

Chapter 6

IgG Subclass Deficiency and Specific Antibody Deficiency

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IgG Subclass Deficiency

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 immunoglobulin 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. IgG subclass deficiencies are clinically relevant **only** when the levels are absent or very low **and** when they are detected in people with recurrent upper and/or lower respiratory infections. In individuals without frequent or severe infections, low levels of IgG subclasses may be a clinically irrelevant finding. In the absence of infections, mild or moderately decreased subclass concentrations should not lead to unnecessary long-term use of immunoglobulin (Ig) replacement therapy. A subclass deficiency needs to be considered and looked for only under special circumstances discussed in this chapter.

Definition

Most of the antibodies (also known as immunoglobulins) in the blood and the fluid that surround the tissues and cells of the body are of the IgG class. This class of antibodies is composed of four different subtypes designated IgG1, IgG2, IgG3, and IgG4. Each subclass is present in different concentrations in the blood and also varies with age. The IgG in the bloodstream is 60 to 70% IgG1, 20 to 30% IgG2, 5 to 8% IgG3, and 1 to 3% IgG4. IgG1 and IgG3 reach normal adult levels by 5 to 7 years of age; while IgG2 and IgG4 levels rise more slowly, reaching adult levels at about 10 years of age.

Each subclass serves predominantly (but not exclusively) a slightly different function in protecting the body against infection. For example, IgG1 and IgG3 subclasses play a role in protection against toxins from bacteria such as diphtheria and tetanus and also viral infections. In contrast, IgG2 predominantly aids in protection against the polysaccharide (complex sugar) capsule of certain disease-producing bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Individuals with IgG Subclass Deficiency are defined as having recurrent infections, persistently low levels of one or more IgG subclasses, and normal concentrations of total IgG, IgM, and IgA. IgG2 or IgG3 deficiencies are the most common IgG subclass deficiencies. Since IgG1 comprises 60% of the total IgG level, having a deficiency of IgG1 usually drops the total IgG level below the normal range, resulting in hypogammaglobulinemia. Because IgG4 does not reach adult levels until the age of 10 years, a diagnosis of IgG4 deficiency should not be made in young children. In addition, it may also be undetectable in the serum of many normal adult individuals, and therefore low IgG4 alone is insufficient evidence of an antibody deficiency disorder.

All individuals with IgG subclass deficiency require additional diagnostic evaluation. This evaluation must include the demonstration of a poor antibody response to vaccine challenge and careful documentation of recurrent infection. If these are **both** present, then the individual can be diagnosed with a clinically significant IgG subclass deficiency necessitating specific treatment.

Clinical Presentations

Most individuals with IgG Subclass Deficiency are completely asymptomatic. They may present, however, to a healthcare provider with recurrent ear and/or sinus infections; bronchitis and pneumonia may also have occurred. These infections are commonly caused by encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, infections common in other people with antibody deficiencies. These types of infections are seen most commonly among those with IgG2 deficiency with or without IgG4 deficiency. Infections occurring in those with selective IgG subclass deficiency may not be as severe as infections in individuals with more significant antibody deficiencies, such as agammaglobulinemia or Common Variable Immune Deficiency (CVID). Individuals with IgG subclass deficiencies may have other types of invasive infections such as episodes of bacterial meningitis or infections of the bloodstream (sepsis), but these are extraordinarily rare. Frequent viral infections have been associated with IgG3 subclass deficiencies.

As in people with Selective IgA Deficiency, allergic diseases and autoimmune diseases are more common in those with IgG subclass deficiency.

Diagnosis

Measurement of IgG subclass levels is not universally recommended as part of the evaluation of antibody mediated immunity in individuals with recurrent or severe infections. Assessing IgG subclasses adds cost and may not add clinical value when total immunoglobulins and specific antibodies are measured. Most clinical immunologists do not obtain or measure IgG subclasses.

When IgG subclasses are measured, all four should be measured at the same time. An abnormal level should be confirmed at least one month after the first measurement. It is important to consider that IgG subclasses vary over time and among different laboratories. In addition, normal range values are usually defined as those values found in 95% of normal individuals of that person's age. This means that 2.5% of normal individuals will be considered deficient, and 2.5% of normal individuals will have values above that range. (See Laboratory Tests Chapter.)

Measurement of IgG subclasses can be recommended in the presence of known associated abnormalities, particularly if recurrent infections are also present. These circumstances include individuals with:

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

Inheritance

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 Selective IgA Deficiency or CVID. A partial gene deletion has been found in a few individuals with IgG subclass deficiency. Rarely individuals with complete absence of IgG2 due to deletion of the gene coding for its production have been described.

Treatment

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. It is important to encourage patients to continue normal activities of daily living, such as school or work.

A trial (6 months) of immunoglobulin replacement therapy may be considered in patients with recurrent infections affecting quality of life, who have failed antibiotic therapy. (See Immunoglobulin Replacement Therapy Chapter.) At minimum, most insurers before they will approve Ig therapy will require documentation demonstrating failure of such conservative treatment in addition to persistently low IgG subclass levels and deficient antibody responses to vaccines. Children diagnosed with IgG subclass deficiency should be reevaluated with increasing age, as many appear to outgrow their IgG subclass deficiencies.

Expectations

The natural history of individuals with a clinically significant 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 with a persistent deficiency and impaired antibody responses, the use of prophylactic 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. IgG subclass deficiencies, however, may persist in some children and adults. In some instances, a selective IgG subclass deficiency may evolve into a more serious antibody deficiency, such as Common Variable Immune Deficiency (CVID). (See Common Variable Immune Deficiency.) At this time, it is not possible to determine which individuals will have the transient type of subclass deficiency and which individuals may later evolve into a more significant immunodeficiency. For these reasons, regular reevaluation of immunoglobulin levels and function, as well as IgG subclass levels, is necessary.

Specific Antibody Deficiency

Among the five classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE, IgG has the predominant role in protection against infection. Some people have normal levels of immunoglobulins and all subclasses of IgG, but they do not produce sufficient specific IgG antibodies that protect them from some viruses and bacteria. People who produce normal immunoglobulin levels but who lack the ability to produce protective IgG antibodies against the types of organisms that cause upper and lower respiratory infections are said to have Specific Antibody Deficiency (SAD). SAD is sometimes termed partial antibody deficiency or impaired polysaccharide responsiveness.

Definition

Each individual IgG molecule is uniquely designed to protect against a specific pathogen. We call these molecules specific antibodies, and they are usually formed in response to natural exposure to bacteria and viruses, or through exposure to vaccines. Some of these antibodies can be measured in the laboratory, and these levels (or titers) are used to help diagnose problems with immunity.

Children less than 2 years of age often do not have a robust response to infections with bacteria such as *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae*. This is primarily due to an inability to make antibodies against the polysaccharide (sugar) coat that covers these bacteria. Children in this age group typically acquire protection against these microbes through the use of certain vaccines in which a protein is added to elicit

an immunologic response (conjugate vaccines). Most children begin to naturally make stronger immune responses to these bacteria around 2 years of age, and they can then fight off these infections more effectively. Children and adults who fail to develop the immune response to the polysaccharide coating on bacteria (and therefore lack protection to these microbes) but who otherwise have normal antibody levels are diagnosed with having SAD.

Specific IgG antibodies are important in fighting off infections; however, other components of our immune system also work to eradicate bacteria and viruses. T cells, complement proteins, IgM and IgA antibodies (to name a few) are parts of our immune system that work together during a complete immune response. If these other components work well, some individuals with low specific antibody levels may rarely get sick. Antibodies of certain IgG

subclasses interact readily with the complement system, while others interact poorly, if at all, with the complement proteins. Thus, an inability to produce antibodies of a specific subclass or mild deficiencies of other arms of the immune system may render the individual susceptible to certain kinds of infections but not others. These factors must be taken into account before an individual's immune system 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

Recurrent ear infections, sinusitis, bronchitis, and pneumonia are the most frequently observed illnesses in people with SAD. Some individuals will show an increased frequency of infection beginning in the first years of life. In others, the onset of infections may occur later. In general, the infections in individuals with SAD are not as severe as those who have combined deficiencies of IgG, IgA, and IgM, like X-linked Agammaglobulinemia (XLA) or CVID. Some, however, may present with a single severe pneumonia or other infection at the time of diagnosis.

Diagnosis

Problems with specific antibody production may be suspected in children and adults who have a history of recurrent infections of the ears, sinuses, bronchi, and/or lungs. The recommended evaluation usually includes measurement of total immunoglobulins, and antibody levels to specific bacteria such as tetanus, diphtheria, and/or *Streptococcus pneumoniae*. When total immunoglobulins are low, a more profound immunodeficiency may be present. If isolated low antibody levels to *Streptococcus pneumoniae* are found during the initial evaluation, a Pneumococcal vaccine (Pneumovax) is administered and follow-up levels are measured. Individuals older than 1 year of age may be immunized with the pneumococcal polysaccharide vaccine (Pneumovax 23 or Pnu-Immune 23). These vaccines have the ability to induce protective levels to 23 strains (serotypes) of *Streptococcus pneumoniae*. Antibody levels are measured again four to six weeks later to determine if adequate protective antibody levels were produced. It is felt that normal individuals respond to a majority of the serotypes in these vaccines and retain those protective levels for years after receiving them. Antibody responses may not last as long in young children. For therapy, it is also possible to re-immunize with Prevnar 13, a conjugate type of

pneumococcal vaccine, which, for most, may be more immunogenic than Pneumovax. This vaccine, however, cannot be used to diagnose SAD.

A classification for mild, moderate, and severe forms of SAD exists which factors in the individual's age and number of normal post-immunization serotypes to define immunologic severity. Responses in which children respond to less than 50% of serotypes and adults respond to <70% have a moderate form of SAD with an increased risk of upper/lower respiratory tract infections that may warrant treatment. In the experience of many clinical immunologists, however, a normal vaccine response for an individual consists of producing protective titers of antibodies to at least 50% of the serotypes present in the vaccine. Furthermore, there are individuals who may fall into a response zone between 50 to 70% that have significant infections that may warrant a trial of replacement Ig therapy.

An additional subset of people are defined as having a memory phenotype meaning they respond normally initially and subsequently lose protective levels within 6 months.

When interpreting pneumococcal levels, it is important to recognize the variability in testing methodology and subsequent results that may occur among different labs. This highlights the importance of utilizing a detailed clinical history in addition to laboratory findings to guide the immunologic evaluation when considering a diagnosis of SAD.

Inheritance

No clear-cut pattern of inheritance has been observed with SAD.

Treatment

Individuals with SAD frequently have 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 with scarring. Another goal is to maintain individuals with SAD 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 (prophylaxis) of infections.

As in IgG subclass deficiency, the use of Ig replacement therapy for SAD is not as clear-cut as it is for those with XLA or CVID. For individuals

with SAD in whom infections and symptoms can be controlled with antibiotics, Ig replacement therapy is usually not necessary. However, for those with more severe clinical phenotypes whose infections cannot be readily controlled with antibiotics or who have more frequent and severe infections, Ig replacement therapy may be considered.

Since many young children appear to outgrow SAD as they get older, it is important to reevaluate them to determine if the deficiency is still present. If Ig replacement therapy has been previously initiated, reevaluation after a period of time is recommended with discontinuation of Ig therapy for 4 to 6 months before repeat immune testing, and re-immunization with pneumococcal vaccines (if needed) is performed. If the response to vaccination is adequate, Ig replacement therapy may be discontinued and the individual observed. It is reasonable to reevaluate antibody levels periodically to document retention of protective antibody levels. If the diagnosis of SAD is made in teenagers or adults, resolution of the deficiency is less likely.

Expectations

The outlook for individuals with SAD is generally good. Many children appear to outgrow their deficiency as they get older, usually by age 6. For those for whom the deficiency persists, the use of prophylactic antibiotics and, in certain circumstances, the use of Ig therapy may prevent serious infections and the development of impaired lung function, hearing loss or injury to other organ systems.

The natural history of individuals with SAD is not completely understood. SAD seems to occur more often in children, probably due to a delay in the natural maturation of the immune response. Children may outgrow SAD over time. Adults with similar symptoms and poor response to vaccination are less likely to improve over time. Similar to IgG subclass deficiencies, SAD may evolve into CVID. (See Common Variable Immune Deficiency Chapter.) At the present time, it is not possible to determine which individuals will have the transient type of deficiency and in which individuals the deficiency may be permanent or the forerunner of a more wide-ranging immunodeficiency, such as CVID. For these reasons, periodic reevaluation of immunoglobulin levels and specific antibody levels is necessary.

Adapted from: Chapter 5 IgG Subclass Deficiency and Chapter 6 Specific Antibody Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.