

Chapter 4

Selective Immunoglobulin Deficiency: IgA and IgM

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Selective IgA Deficiency

Individuals with Selective IgA Deficiency (SIgAD) lack immunoglobulin A (IgA), but they usually have normal amounts of IgG and IgM. SIgAD is relatively common in people of Caucasian descent and rare in people of Asian descent. In North America, it is the most common form of primary immunodeficiency disease (PID), estimated to affect 1 in 500 people. Many affected have no symptoms and do not even know they have a deficiency until the lack of IgA is noted when they are being evaluated for another condition, such as celiac disease. Those people who are symptomatic may develop a variety of significant clinical problems, including infections, allergies, and autoimmune diseases. It is important to know that, with the exception of an undetectable level of IgA, all other components of the immune system function are usually normal.

Overview

SIgAD is defined as a primary immunodeficiency characterized by an undetectable level of IgA in the blood and secretions but normal IgG and IgM in an individual age 4 and older. IgM and IgG mainly protect people from infections inside body tissues, organs, and blood. While IgA is present in the blood, most of the IgA in the body is in the secretions of the mucosal surfaces, including tears, saliva, and colostrum, as well as genital, respiratory, and gastrointestinal secretions. The IgA antibodies in these secretions play a role in protecting people from infections in the respiratory tract, gastrointestinal tract, and genitourinary tract.

Immunobiology

Individuals with SIgAD lack serum (IgA <7 mg/dl) and secretory IgA, but they do make all the other immunoglobulin classes. Some of the individuals with SIgAD also have IgG subclass deficiency. Among the four IgG subclasses, low IgG2 levels are most commonly observed. In those who have associated

allergic diseases serum IgE levels may be increased. In those with SIgAD who have autoimmune disease, a variety of autoantibodies (like ANA, Rheumatoid factor) may be positive. In most people with SIgAD, there are no problems with cellular immunity, the complement system, or white blood cell function.

Secretory IgA has some differences compared to the IgA present in the blood. Secretory IgA is made of two IgA antibody molecules joined together by a protein called the J chain—J for joining. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) In order for this unit to be secreted, it is attached to another protein called the secretory piece. Therefore, the final secretory IgA unit that protects the mucosal surfaces is actually composed of two IgA molecules joined by the J chain and attached to the secretory piece. The secretory IgA is able to exist in the gastrointestinal tract because it is resistant to gastrointestinal enzymes.

IgA promotes health by regulating the composition and function of microbiota, which regulates metabolism, epithelial barrier integrity, and the immune system.

Clinical Presentation

A common problem in SIgAD is susceptibility to infections. Problems with infections are seen in about half of the individuals with SIgAD. Recurrent ear infections, sinusitis, bronchitis, and pneumonia are the most common infections. Some individuals may develop gastrointestinal infections and other gastrointestinal disorders, such as chronic diarrhea. Another problem in SIgAD is the occurrence of autoimmune diseases. These are found in about one third of individuals who seek medical help. Some of the more frequent autoimmune diseases associated with SIgAD include rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Idiopathic Thrombocytopenic Purpura (ITP) (low platelet counts). Other kinds of autoimmune disease may affect the endocrine system and/or the gastrointestinal system. Allergic disorders are more common among individuals with SIgAD than among the general population. The types of allergies associated with SIgAD include allergic rhinitis, allergic conjunctivitis, eczema, and asthma. Food allergy may also be associated with SIgAD.

Diagnosis

The diagnosis of SIgAD is usually suspected because of chronic or recurrent ear infections, sinusitis, respiratory tract infections, chronic diarrhea, or some combination of these problems. Other individuals are identified when immunoglobulins are ordered for some non-immunologic problem, for example when a person is being evaluated for possible celiac disease. The diagnosis is established when blood tests demonstrate undetectable levels of IgA (reported usually as >7 mg/dl), with normal levels of the other major classes of immunoglobulins (IgG and IgM). The healthcare provider may order several other tests including autoantibodies.

Prevalence and Inheritance

Genetic susceptibility in IgA deficiency is not well defined, but familial inheritance of SIgAD may occur in approximately 20% of cases. SIgAD can be observed in families with Common Variable Immune Deficiency (CVID). There are reports of some individuals with SIgAD being later diagnosed with CVID.

Treatment

Ideal treatment for SIgAD would be to replace IgA. However, no IgA-enriched immunoglobulin (Ig) preparation is available in the U.S. Treatment should be directed toward a specific illness. For example, individuals with chronic or recurrent infections need treatment with appropriate antibiotics. Ideally, antibiotic therapy should be targeted at the specific organism causing the infection. It is not always possible, however, to identify these organisms and their antibiotic sensitivities precisely, and therefore, the use of broad-spectrum antibiotics may be indicated. Certain individuals who have chronic sinusitis or chronic bronchitis may need to stay on long-term preventive antibiotic therapy (antibiotic prophylaxis). In these cases, the healthcare provider and person with SIgAD need to discuss the benefits and risks of the various possibilities and reach mutual agreement regarding treatment.

People with SIgAD (>7 mg/DL) are often considered to be at increased risk of life-threatening allergic reactions, also known as an anaphylactic reaction, to blood and blood products including immunoglobulin (Ig) replacement therapy that may contain traces of IgA. This is thought to be due to antibodies (IgE) against the IgA antibody, which may be found in some IgA-deficient individuals. These reactions, however, are very rare overall. If individuals with SIgAD and IgG2 subclass deficiency have a history of recurrent serious infections, a trial of Ig replacement therapy may be used to prevent infections. If there is a concern about the risk of adverse reactions because of the small amounts of IgA in intravenous immunoglobulin (IVIG) preparations, then it is advised to use subcutaneous immunoglobulin (SCIG). The latter is preferred over low IgA containing preparations administered intravenously because of the following reasons: there is only one IVIG preparation with extremely low IgA, infusions need to be given in a hospital setting and under medical supervision, and anaphylactic reaction to SCIG has not been reported. Individuals with SIgAD who need a blood transfusion should receive washed red cells to remove the plasma that contains the IgA that may cause a transfusion reaction.

As for autoimmune diseases, a variety of therapeutic options exist such as anti-inflammatory drugs, steroids, or biological drugs. As with every treatment, the individual and/or caregiver and their healthcare provider should discuss the treatment plan and best treatment options.

Expectations

Although SIgAD is usually one of the milder forms of immunodeficiency, it may result in severe disease in a subset of people. Therefore, it is difficult to predict the long-term outcome in an individual with SIgAD, although generally the prognosis is considered to be very good. It is important for healthcare providers to continually assess and re-evaluate individuals with SIgAD for the existence of associated diseases and to consider the possibility of diagnosing later with a more extensive immunodeficiency, for example CVID.

Individuals need to inform their healthcare providers of anything unusual, especially fever, productive cough, skin rash, or sore joints. The importance of good communication with the healthcare provider and the initiation of appropriate therapy as soon as necessary cannot be overstated.

Selective IgM Deficiency

Individuals with Selective IgM Deficiency have low levels or lack immunoglobulin M (IgM) but have normal levels of IgA, and IgG. These individuals may have no illness, whereas others develop a variety of illnesses including infections, allergy, and autoimmunity.

Overview

IgM is the largest in size of all immunoglobulins. It is predominantly present in the circulating blood as compared to IgG, which is present both in the circulation and in the tissues, and IgA, which is present predominantly in secretions. IgM is the first immunoglobulin secreted during an initial exposure to infectious organisms or to a vaccine. IgM is also different from other immunoglobulins in that it contains five antibody molecules held together by the J chain. IgM antibodies serve as a first line of defense against bacteria, viruses, and fungi, and in protection against autoimmune diseases and inflammation.

Although described more than 50 years ago, it is only recently that Selective IgM Deficiency is included in the list of forms of PI. It is characterized by low (partial) to absent IgM (complete) in the blood but normal IgG and IgA levels. It occurs equally both in children and adults, and in men and women. Partial Selective IgM Deficiency is more common than previously realized, whereas complete Selective IgM Deficiency is rare. Individuals with Selective IgM Deficiency, partial or complete, may not have any symptoms, and therefore, are unrecognized or undiagnosed. Those individuals who do have symptoms commonly suffer from infections, allergies, and autoimmune diseases. There is no specific

treatment to correct low IgM levels; however, individuals who have this condition and also have impaired responses to vaccines antigens, particularly pneumococcal polysaccharide vaccines, may require Ig replacement therapy.

Immunobiology

Blood levels of IgM are low or absent, but IgA and IgG are normal. In some cases, IgG subclass deficiency may also be seen. One third to one half of individuals with Selective IgM Deficiency make poor response to Pneumovax-23 vaccine. Cellular immunity is normal. Phagocytic cell system and complement system are also normal.

Clinical Presentation

Individuals with Selective IgM Deficiency may be asymptomatic or symptomatic. Of those who are symptomatic, approximately 80% present with predominant bacterial infections. Among infections, most common are chronic sinusitis, upper respiratory tract infections, bronchitis, and pneumonia. Occasionally cellulitis, sepsis and meningitis have been observed. Almost 40% of individuals with Selective IgM Deficiency have allergic diseases including hay fever and asthma. Autoimmune diseases are observed in

about one third of all individuals with Selective IgM Deficiency. Autoimmune diseases are more common in adults than children with Selective IgM Deficiency. Some common autoimmune diseases associated with Selective IgM Deficiency are systemic lupus erythematosus, rheumatoid arthritis, and autoimmune thrombocytopenia. Autoimmune diseases of endocrine glands, like Hashimoto's thyroiditis and Addison's disease, have also been seen in Selective IgM Deficiency.

Diagnosis

Since the symptoms of Selective IgM Deficiency are similar to other antibody deficiencies, such as CVID and SIgAD. Selective IgM Deficiency may be discovered when immunoglobulins are obtained to evaluate someone who is suspected of having a PI. Individuals are also identified when immunoglobulins are ordered for illnesses other than PI. The diagnosis of partial Selective IgM Deficiency is made if the serum IgM level is below 2 standard deviations of the mean for age-matched controls. Complete Selective IgM Deficiency is diagnosed with serum IgM levels less than 5mg/dl. A definitive diagnosis of Selective IgM Deficiency, especially in children, should only be established after months of follow-up. Finally, in order to confirm a diagnosis of primary Selective IgM Deficiency, other possible causes of IgM deficiency must be excluded, such as leukemia, lymphoma, and immune suppressive medications, such as Clozapine.

Prevalence and Inheritance

Inheritance of Selective IgM Deficiency is not known because family studies have not been done. Only a few families with Selective IgM Deficiency have been described. A prevalence of 3 in 10,000 for complete Selective IgM Deficiency, and 3 in 1,000 for partial Selective IgM Deficiency in adults has been reported. However, large-scale and several generation family studies are needed in order to determine the true inheritance and prevalence of Selective IgM Deficiency.

Treatment

Ideal treatment for Selective IgM Deficiency would be to replace IgM. However, no IgM-enriched immunoglobulin preparation is available in the U.S. Approximately one third of individuals with Selective IgM Deficiency who have recurrent infections also have impaired IgG antibody response to vaccines. In such cases, Ig replacement therapy has been used and found to be beneficial. Recommendations for treating infections are similar to SIgAD; however, prophylactic use of antibiotics in Selective IgM Deficiency is generally not recommended. Allergic and autoimmune diseases are generally treated in a similar manner as those diseases in people without a PI.

Expectations

In the majority of reported cases clinical presentation is mild; however, in some cases meningitis and sepsis have been reported. Therefore, it is difficult to predict long-term outcomes for individuals with Selective IgM Deficiency. Serious complications are rare. Although progression to other immunodeficiencies such as CVID have not been reported, long-term follow-up with individuals is still needed. Therefore, even people with mild symptoms should be followed every six months or annually, and assessed to determine if there has been a progression to another immunodeficiency, as well as for the development of any complications such as autoimmune diseases.

Adapted from: Chapter 4 Selective IgA Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.