

ADA-SCID

Adenosine deaminase- deficient severe combined immunodeficiency (ADA-SCID)

Additional information for families

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Supporting families affected
by primary and secondary
immunodeficiency

About this leaflet

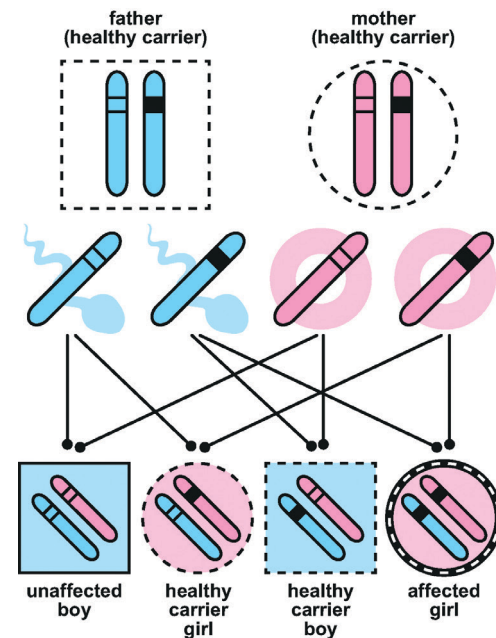
This leaflet has been produced jointly between Immunodeficiency UK, Great Ormond Street Hospital (GOSH) and the Great North Children's Hospital. It describes the adenosine deaminase (ADA)-deficient specific form of severe combined immunodeficiency (SCID) and should be read in conjunction with the general overview leaflet on SCID.

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What is ADA-SCID?

ADA-SCID is a specific form of severe combined immunodeficiency (SCID). It is inherited as an autosomal recessive condition. This means that a child has to inherit the faulty gene from both parents to have the condition. There may be a family history of previously affected children, including in the wider family, if there are first or second cousin marriages or partnerships in the family. More information about autosomal recessive inheritance can be found in our leaflet *Genetic aspects of immunodeficiency*, available on our website at www.immunodeficiencyuk.org.



Mechanism of autosomal recessive inheritance

Diagram: © UCL Health Creatives 2015

What causes it?

ADA-SCID is caused by mistakes (mutations) in the ADA gene, which result in absent or very low levels of the enzyme ADA. Enzymes are proteins that help speed up chemical reactions in the body. Lack of the ADA enzyme causes the build-up of a toxic substance called deoxyadenosine. This prevents cells from dividing effectively.

White blood cells (especially lymphocytes, and more specifically T cells, B cells and natural killer (NK) cells) that are important for a healthy immune system are very sensitive to these toxic effects and fail to develop normally, leading to SCID. However, the ADA gene is important in all cells of the body, and therefore patients with ADA-SCID often also have symptoms and signs outside the immune system. In some cases there may be a low level of working ADA enzyme, leading to a less severe, 'delayed' onset of combined immune deficiency (CID) – please refer to our separate *CID information leaflet* available on our website at www.immunodeficiencyuk.org.

What are the signs and symptoms?

The signs and symptoms of the immunodeficiency in ADA-SCID are the same as in all other forms of SCID. In addition, patients with ADA-SCID can also have some or all of the following problems:

- **Lungs:** toxic effects can cause lung inflammation that mimics the effects of infection and makes babies breathless, sometimes called “ADA-lung”.
- **Brain:** development may be slower than in healthy children and there may be behavioural and psychological problems, such as hyperactivity and poor social behaviour.
- **Bones:** unusual rib ends may be seen on a chest X-ray, and other changes of bone development sometimes occur but do not usually cause symptoms.
- **Hearing:** deafness is sometimes a problem. There may also be problems with other body systems, including the kidneys and liver.

How is it diagnosed?

Infants with typical ADA-SCID become severely ill within the first few months of life. They have poor growth and frequent, severe and unusual infections such as pneumonia with an organism called *Pneumocystis jirovecii* (pronounced “new-mow-sist-iss”) that does not usually cause illness in healthy individuals. Breathing difficulties can also occur in infants with ADA-SCID without any detectable infection.

The UK has been trialling newborn screening for SCID, which tests for T cells in the dried blood spot collected routinely at around a week of age. The results are often available before any signs of illness, enabling pre-emptive treatment to protect babies from infection. If newborn screening is adopted for the whole country, most cases of ADA-SCID will be picked up this way in future.

Blood testing shows a very low lymphocyte count, and basic immunology tests show very low or absent levels of T, B and NK

lymphocytes. Doctors refer to this pattern of SCID as ‘T - B - NK - SCID’, which usually indicates ADA-SCID. The diagnosis can be confirmed by testing blood for ADA enzyme activity (usually <1% of normal in SCID) and follow-up genetic tests.

Other (non-immunology) investigations

If ADA deficiency is confirmed, it is important to assess hearing as early as possible because of the high risk of deafness. A neurodevelopmental assessment will be performed. The need for other investigations will depend on whether other systems of the body are involved.

How is it treated?

The first stages of treatment and precautions are the same as in all forms of SCID. However, in contrast to other forms of SCID, it is possible to replace the missing enzyme using a medication known as PEG-ADA. This is often referred to as enzyme replacement therapy. It is given as a weekly injection into a muscle, for instance, the thigh muscle.

PEG-ADA treatment corrects the ADA and adenosine levels in the blood, and usually leads to gradual improvement and partial correction of immune function. This benefit tends to wear off over a period of years. It can be used until a more definitive therapy is available, such as haematopoietic stem cell transplant (HSCT) or gene therapy. The choice between HSCT or gene therapy will depend on whether there are well-matched donors available



PEG-ADA treatment is given as a weekly injection into a muscle, usually the thigh.

for transplant and will be discussed at length between the parents and the transplant and gene therapy teams.

Clinical trials of gene therapy for ADA deficiency are ongoing in Europe and the USA, with Great Ormond Street Hospital being one of the centres where this treatment is available. A related, commercial gene therapy treatment called Strimvelis is approved by NICE and is available to families as an alternative treatment in Milan. The differences between these gene therapy options will be discussed with the families in detail.

What does this mean for the future?

Long-term follow-up will be important even after successful treatment of ADA-SCID. The non-immune signs and symptoms of ADA-SCID, particularly developmental, behavioural and psychological effects, will need to be carefully monitored and managed. Genetic counselling is important for future family planning as both parents will usually carry a copy of the faulty gene and any subsequent children born will have a 1 in 4 chance of being affected. This risk is the same with every pregnancy. Carrier testing for at-risk family members and prenatal testing for future pregnancies, (including pre-implantation genetic diagnosis), are likely to be available. Please refer to Immunodeficiency UK's booklet *Genetic aspects of immunodeficiency* for further information available on our website at www.immunodeficiencyuk.org.



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My son Calvin received a HSCT in 2019 at 6 months old. He was extremely unwell prior to his diagnosis due to ADA-SCID not being on the newborn screening programme at the time he was born. He received PEG-ADA which helped his lungs, and the toxins slowly decreased to a level where he was stable enough to transplant. I was well supported through the process of HSCT from the team in the Royal Victoria Infirmary in Newcastle. Calvin is now almost 5 years post-transplant and has been saved due to his HSCT.

Georgia, mum to Calvin.

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Is there a support group?

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

It can be helpful to meet another family who has a child with SCID and who has undergone HSCT or gene therapy. Speak to your immunology team, who may be able to arrange a meeting with a suitable family.

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.anthonylan.org.

Glossary of terms

adenosine a chemical that builds up when ADA is absent and is toxic to developing immune cells.

adenosine deaminase (ADA) an enzyme found in lymphocytes (and other cells), responsible for removing certain toxins produced by their metabolism. In its absence, lymphocytes fail to develop and function, which is one of the causes of severe combined immunodeficiency (SCID).

autosomal recessive a type of inheritance where the presence of one copy of a faulty gene does not affect the individual him or herself. However, when two carriers of the same faulty gene have children there is a 25 per cent (or 1 in 4) chance of a child inheriting two copies of the faulty gene (one from each parent) for each pregnancy. If this happens, the child is affected by the disorder.

B cells (B lymphocytes) cells of the immune system derived from bone marrow and involved in the production of antibodies.

enzyme a protein that acts as a catalyst (trigger) to a specific biochemical reaction. Enzymes make the chemistry of cells work.

enzyme replacement therapy treatment to replace a missing or poorly functioning enzyme.

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.

haematopoietic stem cell transplantation (HSCT) the transfer of stem cells from a donor – either related or unrelated – to a recipient. Stem cells may be obtained from bone marrow (by aspiration usually from the hip bones), peripheral blood (PBSCs) or stored umbilical cord blood. 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, thus curing the immunodeficiency.

lymphocytes small white blood cells, normally present in the blood and in lymphoid tissue, that carry out the 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.

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.

natural killer (NK) cells a type of lymphocyte, particularly important in fighting virus infections and protecting against cancer.

PEG-ADA a chemically modified form of ADA that can be given by injection to improve immune function while awaiting corrective treatment.

pneumocystis jirovecii pneumonia a severe form of pneumonia caused by an organism called *Pneumocystis jirovecii*.

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

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About Immunodeficiency UK

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

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

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

Support us by becoming a member of Immunodeficiency UK. It's free and easy to do via our website. Members get monthly bulletins.

Immunodeficiency UK is reliant on voluntary donations. To make a donation, please go to www.immunodeficiencyuk.org/donate



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