XLP1

X-linked lymphoproliferative disorder (XLP1)

Information for families

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Funding medical research into this Silent Killer

Great Ormond Street Hospital for Children NHS Foundation Trust

THE great north CHILDREN'S HOSPITAL

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this leaflet

This information 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. It explains the rare immune condition called X-linked lymphoproliferative type 1 (XLP1) disorder. XLP1 is also known as Duncan's disease, SAP deficiency and classic XLP. Type 2 XLP is quite different from type 1 and is described in a separate information leaflet.

The information has been reviewed by the Immunodeficiency UK Patient Representative Panel and by families affected by XLP1. It has been endorsed by the Immunodeficiency UK Medical Panel.

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What is X-linked lymphoproliferative disorder?

X-linked lymphoproliferative type 1 (XLP1) disorder is a rare immune condition that affects around 1 in every 1 million males. In affected individuals, the body cannot properly regulate an important type of white blood cell (lymphocytes) in response to a viral infection, usually the Epstein-Barr virus that causes glandular fever. The resulting excessive number of lymphocytes is known as lymphoproliferation.

What causes XLP1?

XLP1 is caused by a mutation (change) in a gene named *SH2D1A*, which is important for producing a protein that regulates cells of the immune system, known as lymphocytes. This protein – called SAP (short for 'SLAM-associated protein') – may be absent or abnormal so that it affects the development of specific lymphocytes called Natural Killer (NK) cells and the self-destruct pathway when cells are no longer needed.

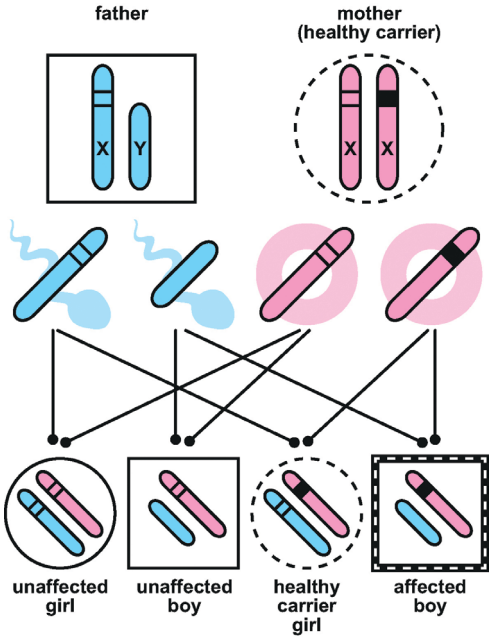

Figure 1:
Mechanism of X-linked inheritance

Diagram: © UCL Health Creatives 2015

Inheritance and XLP1

In many cases, XLP1 is an inherited condition, meaning it is passed on in families in the same way that physical characteristics, such as eye colour, are passed from parent to child. It is caused by a mutation (change) in a child's genetic make-up. Specialists in genetics and genetic counselling are on hand to talk through the inheritance of XLP1 with you if needed, and PID UK has a separate information leaflet devoted to the genetics of primary immunodeficiency, available on our website at **www.immunodeficiencyuk.org**.

X-linked disorders, such as XLP1, are the result of mutations in genes on the X chromosome and almost exclusively affect males. It is very rare for a female to develop symptoms of XLP1. A female who has a mistake on one of her two X chromosomes also has a normal X chromosome, which compensates for the abnormal one. This means that in almost all such situations, the female is healthy

but is a ‘carrier’. A male who inherits an X chromosome carrying a mutation does not have a second X chromosome to compensate, so may be affected by an ‘X-linked recessive’ disorder.

Sometimes mutations can just happen by chance (sporadically) and are not inherited from parents.

What are the signs and symptoms?

The symptoms of XLP1 are very variable and can be divided into three groups as follows:

Haemophagocytic lymphohistiocytosis (HLH)
HLH occurs when the body reacts inappropriately to a ‘trigger’, usually an infection. Instead of fighting off the infection, some white blood cells (T-cells and macrophages) become over-activated, causing severe inflammation and damage to tissues, such as the liver, spleen and bone marrow. HLH affects around half of all children diagnosed with XLP1. Immunodeficiency UK has a separate information leaflet devoted to HLH, available on our website at **www.immunodeficiencyuk.org**.

Hypogammaglobulinaemia
This is the medical term for reduced levels of antibodies (immunoglobulin) in the blood, which leads to recurrent infections, such as coughs, colds and upset stomach.

Lymphoma
Children with XLP1 have a greatly increased risk of developing lymphoma (cancer of the immune system cells) compared with the general population. Lymphoma causes symptoms such as fever, fatigue, weight loss, loss of appetite and/or sudden enlargement of one or a few lymph nodes.

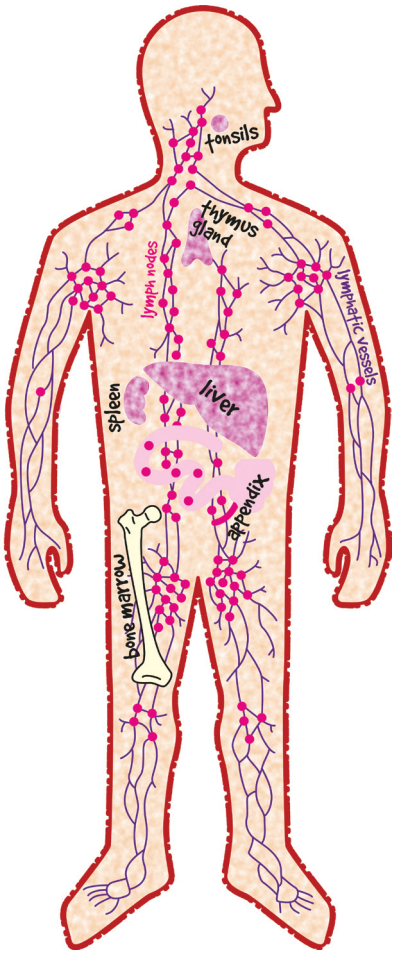

Figure 2:
Lymph nodes are located in groups in the body. They are small glands that filter lymph, the fluid that circulates through the lymphatic system.

Other symptoms
A variety of other symptoms have been reported. These include bone marrow failure, causing anaemia and vasculitis.

Children often have an unremarkable childhood until primary-school age and exposure to the Epstein-Barr virus. This appears to trigger the development of symptoms, although the number and severity of symptoms is variable.

How is it diagnosed?

The most important step is recognising that there is a problem with the immune system and involving the right specialists to investigate and treat further. Diagnosis depends on the recognition of suggestive clinical features, along with blood tests. There are many conditions that can cause similar symptoms and it is important that careful evaluation is performed to exclude any of these.

Blood tests are the main form of diagnosis and will be used to measure the levels of SAP present in the blood. If SAP is found to be absent or in low level, the presence of a gene mutation will also be checked through a blood sample.

A sample (biopsy) of bone marrow may also be taken, along with small samples of lymph node tissue. Bone marrow is the spongy tissue inside bones and contains cells that produce white blood cells, red blood cells and platelets. Bone marrow aspiration is a procedure that involves using a syringe to aspirate (‘suck out’) liquid bone marrow, usually from the hip bone. If there are neurological symptoms, such as headache, vomiting, irritability, visual disturbances or seizures, a sample of cerebrospinal fluid may be taken by lumbar puncture.

How is it treated?

As XLP is such a rare disease, treatment is usually coordinated by a specialist centre experienced in treating rare immune disorders. There are two specialist centres in the UK that treat children with XLP1 – Great Ormond Street Hospital in London, and the Great North Children’s Hospital in Newcastle.

The aim is to give enough treatment to control the overactive lymphocytes without losing protection against infection, while avoiding other side effects. Some people affected by XLP1 are more likely to develop infections than normal and may benefit from regular (prophylactic) antibiotics and immunoglobulin replacement. ‘Live’ vaccines should be avoided. In many cases, an inactive form of a vaccine is available.

If lymphoproliferation is severe, giving immunosuppressant medications to dampen down (suppress) the immune system may be helpful. These medications reduce the overreaction and lessen the risk of tissue damage. Suppressing the immune system often involves courses of corticosteroids and chemotherapy medicines, usually given into a vein (intravenously) in hospital.

This treatment usually puts the condition into 'remission' but does not offer a cure. The only definite 'cure' for XLP at present is a haematopoietic stem cell transplant (HSCT), where the bone marrow is replaced with donated stem cells that do not contain the overactive immune cells.

What does this mean for the future?

The outlook for children with XLP1 is improving all the time, owing to better recognition of the condition and improved diagnostic testing so that treatment can be started as quickly as possible. New types of medicine are also being developed to treat HLH more effectively and with fewer side effects. HSCT is currently the only cure for XLP1 but researchers are working hard to develop gene therapy as an alternative.

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

Is there a support group?

The XLP Research Trust offers support and advice to families affected by XLP 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**

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 leaflet *How to become a bone marrow donor* can be obtained from Anthony Nolan 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.

biopsy surgical removal of a small sample of tissue for examination under a microscope for diagnostic purposes.

bone marrow transplantation *see* haematopoietic stem cell transplant (HSCT).

Epstein-Barr virus the extremely common virus that causes glandular fever. It is part of the herpes family of viruses and is passed on through contact with bodily fluids, including saliva.

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.

haematopoietic stem cell transplant (HSCT) the transfer of stem cells from a donor – either related or unrelated – to a recipient. Stem cells may be obtained from bone marrow (from the hip bone – this is also known as bone marrow transplantation), peripheral blood (PBSCs), or from 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, curing the immunodeficiency.

haemophagocytic lymphohistiocytosis (HLH) a rare immune disorder where the body reacts inappropriately to a 'trigger', usually an infection.

hypogammaglobulinaemia low levels of immunoglobulin in the bloodstream.

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.

immunosuppressants medications that suppress or 'dampen down' the immune system; used to suppress inflammation and autoimmunity.

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.

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.

lymphoma a cancerous growth of lymphocytes.

lymphoproliferation excessive numbers of lymphocytes, causing enlarged lymph nodes, liver and spleen, and sometimes affecting other organs.

macrophage a type of cell that engulfs and digests microbes, damaged or dead cells. They also take part in the anti-inflammatory response to decrease immune reactions.

mutation a change in the structure of a gene or group of genes. When they occur in the germline (eggs/sperm), 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 viral infections and protecting against cancer.

proliferation excessive production or reduced destruction.

signalling lymphocyte activation molecule associated protein (SAP) the protein affected in XLP1.

T-cells (or T-lymphocytes) lymphocytes that develop in the thymus, an organ in the chest. They are important players in the immune response.

vasculitis inflammation of blood vessels.

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 one to compensate for the faulty one. Boys inherit one X chromosome and one Y chromosome, so the effects of the faulty X chromosome are not cancelled out.

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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