IgG deficiencies

IgG subclass deficiencies

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IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this booklet

This booklet provides information on IgG subclass deficiencies. It 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 this condition but should not replace advice from a clinical immunologist.

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Summary

Immunoglobulin G (IgG) is the main type of immunoglobulin (also called antibody) in the blood that helps the body to fight bacterial infections and prevent viral infections. It is made up of four different types called IgG subclasses, known as IgG1, IgG2, IgG3 and IgG4. These have different roles in the body in fighting infection. Having one or more of these subclasses missing may result in IgG subclass deficiency – a group of conditions where there is a low level of one or more of the IgG subclasses in the blood, but where measured levels of all the major immunoglobulins (IgA, IgM and also, frequently, the total amount of IgG itself) are normal. IgG subclass deficiency may also occur in conjunction with IgA deficiency. IgG subclass deficiencies belong to a family of conditions known as primary antibody immunodeficiencies.

People with IgG subclass deficiency may suffer from infections or may be completely healthy. Infections may be recurrent and mainly involve the respiratory system, usually the ears, nose and throat, but the severity of symptoms varies widely from patient to patient. In some people, low levels or even complete absence of an IgG subclass is not associated with any increased incidence of infection. In others, a low IgG1, IgG2 or IgG3 subclass level may be the only detectable abnormality in the context of a significant history of infections. This has led to a continuing debate and uncertainty among immunologists about the significance of individual IgG subclass deficiencies.

IgG subclass levels are lower in children and levels increase naturally to normal over time without the need for medical intervention. Diagnosis of clinically significant IgG subclass deficiency depends on careful evaluation of individuals and their test results, including how well the patient's immune system responds to different types of vaccines (immunisation).

The outlook for patients with selective IgG subclass deficiency is generally good. Low IgG subclass levels in children are very likely to improve with age and return to normal by around the age of 10–12 years. Treatment (where necessary) in most children requires only occasional use of antibiotics to clear infections as they occur; in more severe infections, antibiotics are used on a continuous basis to prevent infections taking hold. For patients with a persistent deficiency and significant documented infections, immunoglobulin replacement therapy may be used in certain circumstances to prevent serious infections and complications, such as impaired lung function, hearing loss or injury to other organ systems.

In occasional cases, particularly where there is associated IgA deficiency, selective IgG subclass deficiency may develop or evolve into a more serious kind of antibody deficiency, such as common variable immune deficiency (CVID). It is not yet possible to tell which patients will have the transient type of subclass deficiency and which patients may later develop a more significant immunodeficiency. For these reasons doctors will want to evaluate a patient's immunoglobulin levels and their function regularly and over a lengthy period.

How did I get IgG subclass deficiency?

The cause of IgG subclass deficiency is not known and there is no clear-cut pattern of inheritance.

Family history may play a part. In some families there is more than one individual affected by IgG subclass deficiency, or there may be other family members with selective IgA deficiency. In a very small proportion of patients there is complete absence of an individual IgG subclass as a result of a deletion of a part of the relevant gene complex on chromosome 14, which is involved in the manufacture of immunoglobulins; this is very rare, and is not necessarily associated with increased susceptibility to infection. It is more typical simply to find lower levels than usual, implying that the gene is present but does not function normally.

What are the symptoms of IgG subclass deficiency?

The symptoms you may recognise and which may have led your doctor to a diagnosis of IgG subclass deficiency are those associated with recurrent respiratory infections.

These usually affect the upper airways and include infections of the:

- Throat
- Ear
- Sinuses, causing sinusitis.

In some cases infections can also occur in the lower respiratory tract (lungs).

What causes infection in IgG subclass deficiency?

Common infections in IgG subclass deficiency are due to:

- Viruses
- Encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (which may in some cases cause severe lung infections).

In patients with low IgG subclass levels symptoms are usually milder than in those with other types of antibody deficiency (e.g. CVID or X-linked agammaglobulinemia (XLA)).

How is IgG subclass deficiency diagnosed?

The diagnosis is made using a sample of the patient's blood. In general the diagnosis is not straightforward and involves blood tests for levels of IgG, IgA and IgM as well as immunisation with protein and polysaccharide (types of sugar) vaccines. Measurement of IgG subclass levels is not usually undertaken as part of the initial evaluation in patients with recurrent infections.

To diagnose IgG subclass deficiency the clinical immunologist will test the total immunoglobulin levels (IgG, IgA and IgM). If these are all normal, but there is still concern about the frequency or severity of infections and no other explanation has been found, then the levels of IgG subclasses (IgG1, IgG2, IgG3 and IgG4) may be measured. If a low level of IgG subclass is found, your doctor may need this test to be repeated at least once as levels of IgG subclasses can vary from time to time. In patients with IgA deficiency who have more severe infections than expected, IgG subclasses may be measured since there is an association between deficiencies of IgA and IgG2.

Further tests are needed if an IgG subclass deficiency is suspected to help confirm fully a diagnosis of immunodeficiency. These include a careful and detailed history and further laboratory investigations, such as important tests to check how the immune system reacts and makes specific immunoglobulins (or antibodies) in response to different types of vaccines.

To do this the doctor will look at your immune responses to proteins (e.g. by vaccination against tetanus). The doctor will look for the presence of antibodies in your blood against the protein.

Most patients with selective IgG subclass deficiency make normal responses to protein vaccines. A polysaccharide vaccine such as Pneumovax® is used for older children and adults. This approach has become complicated because the national childhood immunisation schedule now includes vaccination against *Streptococcus pneumoniae* with a newer vaccine (called Prevenar®) that does not rely on polysaccharide responses. In vaccinated children this means that polysaccharide responses cannot be easily assessed using Pneumovax®. In patients in whom it is considered important to establish if they can make a polysaccharide response there are other polysaccharide vaccines that can be used, such as Salmonella. Demonstration of poor antibody responses to polysaccharide antigens in an individual with an IgG subclass deficiency (particularly IgG2 deficiency, with or without IgA deficiency) may imply a more significant degree of immune deficiency and in a few cases may be the forerunner to development of CVID.

Treatment

Treatment of IgG subclass deficiency depends on the severity of the symptoms. In many cases no regular treatment of any kind is needed. If infections are mild and infrequent, and the person's quality of life is not significantly affected, treatment can be limited to the early use of antibiotics when an infection occurs. In such cases it may be reasonable to keep a supply of antibiotics at home, which can be started when symptoms develop.

If infections are more severe and/or are occurring frequently and time is being lost from work or school, or in the case of a child if growth and/or development is being affected, then regular low dose (prophylactic) antibiotics may be introduced to prevent development of infections. In many patients this is very successful. If there are recurrent bacterial infections, appropriate antibiotics should be chosen according to the sensitivities of the organisms isolated on culture. Additional immunisation with pneumococcal vaccines may also be used to enhance immunity.

What happens if I have severe symptoms?

A very small subgroup of patients with IgG subclass deficiency who have severe symptoms or serious infections that are not controlled by antibiotic prophylaxis may justify a test trial of immunoglobulin replacement therapy. These patients usually have other associated abnormalities, such as IgA deficiency and/or defective specific antibody production to vaccines.

The decision to begin immunoglobulin replacement therapy for patients remains controversial. It involves careful consideration by clinical immunologists and is not commonly used. Indications for this treatment are persistently low IgG subclass levels, deficient antibody responses to vaccines, and clearly recorded evidence of failure to control infections using antibiotic prophylaxis. Usually therapeutic immunoglobulin is given as an initial trial for a full year (to avoid seasonal variation of infections), with rigorous monitoring to confirm if it is working well.

A small minority of patients affected by IgG subclass deficiency may progress and develop CVID. Those with sufficiently severe clinical problems and immunological abnormalities to justify immunoglobulin therapy may be more likely to progress and your doctors will monitor this carefully.

Children and IgG subclass deficiency

Low levels of IgG subclasses in children are very likely to improve with age, and in many cases will return to normal with time. For this reason, measurement of IgG subclasses in children is undertaken only in exceptional circumstances. Treatment in most children requires only intermittent or prophylactic antibiotics. If immunoglobulin therapy is started it is essential that the need for this treatment is re-evaluated after a period. This may include a trial period when immunoglobulin treatment is stopped, and this usually takes place during the summer months. Doctors will carefully monitor your child clinically and also reassess their IgG subclass levels after 3–6 months of treatment. In many cases the deficiency will have resolved and treatment will no longer be needed.

Immunisation

Most vaccines are safe to be administered to patients with low IgG subclass levels, provided that other tests of immune function are normal. The infant and childhood vaccination schedule can be followed as normal. Vaccinations required in adulthood can be discussed with your clinical immunology team.

If immunoglobulin therapy is started, no further routine infant or childhood immunisations should be given while this treatment continues. If immunoglobulin treatment is subsequently stopped, the doctor will want to do more tests of immunity to organisms in the routine immunisation schedule (e.g. tetanus). Using this information doctors will decide what catch-up and/or booster vaccines are needed.

Glossary of terms

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.

B-cell – a type of white blood cell (lymphocyte) that produces antibodies.

chromosome – a long threadlike strand of DNA that carries a set of genes. Normally humans have 23 pairs of chromosomes.

common variable immune deficiency (CVID) – a primary antibody deficiency. People with CVID have either no immunoglobulins in the blood or low levels and require immunoglobulin replacement therapy on a regular basis.

deficiency – a lack or shortage.

encapsulated bacteria – a special type of bacteria covered by a coating of complex sugars. This makes these bacteria harder to be treated by antibiotics. Encapsulated bacteria can be a major cause of respiratory infections.

gene – the fundamental unit of inheritance that carries the instructions for how the body grows and develops.

immune deficiency – when the immune system's ability to fight infectious disease is compromised or entirely absent.

immune response – the processes that protect the body against infection and disease.

immunoglobulin level – a measurement of how much immunoglobulin you have.

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.

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

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.

lymphocyte – a white blood cell that works to fight infection in the body. One type of lymphocyte is called a 'B-cell'. This type of lymphocyte makes antibodies.

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

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

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

polysaccharide vaccine – a vaccine that works against encapsulated bacteria.

primary antibody deficiency – covers a range of disorders resulting from the failure of the immune system to produce sufficient antibodies in the bloodstream to fight infections.

prophylactic/prophylaxis – something that works to defend or protect against 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 bodies.

respiratory tract – the airway passage involved in breathing that leads from the mouth/nose to the lungs.

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

transient – something that happens for a short period of time and then goes away.

X-linked agammaglobulinemia (XLA) – a condition that affects the body's ability to make antibodies and fight infections. It belongs to a group of conditions known as primary antibody deficiencies. It is also known as Bruton's agammaglobulinemia.

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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