HIGM
syndromes

Hyper immunoglobulin M syndromes

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Supporting families affected by primary and secondary immunodeficiency

About this booklet

This booklet provides information on hyper immunoglobulin M (HIGM) syndromes. It covers the most common form, CD40 ligand deficiency (also known as X-linked HIGM), and rarer forms of this primary immunodeficiency, such as CD40 deficiency, HIGM with ectodermal dysplasia, AID deficiency and UNG deficiency. The information has been produced by the Immunodeficiency UK Medical Advisory Panel and Patient Representative Panel to help answer the questions patients and their families may have about these conditions. It should not, however, replace advice from a clinical immunologist.

Contents

Hyper immunoglobulin M syndromes (HIGM)
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Summary

Hyper immunoglobulin M (HIGM) syndromes are a group of conditions that affect how the body's immune system makes antibodies and fights infections. People with an HIGM condition are unable to make protective antibodies and therefore become susceptible to frequent and recurrent infections.

Antibodies are specialised immune proteins, also known as immunoglobulins. They are normally found in the blood and body fluids. There are three major types of immunoglobulin.

- **Immunoglobulin G (IgG)** is the most abundant and common immunoglobulin, found in blood and tissue fluids. IgG functions mainly against bacteria and some viruses.
- **Immunoglobulin A (IgA)** is found in blood, tears and saliva, and protects the tissues of the respiratory, reproductive, urinary and digestive systems.
- **Immunoglobulin M (IgM)** is found in the blood and functions in much the same way as IgG, but it is formed earlier in the immune response.

Antibodies are made by a type of white blood cell called B-cells (sometimes referred to as B lymphocytes). A normal immune system relies on complex interactions between B-cells, the different antibodies that they produce and other cells of the immune system (e.g. T-cells or T lymphocytes) to protect us from getting infections. In HIGM conditions there are low levels of some antibody classes (IgG and IgA) with normal or raised levels of IgM.

Different genetic causes (variants) can lead to HIGM, and five different forms of HIGM have been identified to date. These include CD40 ligand deficiency, also known as X-linked HIGM (the most common form), CD40 deficiency, HIGM with ectodermal dysplasia, AID deficiency and UNG deficiency. The genetic variants can affect how B-cells work to make protective antibodies, and how B-cells work with T-cells to help the immune system work properly. They are inherited conditions, have different inheritance patterns and affected families should receive genetic counselling.

Type	Gene affected	Inheritance pattern	Affects
CD40 ligand deficiency (X-linked HIGM)	CD40 ligand	X-linked recessive	Males only
CD40 deficiency	CD40	Autosomal recessive	Males and females
HIGM with ectodermal dysplasia	NEMO-IKKγ	X-linked recessive	Males only
AID deficiency	AID	Autosomal recessive	Males and females
UNG deficiency	UNG	Autosomal recessive	Males and females

Common symptoms are frequent and severe infections in infancy and early childhood. As a number of different cells are involved, a range of common infections are seen, as well as more unusual infections (known as opportunistic infections). Common infections include chest infections (including opportunistic infections such as pneumonia caused by Pneumocystis jirovecii), sinus infections (sinusitis) and ear infections (otitis). Infections often cause the individual affected to have chronic diarrhoea and he/she may fail to gain weight and grow at the expected rate, known as failure to thrive.

The mainstay of treatment is replacement immunoglobulin and antibiotics. Haematopoietic stem cell transplantation, such as a bone marrow transplant, should be considered for patients. Many people affected lead normal, healthy lives, provided they receive adequate replacement immunoglobulin and appropriate treatment for infections.

How did I get HIGM?

Different faulty genes are linked to the various types of HIGM. They are inherited, passed down to other generations, in different ways. You can find information on the different patterns of inheritance below and on the Immunodeficiency UK website at **www.immunodeficiencyuk.org**.

CD40 ligand deficiency, also known as X-linked HIGM, is inherited in an X-linked recessive pattern. CD40 ligand deficiency is caused by variants in the CD40 ligand gene (also known as CD154). This gene encodes the instructions to make a protein called CD40 ligand found on the surface of T-cells. The protein CD40 ligand is essential for T-cells to interact with other cells of the immune system, such as B-cells, which are involved in making antibodies. CD40 ligand is important in enabling T-cells to mature and carry out their functions with other cells of the immune system. In the absence of normal CD40 ligand, T-cells are unable to instruct B-cells to switch antibody production from IgM to IgG, IgA or IgE antibodies. Approximately 30 per cent of cases of CD40 ligand deficiency arise as 'new genetic faults' and in these cases there is no previous history of the disorder in the family.

CD40 deficiency is inherited in an autosomal recessive pattern. It is a B-cell defect caused by faults in the CD40 gene. This gene provides the instructions to make the protein CD40, which is present on the surface of mature B-cells and other cells of the immune system. The CD40 protein plays an important role in interacting with CD40 ligand on T-cells. The condition associated with CD40 deficiency is almost identical to CD40 ligand deficiency.

HIGM with ectodermal dysplasia (HIGM-ED) is an X-linked recessive disorder. The abnormality is caused by faults in the gene encoding NEMO-IKKγ, which is needed to activate an important signalling molecule, NFkB. Patients with HIGM-ED have skin and teeth abnormalities, thin or fine hair alongside other problems.

AID deficiency is inherited in an autosomal recessive pattern. It is a B-cell defect caused by faults in the gene-making instructions for the enzyme called activation-induced cytidine deaminase. This gene is involved in B-cells switching their antibody production from IgM to IgG, IgA or IgE. The other functions of T-cells related to CD40 ligand are not affected, so patients with AID deficiency are less likely to have opportunistic infections.

UNG deficiency is inherited in an autosomal recessive pattern. It is caused by faults in the gene giving instructions to make the enzyme uracil-DNA glycosylase. Similar to AID deficiency, patients affected are less likely to have infections caused by opportunistic organisms.

What are the symptoms of HIGM?

How the symptoms present depends on which genetic defect is causing the HIGM.

CD40 ligand deficiency

In CD40 ligand deficiency (X-linked HIGM) children usually become ill between the ages of six months and two years, once the protective antibodies they received from their mother during pregnancy have disappeared. If the underlying immunodeficiency is not spotted and treated appropriately, there can be a risk of permanent damage to the lungs, sinuses or ears.

Features that may lead to a diagnosis of CD40 ligand deficiency being considered include:

- severe and/or very frequent infections usually affecting the ears, throat and chest
- pneumonia known as Pneumocystis jirovecii pneumonia – common in infants with CD40 ligand deficiency
- enlarged tonsils, liver and spleen
- diarrhoea – one particular infection that causes diarrhoea and is commonly associated with CD40 ligand deficiency is Cryptosporidium parvum
- infections involving bones and joints, causing osteomyelitis (infection of the bone) or arthritis
- neutropenia – lack of white blood cells known as neutrophils, linked to the development of mouth ulcers
- anaemia
- inflammation and ulceration of the bottom (rectum), known as proctitis
- low platelet count (thrombocytopenia), leading to bruising
- enlarged lymph nodes – found in AID and UNG deficiency.

Infections in CD40 ligand deficiency are caused mainly by bacteria, but viruses, fungi and parasites may be involved. These include:

- Pneumocystis jirovecii – a fungal infection causing Pneumocystis jirovecii pneumonia
- Cytomegalovirus – a virus causing lung and bowel infections
- Cryptococcus – a fungus causing lung and brain infections
- Cryptosporidium – a parasite that causes bowel and gall bladder infection.

CD40 deficiency

The symptoms associated with CD40 deficiency are almost identical to CD40 ligand deficiency (X-linked HIGM) (as described above).

Ectodermal dysplasia

Ectodermal dysplasia with immunodeficiency (HIGM with ectodermal dysplasia) may be suspected in a patient with ectodermal dysplasia and recurrent infections, with normal or elevated IgM and low IgG, IgA and IgE levels.

AID deficiency and UNG deficiency

Generally patients with these conditions have recurrent bacterial infections and respond well to treatment with replacement immunoglobulin.

How is HIGM diagnosed and why can diagnosis take a long time?

Diagnosis of HIGM is based on the clinical symptoms and the results of testing. Although the name of this disorder might lead people to expect high levels of IgM, this is often not the case and not found in all patients.

CD40 ligand deficiency (X-linked HIGM) should be considered in any boy presenting with a reduction in all types of immunoglobulin (known as hypogammaglobulinemia). The most usual findings are low or absent levels of IgG and IgA (with either normal or high levels of IgM). Testing for CD40 ligand deficiency includes looking for the absence of CD40 ligand on activated T-cells. However, in some forms of CD40 ligand deficiency, CD40 ligand may be expressed at low levels and a definitive diagnosis depends on identifying the precise defect in the CD40 ligand gene using DNA analysis. In the UK this can be done at the London North East Thames Regional Genetic Centre at Great Ormond Street Hospital.

It is possible to analyse DNA from female family members to find out whether they are carriers of CD40 ligand deficiency and to offer a prenatal genetic diagnostic testing very early in pregnancy, should the family wish it.

AID deficiency or UNG deficiency are suspected if the patient has the characteristics of the X-linked form but is a female patient and/or has a normal CD40 ligand gene with normal expression on activated T-cells.

Associated health complications

Liver disease

There is a high rate of liver disease in HIGM. The most common form of liver disease in HIGM is sclerosing cholangitis and involves abnormalities of the bile ducts, which can progress to severe liver damage and liver failure. The cause is uncertain. It is likely that infection with cryptosporidium plays a role, but autoimmunity and infection with viruses may also be involved.

Chronic liver disease can progress to liver cancer. There is also an increased incidence of cancer in the gastrointestinal tract (the gut). Owing to the high rate of serious liver problems and cancer in CD40 ligand deficiency, haematopoietic stem cell transplantation is considered for all those affected and if successful can cure the immunodeficiency.

Autoimmune disorders

Autoimmune disorders may also occur in patients with HIGM. These may include arthritis, low platelet counts (thrombocytopenia), anaemia, hypothyroidism and inflammatory bowel disease.

Patients with AID deficiency or UNG deficiency also have an increased incidence of autoimmunity and lymph node enlargement.

Treatment

With all forms of HIGM, keeping well involves preventing infection and monitoring your health. In general, this entails:

- regular immunoglobulin replacement therapy, either subcutaneously or intravenously, to replace the missing IgG. This can sometimes result in a reduction or normalisation of the serum IgM level
- treatment with antibiotics to help resolve infections
- avoiding all live vaccines because these can be a source of infection. You must check with your doctor what vaccines are recommended
- monitoring your health to look out for signs of long-term damage to organs. This may mean regular assessments by ear, nose and throat specialists and respiratory specialists, as well as specialised scans to detect early signs of lung damage
- careful monitoring for signs of liver problems. This will involve having regular blood liver function tests, special X-rays and sometimes a liver biopsy

- paying careful attention to dental hygiene, because tooth decay can be a source of infection and ill health.

Patients with persistent neutropenia (low levels of the white blood cells called neutrophils) may need granulocyte colony stimulating factor treatment, which stimulates the bone marrow to increase neutrophil production.

Anaemia (low levels of red blood cells) and thrombocytopenia (low levels of platelets) may improve with higher doses of immunoglobulin.

In addition for CD40 ligand deficiency, preventing infection and monitoring your health includes:

- taking daily antibiotics (prophylaxis) to prevent pneumonia due to Pneumocystis jirovecii. This is especially used for affected infants with CD40 ligand deficiency as they are at high risk of developing Pneumocystis jirovecii pneumonia during the first two years of life. Typical prophylaxis is trimethoprim/sulfamethoxazole

- protecting against infection from cryptosporidium, a parasite sometimes found in water. You should contact the authorities responsible for your local water supply and ask if the water is safe and tested for cryptosporidium. If not, it is advised to boil all drinking water, or install a professionally fitted high performance (<1 micron) filter on domestic water supplies. Avoid bathing in rivers, lakes and pools.

Cure

Haematopoietic stem cell transplantation, such as a bone marrow transplant, can offer a permanent cure for people with CD40 ligand deficiency. Ideally it is performed prior to the onset of life-threatening complications and organ damage. Bone marrow transplantation has been used successfully in patients with CD40 ligand deficiency and CD40 deficiency. Significant advances are being made using matched unrelated donor transplants so that more people affected can be treated.

The need for transplantation is determined by the severity of the disease and the availability of a matched donor. For HIGM-ED, where there may be a severe T-cell involvement, bone marrow transplant may be considered.

Immunisation

No immunisations are necessary if a patient is on immunoglobulin replacement therapy. For others, live vaccines should be avoided. Talk with your clinical immunology team before receiving a vaccine.

Glossary of terms

anaemia a condition resulting from having fewer red blood cells than normal or where there is less haemoglobin than normal in each red blood cell.

antibody a type of protein (immunoglobulin) that is produced by certain types of white blood cells (plasma cells – a type of B-cell). The role of antibodies is to fight bacteria, viruses, toxins and other substances foreign to the body.

arthritis a condition that causes pain and inflammation in a joint.

autoantibody an antibody that attacks the body's own tissues.

autoimmune/autoimmunity when an individual's immune system attacks the body's own tissues or vessels.

autosomal recessive a type of inheritance where the presence of one copy of a faulty gene does not affect the individual. 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-cell a type of white blood cell (lymphocyte) that produces antibodies.

cryptococcus a fungus causing lung infections.

cryptosporidium a parasite found in faeces and sewage-contaminated water.

cytomegalovirus a virus causing lung and bowel infections.

deficiency a lack or shortage.

ectodermal dysplasia a group of closely related conditions that affect the development or function of the teeth, hair, nails and sweat glands.

enzyme a protein that carries out biological reactions in the body.

genetic analysis a study of the genetic code (DNA) that makes genes.

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 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 from stored umbilical cord blood. The donor stem cells replace the recipient's bone marrow, giving him/her a new immune system and curing the immunodeficiency.

hypogammaglobulinemia a condition where the blood has abnormally low levels of immunoglobulins (antibodies) that help fight infection.

hypothyroidism the name given to the condition resulting from an underactive thyroid gland. This means that it is not producing enough thyroid hormone for the body's needs.

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 a plasma-based treatment. The immunoglobulin contains antibodies that help fight infection. This treatment can be given through a vein or through the skin.

immunoglobulins proteins (globulins) in the body that act as antibodies. They work to 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.

inflammatory bowel disease the name of a group of disorders in which the intestines (small and large intestines or bowels) become inflamed (red and swollen).

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

intravenous inside or into a vein; e.g. an immunoglobulin infusion may be given directly into a vein.

ligand a substance that forms a complex with another molecule to serve a biological purpose.

live virus vaccine a vaccine that uses a weakened (or attenuated) form of a virus. Examples are the chickenpox and MMR vaccines.

lymph nodes small, bean-sized organs of the immune system distributed widely throughout the body. They are the home for the many types of cells that are important in fighting infections.

neutropenia a low level of neutrophils, a type of white blood cell.

opportunistic infection an infection caused by bacteria, viruses, fungi or protozoa that take advantage of an opportunity not normally available, such as in people with a weakened immune system.

organism a single-celled life form; e.g. a bacteria, virus or fungus. It can also mean an individual plant or animal.

otitis media inflammation or infection of the ear.

plasma the liquid component of blood without the cells (but with all the proteins).

plasma cell a specific type of B-cell that is found within the bone marrow or lymph nodes. Plasma cells are responsible for the majority of high-quality antibody production.

platelet a blood cell that works to prevent bleeding in the body by producing blood clots.

pneumocystis jirovecii a fungal infection causing Pneumocystis jirovecii pneumonia.

pneumonia a swelling (inflammation) of the tissue in one or both of the lungs. It is usually caused by an infection.

prenatal genetic 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 form of prenatal diagnosis.

primary immunodeficiencies (PIDs) a group of more than 300 rare, chronic disorders in which part of the body's immune system is missing or functions improperly. Distinguished from secondary immune deficiencies, which are caused by other factors such as drugs or concurrent disease.

protein one of the basic building blocks of life. Proteins make up the structure and determine the function of the cells that make up all the tissues of our body.

sclerosing cholangitis swelling (inflammation), scarring and destruction of the bile ducts inside and outside of the liver.

sinuses air-filled space within the bones of the face and around the nose. Infection of the sinuses is called sinusitis.

subcutaneous under the skin; e.g. an immunoglobulin infusion may be given under the skin in the lower stomach or thigh.

T-cell a type of white blood cell (lymphocyte) that helps the immune system work properly to fight infection.

thrombocytopenia any condition with low platelets.

variant a change in the structure of a gene or group of genes. Such changes can be passed on to the next generation. Many variants cause no harm, but others can cause genetic disorders such as primary immune deficiencies.

X-linked refers to the inheritance of disorders caused by variants 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.

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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.

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