

X-linked Agammaglobulinaemia

Summary

X-linked agammaglobulinaemia (XLA also known as Bruton's agammaglobulinaemia), is the name for a condition that affects the body's ability to make antibodies and fights infections. It belongs to a group of conditions known as antibody deficiencies. XLA affects only boys and its features include repeated episodes of bacterial infections affecting the ears, sinuses, nose, eyes, skin and the gastrointestinal tract. It is a rare condition with about 5 – 10 people in a million affected.

Antibodies belong to a particular type of protein, called immunoglobulin, normally found in blood and body fluids. There are three major types of immunoglobulin, known as:

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

All types are made up of antibodies against the germs that an individual has met during the course of their life.

Antibodies are made by white blood cells called B lymphocytes or sometimes referred to as B-cells. In XLA there are genetic changes known as mutations in the Bruton's tyrosine kinase (BTK) gene. These mutations block the development of normal, mature B-cells that would normally make antibodies. As a result, people with XLA have very few mature B-cells and cannot make immunoglobulins; that is, the antibodies that are needed to protect the body against infections.

The aim of treatment in XLA is to replace the missing or defective antibodies with purified immunoglobulins from the blood of healthy donors, in order to reduce the frequency and severity of infections. Although not a cure for XLA, immunoglobulin replacement therapy is often enough to keep patients healthy so that those affected can lead full and relatively normal lives. Children with XLA should take part in regular school activities, including exercise, and do not need to be limited in what they can do. It is important for the school to be aware of the diagnosis.

Antibiotics are often needed to treat breakthrough bacterial infections that will occur from time to time. A few individuals may need to take antibiotics every day to protect them from infection or to treat chronic sinusitis or chronic bronchitis. Patients with bronchiectasis (widening and scarring of bronchial airways) may need help from a physiotherapist to help clear their airways.

How did I/my child get XLA?

XLA is caused by mutations in the BTK gene that is present on X chromosomes. The BTK gene makes the enzyme Bruton's tyrosine kinase, which is needed to instruct B-cells to mature and produce antibodies.

More than 600 different mutations in the BTK gene have been found to cause XLA. Most mutations result in the absence of the BTK enzyme or an abnormal BTK protein that is quickly broken down in the cell. Without functional BTK enzyme there is no development of B-cells – and so a lack of antibodies – and this results in an increased susceptibility to bacterial infections.

It is an inherited condition meaning it is passed down through the generations. It follows what is called an X-linked recessive pattern of inheritance with transfer of a defective gene on one of the two X chromosomes of a mother to a son. This means that for every boy that is conceived to a carrier mother there is a 50/50 chance that they will have XLA. This has implications for family planning. Mothers, their maternal aunts and sisters may be carriers and should receive genetic counselling. Daughters that are born to carrier mothers should also be tested once they are old enough to give informed consent as there is a 50/50 chance they might carry the faulty gene.

Affected fathers can have carrier daughters but their sons will not be affected by XLA or be carriers of the condition.

Family planning and XLA

Prenatal genetic diagnosis is available for families in which XLA has already been diagnosed and your health team will be able to refer you for advice about the risks of prenatal testing.

What are the symptoms of XLA?

Boys with XLA develop bacterial infections because they lack protective antibodies. Infections usually affect those surfaces that are exposed to bacteria, such as the tissue surfaces that line the lung and gut.

In XLA serious bacterial infections may occur, such as meningitis or pneumonia. Such infections usually begin in infancy or early childhood, typically at six to nine months of age when the protective antibodies that have been passed from the mother to the unborn child via the placenta, are broken down. This leaves an affected boy with no antibodies for fighting infections.

People with XLA may have repeated, severe or persistent infections. Here are some common features that you may recognise and that may have led your clinician to a diagnosis of XLA:

- Sinusitis – inflammation of the air-filled spaces (paranasal sinuses) that surround the nose
- Inner ear infections such as otitis media
- Throat infections such as tonsillitis or laryngitis
- Chest infections such as bronchitis and pneumonia
- Stomach and intestinal infections including giardiasis (a parasitic infection) resulting in persistent diarrhoea or weight loss
- Skin infection, such as abscesses, boils
- Eye infections such as conjunctivitis
- Urinary tract infection (cystitis)

- Meningitis
- Joint infections (osteomyelitis)
- Blood poisoning (septicaemia)
- Very small/absent tonsils and lymph nodes (the glands in the neck) may be a physical sign of XLA, since these are the sites where the B-cells would normally be present.

What are the common causes of infection in XLA?

Infections affecting the lung, ear and sinuses are commonly caused by these organisms:

Streptococcus pneumoniae
Haemophilus influenzae
Staphylococcus aureus

and infections in the gut by:

Campylobacter
Salmonella
Giardia

People with XLA are usually able to cope with most viral infections, including measles and chicken pox, without any problems. In rare cases enteroviruses, such as polio, can cause serious infection but this is uncommon for those on adequate replacement immunoglobulin therapy.

How is XLA diagnosed?

Antibody deficiency will be considered in individuals presenting with repeated, severe or persistent infections. These individuals will usually be referred to a specialist for further assessment, following which an immunologist should be consulted.

Making the diagnosis

A clinical immunologist usually makes the diagnosis of XLA.

Diagnosis is confirmed by blood tests. Tests may be intensive at the beginning of this investigative process.

- The level of IgG, IgA and IgM
- The function of any antibodies that are present, to see how well they react to microbes, if at all (unlikely in XLA). This is done by test immunisations using safe dead or fragmented organism vaccines
- How many lymphocytes (the white blood cells involved in immunity) there are in the blood
- How many B-lymphocytes are present in the blood, as well as the other major type of lymphocytes (needed to fight viruses) known as T-cells. In XLA, mature B-cells are not present in blood but T-cell levels will be normal.

A definite diagnosis is made by looking for mutations in BTK gene using genetic analysis. When a specific defect is found, the doctors will often test female members of the family to diagnose those who carry the abnormal X-chromosomes.

Treatment

At present there is no cure for XLA but affected boys can grow up to lead normal productive lives if they keep to the treatments recommended and have regular check ups with an immunologist.

The main treatment for XLA is replacing the missing antibodies using immunoglobulin (Ig) replacement therapy. This treatment can be given intravenously (dripped into a vein through a needle in the arm or hand) or subcutaneously (injected under the skin in the lower stomach or thighs). This treatment is usually needed every week for subcutaneous therapy or every 2-4 weeks for intravenous therapy, depending on the individual. The dose is monitored by looking at how well the treatment protect against infections, since adequate therapy reduces the rate and severity of bacterial infections and may prevent them entirely. The doctor will also do blood tests periodically (typically every 3-6 months, although this may be more frequent depending on your centre's local policies) to check levels of IgG and for any possible complications.

Additional treatments focus on taking steps to reduce the number and severity of infections. This includes prompt long-term treatment with broad-spectrum antibiotics or more specific antibiotics if the bugs causing the infection are known. If lung problems have developed such as bronchiectasis, where the airways of the lungs become abnormally widened leading to a build-up of excess mucus, physical therapy such as physiotherapy and specific exercises may be needed to remove the mucus from the lung airways.

Are there any associated health problems with XLA and how will my/my child's health be monitored?

Yes some people with XLA, but not all, may have or may develop other health problems. Monitoring is usually by clinical review (check up), infrequent blood tests and for some people tests of breathing function.

Your clinical immunologist will be on the look out for the complications and will work with other clinical specialists to offer you the most appropriate advice and treatments.

Lung and sinus problems

If chronic lung or sinus disease, such as bronchiectasis, has developed before diagnosis, those affected may have a reduced ability to exercise. Your doctor may refer you for 'lung function tests'. These are tests that measure how well your lungs are working. You may be referred to a physiotherapist and specific exercises may be recommended to remove the mucus from the lung airways to improve your lung health. People with chronic sinus disease may be referred to an Ear, Nose and Throat specialist for advice on other treatments, including physical treatments, to reduce the risk of further sinus damage.

Painful joints and arthritis in XLA

Joint disease (arthritis) usually affecting the knees can occur. This usually only occurs in individuals not receiving Ig replacement therapy and is thought to be related to infection with enteroviruses and Mycoplasma.

Gut problems in XLA

Inflammatory bowel disease (like Crohn's disease) can occur in XLA and is thought to be a complication of repeated, severe or persistent bowel infection.

Other problems

Sometimes a condition known as neutropenia – a reduction in the number of neutrophils (a type of white blood cell) – may happen. This is usually temporary and is only seen in individuals not receiving Ig replacement therapy.

Immunisation

Not all vaccines are safe to be administered to patients with XLA and therefore you should discuss any recommended or required vaccinations with your clinical immunology team, before a vaccine is given.

This patient information was reviewed by the PID UK Medical Advisory Panel and Patient Representative Panel (May 2014; review date May 2015).

About Primary Immunodeficiency UK

Primary Immunodeficiency UK (PID UK) is a national organisation supporting individuals and families affected by primary immunodeficiency (PIDs).

Our website 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. Visit www.piduk.org for further information.

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