

## **IgG subclass deficiencies**

### **Summary**

Immunoglobulin G (IgG) is the main type of immunoglobulin (also called antibody) in the blood, which 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 amongst immunologists about the significance of individual IgG subclass deficiencies.

IgG subclass levels are lower in children and levels increase naturally to normal levels 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 subclasses in children are very likely to improve with age and return to normal by around the age of 10-12. Treatment (where required) 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, the use of immunoglobulin replacement therapy may be given 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 of IgG subclass deficiencies because the cause of IgG subclass deficiency is not known.

Family history may play a part. In some families there is more than one individual affected by an IgG subclass deficiency, or there may be others in the family 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 usual 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 that 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. Common Variable Immune deficiency (CVID) or X-linked Agammaglobulinaemia (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 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 that 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. This includes 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 doctors will look at your immune responses to proteins (for example by vaccination against Tetanus). The doctor will look for the presence of antibodies in blood against the protein. Most patients with selective IgG subclass deficiencies make normal responses to protein vaccines.

A polysaccharide vaccine such as Pneumovax® II is used for older children and adults. This approach has become complicated because the national childhood immunisation schedule now includes vaccination against Streptococcus pneumonia with a newer vaccine, called Prevenar® 13, that does not rely on polysaccharide responses. In vaccinated children this means that polysaccharide responses cannot be easily assessed using Pneumovax® II. 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 (Ig) 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 Ig 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 deficiencies 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 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 only undertaken 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 re-assess IgG subclass levels after 3-6 months off 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.

*This patient information was reviewed by the PID UK Medical Advisory Panel and Patient Representative Panel (November 2014; review date November 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](mailto:hello@piduk.org) or on 0800 987 8986 where you can leave a message. Visit [www.piduk.org](http://www.piduk.org) for further information.

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