Selective IgA Deficiency

Chapter 4

Individuals with Selective IgA Deficiency lack IgA, but usually have normal amounts of the other types of immunoglobulins. Selective IgA Deficiency is relatively common in Caucasians. Many affected people have no illness as a result. Others may develop a variety of significant clinical problems.

Definition of Selective IgA Deficiency

Selective IgA Deficiency is defined as a primary immunodeficiency characterized by an undetectable level of immunoglobulin A (IgA) in the blood and secretions but no other immunoglobulin deficiencies.

There are five types (classes) of immunoglobulins or antibodies in the blood: IgG, IgA, IgM, IgD and IgE. IgG is present in the largest amount, followed by IgM and IgA. IgD is much lower, and IgE is present in only minute amounts. IgM and IgG mainly protect us from infections inside our 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, colostrum, genital, respiratory and gastrointestinal secretions.

The IgA antibodies in the secretions play a major role in protecting us from infections in these areas. IgG and IgM are also found in secretions but not in nearly the same amount as IgA. IgA present in these secretions is also termed secretory IgA. If human mucosal surfaces were spread out flat, they would cover an area equal to one and a half tennis courts, so the importance of IgA in protecting mucosal surfaces cannot be overstated.

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 chapter titled "The Immune System and Primary Immunodeficiency Diseases.")* In order for this unit to be secreted, it must also be 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.

Although individuals with Selective IgA Deficiency do not produce IgA (or produce only extremely small amounts), they do make all the other immunoglobulin classes; hence the term Selective IgA Deficiency. Furthermore, the functions of their T-lymphocytes, phagocytic cells and complement systems are all normal.

Clinical Features of Selective IgA Deficiency

Selective IgA Deficiency is one of the most common primary immunodeficiency diseases. Studies have indicated that as many as one in every 500 Caucasian people has Selective IgA Deficiency. The rate of occurrence may be different in other ethnic groups.

Many of these individuals appear healthy, or have relatively mild illnesses, and are generally not sick enough to be seen by a doctor and may never be discovered to have IgA deficiency. On the other hand, there are individuals with Selective IgA Deficiency who

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have significant illnesses. Currently, it is not understood why some individuals with IgA deficiency have almost no illness while others are very sick.

Also, it is not known precisely what percent of individuals with IgA deficiency will eventually develop complications; estimates range from 25% to 50%. Some patients with IgA deficiency also have very low levels of certain IgG subclasses (usually IgG2 and/or IgG4). That may be part of the explanation of why some patients with IgA deficiency are more susceptible to infection than others, but this is not the case for all patients with IgA deficiency who develop complications or for those who have low IgG2 and/or IgG4 in addition to absent IgA.

A common problem in Selective IgA Deficiency is susceptibility to infections. This is seen in about half of the patients with IgA deficiency that come to medical attention. Recurrent ear infections, sinusitis, bronchitis and pneumonia are the most common infections seen in patients with Selective IgA Deficiency. Some patients also have gastrointestinal infections and chronic diarrhea. The occurrence of these kinds of infections is easy to understand since IgA protects mucosal surfaces. These infections may become chronic. Furthermore, the infection may not completely clear with treatment, and patients may have to remain on antibiotics for longer than usual. Sometimes long-term antibiotic prophylaxis is needed to keep them free from infections.

A second major problem in IgA deficiency is the occurrence of autoimmune diseases. These are found in about 25% to 33% of patients who seek medical help. In autoimmune diseases, individuals produce antibodies or T-lymphocytes, which react with their own tissues

with resulting inflammation and damage. Some of the more frequent autoimmune diseases associated with IgA deficiency are: rheumatoid arthritis, systemic lupus erythematosus and immune thrombocytopenic purpura. Other kinds of autoimmune disease may affect the endocrine system and/or the gastrointestinal system.

Allergies may also be more common among individuals with Selective IgA Deficiency than among the general population. These occur in about 10-15% of these patients. The types of allergies vary. Asthma is one of the common allergic diseases that occurs with Selective IgA Deficiency. It has been suggested that asthma may be more severe, and less responsive to therapy, in individuals with IgA deficiency than it is in people with normal IgA. Food allergy may also be associated with IgA deficiency. It is not certain whether there is an increased incidence of allergic rhinitis (hay fever) or eczema in Selective IgA Deficiency.

The causes of Selective IgA Deficiency are unknown. It is likely that there are a variety of causes, and this explains why the symptoms or health problems may vary from individual to individual.

Low but detectable serum IgA (sometimes called partial IgA deficiency), like undetectable serum IgA, is also relatively common. Similarly, most people with low serum IgA have no apparent illness. Some people with low serum IgA have a clinical course very similar to people with Common Variable Immune Deficiency (CVID). *(See chapter titled "Common Variable Immune Deficiency.")*

Diagnosis of Selective IgA Deficiency

The diagnosis of Selective IgA Deficiency is usually suspected because of chronic or recurrent infections, autoimmune diseases, chronic diarrhea or some combination of these problems. Other patients are identified when immunoglobulins are ordered for some non-immunologic problem. The diagnosis is established when blood tests demonstrate undetectable levels of IgA (reported usually as < 5-7 mg/dL), with normal levels of the other major classes of immunoglobulins (IgG and IgM).

Occasionally, some patients with IgA deficiency may also have low levels of IgG2 and/or IgG4 and associated antibody deficiency. B-cell numbers and the numbers and functions of T-lymphocytes are normal. *(See chapters titled "Specific Antibody Deficiency" and "IgG Subclass Deficiency.")*

Several other tests that may be important include a complete blood count, measurement of lung function and urinalysis. Other tests that may be obtained include measures of thyroid function, kidney function, nutrient absorption in the GI tract and antibodies directed against the body's own tissues (autoantibodies).

Inheritance of Selective IgA Deficiency

Familial inheritance of Selective IgA Deficiency occurs in approximately 20% of cases and, within families, Selective IgA Deficiency, CVID and Transient Hypogammaglobulinemia of Infancy may be associated.

If family members are suspected of having immune problems, immunoglobulin levels may be obtained to determine a familial pattern of disease.

Treatment of Selective IgA Deficiency

It is not currently possible to replace IgA in patients with IgA deficiency, although research toward purification of human IgA is ongoing. However, it remains to be seen if replacement of IgA by any route (IV, oral or topical) will be beneficial for humans with IgA deficiency, in part because IgA in the serum, unlike IgG, does not remain in the circulation for very long.

Treatment of the complications associated with Selective IgA Deficiency should be directed toward the particular problem. For example, patients with chronic or recurrent infections need appropriate antibiotics. Ideally, antibiotic therapy should be targeted at the specific organism causing the infection. Unfortunately, it is not always possible to identify these organisms and their antibiotic sensitivities precisely, and the use of broad-spectrum antibiotics may be necessary.

Certain patients who have chronic sinusitis or chronic bronchitis may need to stay on long-term preventive antibiotic therapy (antibiotic prophylaxis). It is important that the doctor and the patient communicate closely so that appropriate decisions can be made regarding therapy.

As mentioned above, some patients with IgA deficiency also have IgG2 and/or IgG4 subclass deficiency and/or a deficiency of antibody production. However, these

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laboratory findings do not always predict a greater frequency or severity of infections. If a patient has many infections, poor vaccine antibody responses and fails other preventive treatment (for example, antibiotic prophylaxis) a trial of immunoglobulin replacement therapy may be considered. *(See chapter titled "Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.")*

Patients with Selective IgA Deficiency are often considered to be at increased risk of life-threatening allergic reactions, or anaphylaxis when they receive blood products, including intravenous immunoglobulin (IVIG), that contain some IgA. This is thought to be due to IgG (or possibly IgE) anti-IgA antibodies, which may be found in some IgA-deficient individuals. However, most patients with IgA deficiency do not have adverse reactions to blood products or IVIG.

There is no consensus among experts in this field regarding the exact magnitude of the risk of these types of reactions in patients with IgA deficiency, or the need for caution or measurement of anti-IgA antibodies before administration of blood or IVIG. However, these reactions are very rare overall. Furthermore, anaphylaxis has not been reported in patients with IgA deficiency receiving subcutaneous immunoglobulin infusions.

There are a variety of therapies for the treatment of autoimmune diseases. Anti-inflammatory drugs, such as aspirin, ibuprofen or naproxen, are used in many diseases that cause joint inflammation. Steroids may also be helpful in a variety of autoimmune diseases. Many biological drugs (monoclonal antibodies) have also been developed to treat inflammatory and autoimmune diseases. If autoimmune disease results in an abnormality of the endocrine system, replacement therapy with hormones may be necessary.

Treatment of the allergies associated with IgA deficiency is similar to treatment of allergies in general. It is not known whether immunotherapy (allergy shots) is helpful in the allergies associated with Selective IgA Deficiency; although there is no evidence of any increased risk associated with this therapy in these patients.

The most important aspect of therapy in IgA deficiency is close communication between the patient (and/or the patient's family) and the physician so that problems can be recognized and treated as soon as they arise.

Expectations for Patients with Selective IgA Deficiency

Although Selective IgA Deficiency is usually one of the milder forms of immunodeficiency, it may result in severe disease in some people. Therefore, it is difficult to predict the long-term outcome in an individual patient with Selective IgA Deficiency.

In general, the prognosis in Selective IgA Deficiency depends on the prognosis of the associated diseases. It is important for physicians to continually assess and reevaluate patients with Selective IgA Deficiency for the existence of associated diseases and the development of more extensive immunodeficiency. For example, rarely, IgA deficiency will progress to become CVID with its associated deficiencies of IgG and/or IgM.

The physician should be notified of anything unusual, especially fever, productive cough, skin rash or sore joints. The importance of good communication with the physician and the initiation of therapy as soon as disease processes are recognized cannot be overstated.