty version of that gene.

genetic counselling  advice from a specialist geneticist regarding the implications of carrying or being affected by a genetic disorder.

Geneticist  an expert in the study of genes and heredity.

haematopoietic stem cells  cells from which all blood cells and immune cells are derived.

haematopoietic stem cell transplantation (HSCT)  transfer of bone marrow (obtained by a medical procedure) or stem cells (obtained from blood or stored umbilical cord blood) from a donor – either related or unrelated – to a recipient. Haematopoietic means blood-forming. The donor cells are given by intravenous infusion and make their way to the recipient bone marrow to provide a new immune system, curing the immunodeficiency.

HLH (haemophagocytic lymphohistiocytosis)  a very severe condition causing high fevers, low blood counts and enlarged liver, spleen and lymph nodes, which can occur in patients with some forms of CID.

immune deficiency  when the immune system’s ability to fight infectious disease is compromised or entirely absent.

immune system  the structures and processes that protect the body against infection and disease.

immunoglobulin replacement therapy  administration of immunoglobulin purified from plasma to people with immune deficiency. The immunoglobulin contains antibodies that help protect against infection. This treatment can be given through a vein or under the skin.

immunoglobulins  proteins (globulins) in the body that act as antibodies. They work to protect against and fight off infections. They are produced by specialist white blood cells (plasma cells/B cells) and are present in blood serum and other body fluids. There are several different types (IgA, IgE, IgG and IgM), and these have different functions.

immunologist  a consultant specialising in the care of patients with immune disorders.

inheritance  passing down of genetic information from parents to children.

leucocytes (white blood cells)  a group of small, colourless blood cells that play a major role in the body’s immune system. There are five basic types of white blood cells: monocytes, lymphocytes, neutrophils, eosinophils and basophils.

lymphocytes  small white blood cells, normally present in the blood and in lymphoid tissue, that carry out specialised functions of the immune system. There are two major forms of lymphocytes, B cells and T cells, which have distinct but related functions in generating an immune response and are responsible for immunological ‘memory’.

MMR vaccine  a live vaccine against measles, mumps and rubella (German measles).
mutation a change in the structure of a gene or group of genes. Such changes can be passed on to the next generation. Many mutations cause no harm, but others can cause genetic disorders, such as primary immune deficiencies.

opportunistic infection an infection occurring in immunodeficient or immunosuppressed persons, caused by organisms that do not cause disease in people with normal immune systems.

organ a group of tissues that work together to carry out particular, vital functions.

paediatrician consultant specialising in the care of children.

Pneumocystis jirovecii pneumonia (PJP) an ‘opportunistic’ infection that does not usually cause illness except in people with defective immune systems; in this case, defective T cell function. PJP is a severe form of pneumonia.

pre-implantation diagnosis testing of very early embryos for a specific genetic disorder, performed following in vitro fertilisation (IVF). Only available in highly selected cases.

prenatal diagnosis testing during a pregnancy for specific genetic disorders. Usually performed by ‘chorionic villous sampling’ – taking a sample of tissue from the developing placenta, and testing DNA obtained from this tissue. Amniocentesis (performed later in pregnancy) is another route to prenatal diagnosis.

Recombination activating gene (RAG) deficiency a specific form of CID caused by faults (mutations) in one of the RAG genes.

rotavirus a common virus that causes diarrhoea, which can be persistent in children with primary immune deficiency.

severe combined immune deficiency (SCID) a failure of T cell development, which causes severe susceptibility to infection in infancy.

subcutaneous ‘under the skin’. It also refers to anything relating to the loose cellular tissue beneath the skin; for example, an immunoglobulin infusion given directly into the tissue directly beneath the skin is said to be given subcutaneously.

T cells (or T lymphocytes) specialised lymphocytes that develop in the thymus, an organ in the chest. They are responsible, in part, for carrying out the immune response.

thrush (candida) a common fungal infection in young infants, often affecting the mouth or nappy area. It can be severe and persistent in children with immune deficiency.

thymus a bow-tie shaped lymphoid organ located behind the upper portion of the sternum (breastbone). The thymus is the chief ‘educator’ of T cells. This organ increases in size from infancy to adolescence, and then begins to shrink.

thyroid gland a gland in the neck that is responsible for the production of thyroxine.

VZV (varicella zoster virus) the virus that causes chickenpox and shingles.

Wiskott-Aldrich syndrome a specific form of CID caused by faults (mutations) in the WASP gene; characterised by severe eczema, bleeding problems and infections.
Primary Immunodeficiency UK (PID UK) is a national organisation supporting individuals and families affected by primary immunodeficiencies (PIDs).

We are the UK national member of the International Patient Organisation for Primary Immunodeficiencies (IPOPI), an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website at www.piduk.org provides useful information on a range of conditions and topics, and explains the work we do to ensure the voice of PID patients is heard.

If we can be of any help, please contact us at hello@piduk.org or on 0800 987 8986, where you can leave a message.

Support us by becoming a member of PID UK. It’s free and easy to do via our website at www.piduk.org/register or just get in touch with us. Members get monthly newsletters.

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