

IgG subclass deficiency and specific antibody deficiency

Definition of Subclass Deficiency

Antibodies are made of proteins 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 bathes the tissues and cells of the body are of the IgG class. The IgG class of antibodies is itself composed of four different subtypes of IgG molecules called the IgG subclasses. These are designated IgG1, IgG2, IgG3 and IgG4. Patients who suffer recurrent infections because they lack, or have very low levels of, one or two IgG subclasses, but whose other immunoglobulin levels, including total IgG, are normal, are said to have a selective IgG subclass deficiency.

While all the IgG subclasses contain antibodies, each subclass serves somewhat different functions in protecting the body against infection. For example, the 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, antibodies against the polysaccharide (complex sugar) coating (capsule) of certain disease-producing bacteria (e.g. the pneumococcus and *Haemophilus influenzae*) are

predominantly of the IgG2 type. Some of the IgG subclasses can easily cross the placenta and enter the unborn infant's bloodstream, while others do not. Antibodies of certain IgG subclasses interact readily with the complement system, while others interact poorly, if at all, with the complement protein. Thus, an inability to produce antibodies of a specific subclass may render the individual susceptible to certain kinds of infections but not others.

The IgG circulating 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 antibodies to the polysaccharide coatings of bacteria, antibodies that are most commonly of the IgG2 subclass, develops more slowly than the ability to make antibodies to proteins. These factors must be taken into account before an individual is considered to be abnormal, either by virtue of having a low IgG subclass level or an inability to make a specific type of antibody.

Clinical Presentation of Subclass Deficiency

Recurrent ear infections, sinusitis, bronchitis and pneumonia are the most frequently observed illnesses in patients with IgG subclass deficiencies. Both males and females may be affected. Some patients will show an increased frequency of infection beginning in their second year of life. In other patients the onset of infections may occur later. Often a child with IgG subclass deficiency will first come to the physician's attention because of recurrent ear infections. Somewhat later in life, recurrent or chronic sinusitis, bronchitis and/or pneumonia may make their appearance. In general, the infections suffered by patients with selective IgG subclass deficiencies are not as severe as those suffered by patients who have combined deficiencies of IgG, IgA and IgM (for example X-linked agammaglobulinemia or

common variable immunodeficiency). Very rarely, IgG subclass deficient patients have suffered recurrent episodes of meningitis or bacterial infections of the bloodstream (e.g. sepsis).

Selective IgG1 subclass deficiency is very rare. IgG2 subclass deficiency is the most frequent subclass deficiency in children, while IgG3 subclass deficiency is the most common deficiency seen in adults. IgG4 deficiency most often occurs in association with IgG2 deficiency. The significance of isolated, or selective, IgG4 deficiency is unclear at this time. Since many normal children under 10 years of age have undetectable IgG4, IgG4 deficiency is generally not accepted as a diagnosis in this age group.

Diagnosis of Subclass Deficiency

IgG subclass deficiency may be suspected in children and adults who have a history of recurrent infections of the ears, sinuses, bronchi and/or lungs. An individual is considered to have a selective IgG subclass deficiency if one or more of the IgG subclass levels in their blood is below the normal range for age and the levels of other immunoglobulins (i.e. total IgG, IgA and IgM) are normal or near normal.

An individual may have very low levels or absence of one or more IgG subclasses and yet the total amount of IgG in their blood may be normal or near normal. Therefore, in order to make the diagnosis of selective IgG subclass deficiency, measurement of IgG subclasses is required along with measurement of serum IgG, IgA, and IgM.

It is important to consider that the concentrations of IgG subclasses vary up or down over time and the normal ranges used in different laboratories also vary. Normal values are usually "defined" as those values between two standard deviations below and above the average for that person's age. Unfortunately, that may give the impression to some physicians and patients that individuals below the second standard deviation are abnormal when 2.5% of normal individuals fall below this level. The finding of a mild IgG subclass deficiency should prompt re-evaluation over a period of months before calling that person abnormal. Subclass deficiencies need to be interpreted by taking into account the clinical status of the patient as well as the ability to produce specific antibodies in response to childhood vaccines.

IgG subclass deficiencies may accompany IgA deficiency (see chapter titled *Selective IgA Deficiency*). Combined deficiencies of IgA with IgG2 and IgG4 deficiency are frequently observed. IgG2 and IgG4 deficiency as well as IgA and IgE deficiency also occur in association with Ataxia Telangiectasia (see chapter titled *Ataxia Telangiectasia*).

Many patients with selective IgG2 subclass deficiency or IgA and IgG2 deficiency are unable to produce protective levels of antibody when immunized with unconjugated polysaccharide vaccines against *Streptococcus pneumoniae* (the pneumococcus) or *Haemophilus influenzae* bacteria. Some patients may also be unable to produce protective levels of antibody when immunized with polysaccharides that are also conjugated to proteins. Patients with IgG subclass deficiencies usually make normal amounts of antibodies to protein vaccines such as the diphtheria and tetanus toxoids in the routine DPT immunizations.

Patients with IgG subclass deficiencies have normal numbers of B and T-lymphocytes and their T-lymphocytes function normally when tested.

An additional subset of patients have normal immunoglobulin levels and normal IgG subclasses, yet fail to produce protective antibody levels in response to infections with *Streptococcus pneumoniae* or to vaccines against this bacteria. These patients are thought to have a Specific Antibody Deficiency (SAD) and are usually grouped along with patients with IgG subclass deficiency.

Natural History of Subclass Deficiency

The natural history of patients with selective IgG subclass deficiency is not completely understood. Selective IgG subclass deficiencies occur more often in children than in adults and the type of subclass deficiency in children (i.e. predominantly IgG2) differs from that most commonly seen in adults (i.e. IgG3). These findings suggested that at least some children may "outgrow" their subclass deficiencies. In fact, recent studies have shown that many, but not all, children who were subclass deficient during early childhood (i.e. under the age of 5 years) develop normal subclass levels as well as the ability to make antibodies to polysaccharide

vaccines as they get older. However, IgG subclass deficiencies may persist in some children as well as in adults and in some instances a selective IgG subclass deficiency may evolve into common variable immunodeficiency. At the present time, it is not possible to determine which patients will have the transient type of subclass deficiency and in which patients the subclass deficiency may be permanent or the forerunner of a more wide-ranging immunodeficiency, such as common variable immunodeficiency. For these reasons, periodic reevaluation of immunoglobulin and IgG subclass levels is necessary.

Inheritance of Subclass Deficiency

No clear-cut pattern of inheritance has been observed in the IgG subclass deficiencies. 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 common variable immunodeficiency.

Treatment of Subclass Deficiency

Patients with IgG subclass deficiency frequently suffer recurrent or chronic infections of the ears, sinuses, bronchi and lungs. Treatment of these infections usually requires antibiotics. One goal of treatment is to prevent permanent damage to the ears and lungs that might result in hearing loss or chronic lung disease. Another goal is to maintain patients as symptom-free as possible so that they may pursue the activities of daily living such as school or work. Sometimes antibiotics may be used for prevention (i.e. prophylaxis) of infections in patients who are unusually susceptible to ear or sinus infections.

For immunodeficiency diseases in which patients are unable to produce adequate levels of the major immunoglobulin classes (i.e. IgG, IgA and IgM) and fail to make antibodies against proteins as well as polysaccharide antigens (for example, X-linked Agammaglobulinemia and Common Variable Immunodeficiency), immunoglobulin replacement therapy is clearly needed (see chapter titled *Specific Medical Therapy*). The use of immunoglobulin replacement therapy in patients with IgG subclass deficiencies is not as clear cut as it is for X-linked agammaglobulinemia and Common Variable Immunodeficiency patients.

Patients with IgG subclass deficiency and/or specific antibody deficiency have a more limited antibody and immunoglobulin deficiency than patients with X-linked Agammaglobulinemia and Common Variable Immunodeficiency. For patients in whom infections and symptoms can be controlled with antibiotics, immunoglobulin replacement therapy may not be necessary. However, for patients whose infections cannot be readily controlled with antibiotics, or have abnormal antibody responses, immunoglobulin replacement therapy may be considered.

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 immunoglobulin replacement and at least 4-6 months of observation before IgG levels are re-tested. If the subclass deficiency has resolved, immunoglobulin replacement therapy may be discontinued and the patient observed. If the deficiency has persisted, immunoglobulin therapy may be re-instituted. In teenagers and adults, disappearance of the subclass deficiency is less likely.

Expectations for the Subclass Deficiency Patient

The outlook for patients with IgG subclass deficiency is generally good. Many children appear to outgrow their deficiency as they get older. For those patients for whom the deficiency persists, the use of antibiotics and, in certain circumstances, the

use of immunoglobulin replacement therapy may prevent serious infections and the development of impaired lung function, hearing loss or injury to other organ systems.