XIAP

X-linked inhibitor of apoptosis protein (XIAP) deficiency

Information for families

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Together we are Histio UK.org

XLP research trust
Funding medical research into this Silent Killer

THE great north CHILDREN'S HOSPITAL

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this leaflet

This booklet has been produced jointly between Immunodeficiency UK, Great Ormond Street Hospital (GOSH) and the Great North Children's Hospital and in association with the XLP Research Trust and Histio UK. The information has been reviewed by the Immunodeficiency UK Patient Representative Panel and by families affected by X-linked inhibitor of apoptosis protein (XIAP) deficiency. It has been endorsed by the Immunodeficiency UK Medical Panel. The purpose of the booklet is to help answer the questions that families may have about XIAP deficiency. The information contained within it should not, however, replace advice from a clinical immunologist or a geneticist.

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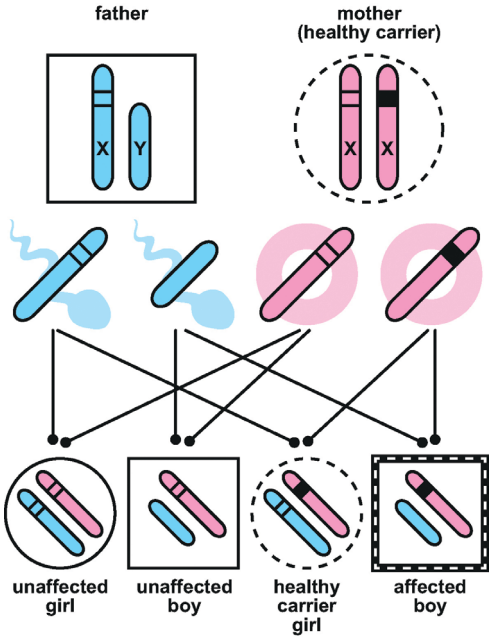
What is XIAP deficiency?

X-linked inhibitor of apoptosis protein (XIAP) deficiency is a rare, inherited immunodeficiency that occurs almost exclusively in boys. Sometimes it is called X-linked lymphoproliferative type 2 disorder (XLP2). It was first recognised in 2006 and since then about 100 boys have been identified as having the disease.

What causes XIAP deficiency?

XIAP deficiency is caused by a mutation (change) in the *XIAP* gene that reduces its protein function. Normally, the XIAP protein does an important job in regulating the body's immune response but, if the XIAP protein does not work, excessive inflammation and damage can occur.

XIAP deficiency is an example of an X-linked disorder, which means that it almost exclusively affects males. This is because the *XIAP* gene is on the X chromosome. Females have two X chromosomes, so a problem in one copy of the *XIAP* gene can be compensated for by the second copy. Such females are healthy carriers of XIAP deficiency. As boys have only one X chromosome, there is no second X chromosome to compensate if they inherit the abnormal copy of the *XIAP* gene, resulting in disease.



Mechanism of X-linked inheritance

Diagram: © UCL Health Creatives 2015

Sometimes the change can also occur as a 'new mutation' that has developed 'out of the blue' or sporadically, in which case there is no previous family history. More information about genetics is available on our website at **www.immunodeficiencyuk.org**.

What are the signs and symptoms?

The hallmarks of XIAP deficiency are:

- recurrent fevers, a rash and low blood count (haemophagocytic lymphohistiocytosis (HLH*), often triggered by the glandular fever virus (Epstein-Barr virus; EBV)
- an enlarged spleen (splenomegaly)
- inflammatory bowel disease, with symptoms of abdominal pain and diarrhoea, sometimes containing blood.

*HLH is a serious condition where the body reacts inappropriately to a 'trigger'. Certain white blood cells (T-cells and macrophages) become over-activated and can cause severe inflammation and damage to tissues. Please refer to Immunodeficiency UK's separate leaflet for more information on HLH available on our website at **www.immunodeficiencyuk.org**.

Other features in XIAP deficiency can include hypogammaglobulinaemia (low immunoglobulin level) and inflammation in other tissues, such as the joints (arthritis).

How is it diagnosed?

A key step is your specialist recognising the clinical pattern as possibly being due to XIAP deficiency. A wide range of blood tests will be carried out, including a full blood count to look for low numbers of each type of blood cell, as well as more specialised tests to check liver function and look for signs and causes of infection. Some tests will need to be performed in a specialist laboratory and will take several days. The diagnosis of XIAP deficiency is confirmed by measuring a low level of XIAP protein in blood cells, as well as genetic tests to identify the underlying genetic change.

Other samples, such as bone marrow or lymph node tissue, may be needed depending on the patient's condition. If there are neurological symptoms, a sample of cerebrospinal fluid may be taken by lumbar puncture. Inflammation of the gut may need to be assessed by looking inside with a flexible endoscope (while the child is asleep under anaesthetic), and many children will need specialised imaging using techniques such as ultrasound, MRI or CT scan. Your medical team will guide you through this process.

How is it treated?

Diagnosis and treatment are usually coordinated by a specialist centre experienced in treating rare immune disorders. The initial aim is to dampen down (suppress) inflammation, when present. This may involve courses of corticosteroids, biologics (targeted antibody treatment) and other therapy, often given in hospital. If children need intensive therapy and monitoring, a semi-permanent line is often placed into a large vein in the neck, under anaesthetic, so that needles are no longer needed.

Inflammatory bowel disease will generally be treated with standard immunosuppressant medicines, although symptoms do not always respond well. If there is evidence of infection, anti-EBV, antibiotics and other anti-infection medicines will be prescribed, and immunoglobulin replacement therapy is often needed. More information on immunoglobulin replacement therapy can be found on our website at **www.immunodeficiencyuk.org**.

Currently, haematopoietic stem cell transplant (HSCT) is the only curative treatment for XIAP deficiency. This is where a child's bone marrow is replaced with stem cells from a healthy donor. However, HSCT in the context of XIAP deficiency has variable outcomes and the condition itself also varies markedly in severity. Therefore, the decision about whether to proceed with a transplant or not needs to be individualised, in discussions between the family and an experienced specialist team. More information on HSCT can be found on our website at **www.immunodeficiencyuk.org**.

What happens next?

The outlook for children with XIAP deficiency has improved, owing to better recognition of the condition, improved diagnostic testing and more effective treatment, including HSCT for complications such as HLH. For those children with XIAP deficiency who do not develop HLH, a good quality of life can often be maintained with prophylactic (preventative) antibiotics and immunoglobulin replacement therapy at home.

Genetic counselling for the family is important and will be offered by the specialist centre. Prenatal diagnosis is available for future pregnancies if desired and provided that the underlying genetic change can be identified. You can find out more information about genetic testing in the Immunodeficiency UK leaflet *Genetic aspects of primary immunodeficiency* available on our website at **www.immunodeficiencyuk.org**.

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**. Immunodeficiency UK is affiliated to the International Patient Organisation for Primary Immunodeficiencies (IPOPI) (**www.ipopi.org**).

The XLP Research Trust offers specific support and advice to families affected by XIAP deficiency and promotes and funds research into the condition. Their website (**www.xlpresearchtrust.org**) includes lots more information and patient stories. Contact them on 01794 521077 or email **info@xlpresearchtrust.org**.

Histio UK offers support and advice to families affected by all types of histiocytosis. Call them on 07850 740241 or visit their website at **www.histiouk.org**.

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

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

bone marrow aspiration a procedure that involves using a syringe to aspirate ('suck out') a sample of liquid bone marrow, usually from the hip bones.

bone marrow transplantation (BMT) the 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).

cerebrospinal fluid a watery liquid that surrounds the brain and spinal cord.

chromosomes thread-like structures located inside the nucleus of cells. Each chromosome is made of protein and DNA.

corticosteroid medicine that dampens down the immune system to reduce inflammation in a range of conditions.

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) one of a family of herpes viruses commonly known to cause glandular fever. Infection with this virus can cause swollen glands, fever, sore throat, loss of appetite, and enlargement of the spleen and liver.

gene a 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.

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

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

haematopoietic stem cell transplantation (HSCT) the 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.

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

immunoglobulin also known as antibody; a type of protein produced by the immune system to fight germs, such as bacteria and viruses.

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.

inflammation the body's biological response to harmful stimuli. It causes symptoms of redness, swelling, heat and pain.

inflammatory bowel disease inflammation inside the bowel, often causing bloody diarrhoea and abdominal pain.

inheritance the passing down of genetic information from parents to children.

intravenous inside or into a vein; for example, an immunoglobulin infusion may be given directly into a vein.

lumbar puncture a procedure to obtain cerebrospinal fluid for diagnostic tests. A needle is inserted through the skin of the back into the space between the bones that make up the spine. This is done using local or general anaesthetic.

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.

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.

spleen an organ in the upper abdomen near the stomach that plays an important role in the immune system.

splenomegaly enlargement of the spleen.

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.

white blood cells (leucocytes) 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.

X-linked refers to the inheritance of disorders caused by mutations in genes carried on the X (or female sex) chromosome. This is also known as sex-linked inheritance. In this situation, girls are usually carriers and boys are affected by the condition. Girls inherit one X chromosome from each parent, so have a normal X chromosome to compensate for the faulty one.

Notes

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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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