

# IgG Subclass Deficiency



## Chapter 5

*The main immunoglobulin (Ig) in human blood is IgG. This is the second most abundant circulating protein and contains long-term protective antibodies against many infectious agents. IgG is a combination of four slightly different types of IgG called IgG subclasses: IgG1, IgG2, IgG3 and IgG4. When one or more of these subclasses is persistently low and total IgG is normal, a subclass deficiency is present. Although this deficiency may occasionally explain a patient's problems with infections, IgG subclass deficiency is a controversial diagnosis and experts disagree about the importance of this finding as a cause of repeated infections.*

*The misdiagnosis of IgG subclass deficiency as a cause of presumed immunodeficiency is common, often leading to the unnecessary long-term use of Ig replacement therapy. A subclass deficiency needs to be considered and looked for only under special circumstances discussed in this chapter.*

## Definition of IgG Subclass Deficiency

Antibodies are also called immunoglobulins. There are five types or classes of immunoglobulin: IgG, IgA, IgM, IgD and IgE. (See chapter titled "The Immune System and Primary Immunodeficiency Diseases.") Most of the antibodies in the blood and the fluid that surround the tissues and cells of the body are of the IgG class. The IgG class of antibodies is composed of four different subtypes of IgG molecules called the IgG subclasses. These are designated IgG1, IgG2, IgG3 and IgG4.

Patients with persistently low levels of one or two IgG subclasses and a normal total IgG level have a selective IgG subclass deficiency.

While all the IgG subclasses contain antibodies to components of many disease-causing bacteria and viruses, each subclass serves a slightly different function in protecting the body against infection. For example, IgG1 and IgG3 subclasses are rich in antibodies against

proteins such as the toxins produced by the diphtheria and tetanus bacteria, as well as antibodies against viral proteins. In contrast, IgG2 antibodies are predominantly against the polysaccharide (complex sugar) coating (capsule) of certain disease-producing bacteria (such as, *Streptococcus pneumoniae* and *Haemophilus influenzae*).

The IgG in the bloodstream is 60-70% IgG1, 20-30% IgG2, 5-8% IgG3 and 1-3% IgG4. The amount of the different IgG subclasses present in the bloodstream varies with age. For example, IgG1 and IgG3 reach normal adult levels by 5-7 years of age while IgG2 and IgG4 levels rise more slowly, reaching adult levels at about 10 years of age. In young children, the ability to make IgG2 antibodies to the polysaccharide coatings of bacteria develops more slowly than the ability to make antibodies to proteins.

## (Definition of IgG Subclass Deficiency continued)

IgG subclass deficiencies affect only IgG subclasses (usually IgG2 or IgG3), with normal total IgG and IgM immunoglobulins and other components of the immune system being at normal levels. These deficiencies can affect only one subclass or involve an association of two subclasses, such as IgG2 and IgG4.

IgG2 or IgG3 deficiencies are the most common IgG subclass deficiencies. Since IgG1 comprises 60% of the total IgG level, deficiency of IgG1 usually drops the total IgG level below the normal range, resulting in hypogammaglobulinemia.

IgG4 is present in very low levels in children younger than 10 years of age, so IgG4 deficiencies are not usually diagnosed before age 10. IgG4 may be undetectable in the serum of many “normal” adult individuals, and therefore low IgG4 alone is insufficient evidence of an antibody deficiency disorder requiring Ig replacement.

All patients with IgG subclass deficiency require more extensive diagnostic evaluation including the

demonstration of a poor antibody response to vaccine challenge before the patient is diagnosed with a clinically significant IgG subclass deficiency necessitating specific treatment that may include Ig replacement therapy.

IgG subclass deficiencies may be associated with other immunoglobulin abnormalities. One common pattern is IgG2 and IgG4 subclass deficiency associated with IgA deficiency. IgG subclass deficiencies are also an integral component of other well-known primary immunodeficiency diseases, such as Wiskott-Aldrich Syndrome and Ataxia-Telangiectasia.

IgG subclass deficiencies are sometimes associated with poor or partial responses to pneumococcal polysaccharides, specifically IgG2 deficiency with or without IgG4 deficiency. Recently, a number of inflammatory diseases, including some forms of pancreatitis, were found to be associated with an elevated IgG4 level. The causes for this elevation are not clear at this point.

## Clinical Presentations of IgG Subclass Deficiency

Patients with any form of IgG subclass deficiency occasionally suffer from recurrent respiratory infections similar to the ones seen in other antibody deficiency syndromes, chiefly infections with encapsulated bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae*. An increased frequency of viral upper respiratory infections may not be an indication of antibody deficiency. Therefore, it is critical to distinguish between infections caused by respiratory viruses from those due to bacterial pathogens.

Often a child with IgG subclass deficiency will first come to a healthcare provider’s attention because of recurrent ear and/or sinus infections, but bronchitis and

pneumonia may also have occurred. The infections in patients with selective IgG subclass deficiency may not be as severe as infections in patients with more significant antibody and immunoglobulin deficiencies, such as Agammaglobulinemia or Common Variable Immune Deficiency (CVID).

However, a few patients with IgG subclass deficiency may appear very similar to patients with severe immunoglobulin deficiencies. Rarely, IgG subclass deficient patients may have recurrent episodes of bacterial meningitis or infections of the bloodstream (sepsis).

## Diagnosis of IgG Subclass Deficiency

Measurement of IgG subclass levels is not universally recommended as part of the evaluation of antibody mediated immunity in patients with recurrent or severe infections. Assessing IgG subclasses adds cost and is not always reliable so that all abnormal values need to be repeated at least once in a separate blood sample. When subclasses are measured, all four subclasses should be determined at the same time.

It is important to consider that IgG subclass levels vary up or down over time, and the normal ranges used in different laboratories also vary. The “normal range” values are usually defined as those values found in 95% of normal individuals of that person’s age. Unfortunately, some physicians and patients forget when using this range that 2.5% of normal individuals will then have values that fall below that “normal” range and 2.5% of normal individuals will have values above that range. (See chapter titled “Laboratory Tests.”) Therefore test values below the “normal range” may not necessarily indicate an abnormally low value, particularly if the value is only a small distance below the stated range.

The finding of an IgG subclass deficiency should prompt reevaluation over a period of months before determining

that the patient is truly immunodeficient. Subclass deficiencies need to be carefully interpreted taking into account the clinical status of the patient as well as the person’s ability to produce specific antibodies in response to vaccines.

Measurement of IgG subclasses can be recommended in the presence of known associated abnormalities, particularly if recurrent infections are also present.

These circumstances include:

- IgA deficient patients with recurrent infections to determine if there is an associated IgG2 and IgG4 subclass deficiency
- Wiskott-Aldrich and Ataxia-Telangiectasia patients at the onset of recurrent infections
- Specific Antibody Deficiency patients with normal total immunoglobulins

Another indication for evaluation could be confirmation of a prior diagnosis of IgG subclass deficiency made at another lab or clinic.

## Inheritance of IgG Subclass Deficiency

No clear-cut pattern of inheritance has been observed in the IgG subclass deficiencies. Both males and females may be affected. Occasionally, two individuals with IgG subclass deficiency may be found in the same family. In some families, IgG subclass deficiencies have been

found in some family members while other family members may have IgA deficiency or CVID. A partial gene deletion has been found in a few patients with IgG subclass deficiency.

## Treatment of IgG Subclass Deficiency

Recurrent or chronic infections of the ears, sinuses and lungs need comprehensive treatment to prevent permanent damage that might result in hearing loss or chronic lung disease. It is also important to encourage patients to continue normal activities of daily living, such as school or work.

The mainstay of treatment includes appropriate use of antibiotics to treat and to prevent infections. The type and severity of infection usually determines the type of antibiotic used and the length of treatment. Additional immunization with pneumococcal vaccines may also be used to enhance immunity.

Ig therapy is an option for selected symptomatic patients that have persistent IgG subclass deficiencies, documented poor responses to polysaccharide vaccines and who fail prophylactic antibiotic therapy. (*See chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”*) The decision to begin Ig replacement therapy needs to be carefully discussed with the healthcare provider, and most insurers will require documentation that more conservative treatment has failed. In addition to lab studies showing persistently low IgG subclass levels and deficient antibody responses to vaccines, this may also include culture

evidence of bacterial infection, X-ray studies consistent with active infection and documentation that antibiotic treatment was unsuccessful in controlling the infections.

Since many young children appear to outgrow their IgG subclass deficiencies, as they get older, it is important to reevaluate the patient to determine if the subclass deficiency is still present. Reevaluation requires discontinuation of Ig replacement therapy (usually in the summer months when infections are less frequent) and at least four to six months of observation before IgG levels are re-tested. If the subclass deficiency has resolved, Ig replacement therapy may no longer be needed. If infections recur, Ig therapy may be reinstated. In teenagers and adults, the subclass deficiency is less likely to be outgrown or resolve.

Patients with frequent infections and persistent IgG subclass deficiencies with normal anti-polysaccharide antibodies should also be treated using adequate prevention, vaccine and antibiotic therapy, perhaps even considering the use of Ig replacement if other treatment fails. However some insurers may not cover the costs of Ig replacement in such cases and the costs associated usually run to many thousands of dollars yearly.

## Expectations for Patients with IgG Subclass Deficiency

The natural history of patients with selective IgG subclass deficiency is not completely understood but the outlook is generally good. Many children appear to outgrow their deficiency as they get older. For those patients with a persistent deficiency, the use of antibiotics and, in certain circumstances, the use of Ig replacement therapy may prevent serious infections and complications such as impaired lung function, hearing loss or injury to other organ systems.

Recent studies have shown that many children with a subclass deficiency in early childhood (younger than 5 years of age) develop normal subclass levels and the

ability to make antibodies to polysaccharide vaccines as they get older. However, IgG subclass deficiencies may persist in some children and adults. In some instances, a selective IgG subclass deficiency may develop into a more serious antibody deficiency, such as CVID. (*See chapter titled “Common Variable Immune Deficiency.”*) At this time, it is not possible to determine which patients will have the transient type of subclass deficiency and which patients may later develop a more significant immunodeficiency. For these reasons, regular reevaluation of immunoglobulin levels and function, as well as IgG subclass levels is necessary.