

Chapter 2

Antibody Deficiency with Absent B Cells

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Some people with primary immunodeficiency diseases (PI) lack the cells that are responsible for producing antibodies (immunoglobulins). They have very low or absent levels of all types of antibodies and an increased risk of infection. People with genetic causes of low or absent antibodies (agammaglobulinemia) have a severe form of antibody deficiency with absent B cells. This results from the failure of precursor-B cells to develop into mature B cells and plasma cells.

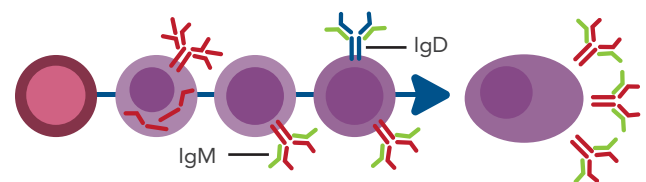
Definition

The basic defect in agammaglobulinemia is an inability of the patient to produce antibodies. Antibodies are an integral part of the body's defense mechanism against germs. When a germ, such as bacteria, lands on a mucous membrane, or enters the body, antibody molecules that recognize the germ stick to its surface. Antibodies bound to the surface of a germ can have one or more effects that are beneficial. For example, some germs must attach to body cells before they can cause an infection and antibodies prevent the germs from sticking to the body's cells. Antibody on the surface of some germs will also activate other body defenses, such as a group of blood proteins called serum complement, which can directly kill the bacteria or viruses. Finally, antibody coated bacteria are much easier for white blood cells (phagocytes) to ingest and kill than are bacteria that are not coated with antibody. All of these actions prevent germs from invading body tissues where they may cause serious infections. Antibodies are also important in the recovery from infections and to protect against getting certain infections more than once. (See The Immune System and Primary Immunodeficiency Diseases Chapter.)

Antibodies are produced by specialized cells in the body, called plasma cells. Plasma cells are derived from B lymphocytes (a type of white cell) that develop in an orderly sequence of steps beginning with stem cells located in the bone marrow. The stem cells give rise to immature lymphocytes that eventually develop into mature lymphocytes including T cells, B cells, or NK cells. A subset of these immature lymphocytes called pro-B

lymphocytes next develop into pre-B lymphocytes, which then give rise to mature B lymphocytes (Figure 2:1). Each B lymphocyte has antibodies on its cell surface. Each B cell makes a slightly different antibody, or immunoglobulin, to allow the body to respond to millions of different foreign substances (also known as antigens), like vaccines or parts of bacteria or viruses. There are specific antibodies designed to recognize each unique antigen. When the B lymphocyte comes into contact with its antigen, it is triggered to mature into a plasma cell. Plasma cells specialize in making and secreting large amounts of specific antibodies.

Figure 2:1 Agammaglobulinemia



The first form of agammaglobulinemia to be recognized, X-Linked Agammaglobulinemia (XLA), was described in 1952 by Colonel Ogden Bruton, MD. This disease, sometimes called Bruton's Agammaglobulinemia or Congenital Agammaglobulinemia, typically affecting boys, was the first type of PI to be identified. Most individuals with XLA have normal numbers of B cell precursors, but very few of these are able to go on to become mature B cells. People with XLA have mutations, or changes, in a gene that is necessary for the normal development of B cells. This gene, discovered in 1993, is named Bruton's Tyrosine Kinase (BTK) in honor of Dr. Bruton.

After BTK was identified as the cause of XLA, it became clear that only about 85% of children with agammaglobulinemia and absent B cells had mutations in BTK. In addition, it had been known for several years that there were girls who had an immunodeficiency that looked just like XLA with agammaglobulinemia and absent B cells, but which could not be explained by X-linked inheritance of BTK mutations.

Since 1996, several genes that can cause agammaglobulinemia with autosomal recessive inheritance (ARA) have been identified. The following genes (and their official gene symbol) have been reported to cause ARA:

- μ heavy chain (IGHM)
- $\lambda 5$ (IGLL1)
- Ig α (CD79A)
- Ig β (CD79B)
- BLNK (BLNK)
- PI3K p85 α (PIK3R1)

In addition, more recently, autosomal dominant forms of agammaglobulinemia have been described due to mutations in LRRC8 (LRRC8A) and E2A (TCF3).

All of these genes code for proteins involved in the maturation of B cells. Individuals with mutations in any of these genes have clinical and laboratory findings that are very similar to those seen in those with mutations in BTK.

Clinical Presentation

Individuals with any form of antibody deficiency with absent B cells are prone to develop infections. These infections frequently occur at or near the surfaces of the mucus membranes, such as the middle ear (otitis), sinuses (sinusitis), lungs (pneumonia), and gastrointestinal tract (infection causing diarrhea). In some instances infections can involve the skin, bloodstream, or internal organs.

In people without antibodies, any of these infections may invade the bloodstream and spread to other areas deep within the body, such as the bones, joints, or brain. Germs that are usually killed or inactivated very effectively by antibodies in healthy people cause infections in people with agammaglobulinemia.

The most common bacteria that cause infections are pneumococcus, streptococcus, staphylococcus, and Hemophilus influenzae. Enterovirus infections (Echovirus, Coxsackie, Polio, etc.) are particularly

troublesome for someone with agammaglobulinemia and can be associated with serious central nervous system infections.

The deficiency of antibody production is present at birth, and infections may begin at any age. Nevertheless, frequent infections often do not occur until sometime between 6-18 months of age because, until then, babies are protected by antibodies they received from their mother during the third trimester of pregnancy.

On physical examination, most individuals with agammaglobulinemia have very small tonsils and lymph nodes, which are the glands in the neck. This is because these tissues are made up of mostly B cells. In the absence of B cells, these tissues are much smaller. In more rare cases of agammaglobulinemia, like LRRC8A, individuals may have uncommon facial features.

In addition to lacking B cells, some people with XLA may also have low neutrophil counts and may develop a rare form of arthritis. Although infrequent, some with antibody deficiency with absent B cells may develop autoimmune or central nervous system disease.

Diagnosis

The diagnosis of agammaglobulinemia should be considered in any individual (male or female) with recurrent or severe bacterial infections, particularly if they have small or absent tonsils and lymph nodes.

The first screening test should be an evaluation of serum immunoglobulins. In most individuals with agammaglobulinemia, all of the immunoglobulins (IgG, IgM, IgA, IgE) are low or absent. In addition, healthy babies make only small quantities of immunoglobulins, particularly IgA and IgE, in the first few months of life, making it difficult to distinguish a healthy baby with a delay in immunoglobulin production from a baby with true immunodeficiency.

If the serum immunoglobulins are low or if the healthcare provider strongly suspects the diagnosis of agammaglobulinemia, the number of B cells in the blood should be measured. A low percentage of B cells (1% or less of the lymphocytes) in the blood is the most characteristic and reliable laboratory finding in someone with agammaglobulinemia.

If a newborn baby has a parent, sibling, maternal cousin, or maternal uncle with agammaglobulinemia, the baby is at risk to have a similar immunodeficiency, and the family and healthcare providers should

immediately determine the percentage of B cells in the blood so that treatment can be started before an affected infant gets sick.

The diagnosis of XLA can be confirmed by demonstrating the absence of BTK protein in monocytes or platelets or by the detection of a mutation in BTK in DNA. Almost every family has a different mutation in BTK; members of the same family, however, usually have the same mutation. The specific gene that causes ARA can be identified by genetic testing.

Inheritance

Antibody deficiency with absent B cells are a group of genetic diseases, and can be inherited or passed on in a family. It is important to know the type of inheritance so the family can better understand why a child has been affected, the risk that subsequent children may be affected, and the implications for other members of the family.

As the name XLA suggests, the BTK gene (which is mutated in XLA) is located on the X chromosome. Since XLA is an X-linked disorder, typically only boys are affected because they have only one X chromosome (XY). Girls can be carriers of the disorder because they have two X chromosomes. Carriers of XLA typically have no symptoms, but they have a 50% chance of transmitting the disease to each of their sons.

Now that the precise gene that causes XLA has been identified, it is possible to test the female siblings (sisters) of a male with XLA, and other female relatives, such as the child's maternal aunts, to determine if they are carriers of the disease and could transmit it to their sons. It is also possible to determine if a fetus of a carrier female will be born with XLA. (See Inheritance Chapter.)

ARA occurs when an individual inherits two copies of a gene (typically one from each parent), each of which has a mutation that makes the gene not function. This is more likely when parents are related in some way to one another, or come from a small, isolated geographic region or close-knit community. In autosomal recessive forms of agammaglobulinemia, an individual who inherits only one gene with a mutation and has one normal gene will not be affected. Individuals with autosomal dominant forms of agammaglobulinemia need to only inherit one copy of the gene mutation to be affected.

Treatment

At this time, the only treatment for individuals with agammaglobulinemia is immunoglobulin (Ig) replacement therapy. There currently is no cure for XLA, but there has been promising research regarding gene therapy for XLA, which is still in the pre-clinical stage. Ig replacement therapy for those with agammaglobulinemia replenishes some of the antibodies that they are lacking. The antibodies are supplied in the form of Ig, also known as gamma globulins or IgG. This Ig replacement therapy can be given directly into the blood stream (intravenously) or under the skin (subcutaneously). (See Immunoglobulin Replacement Therapy Chapter.)

The varying types of Ig replacement therapy contain antibodies that substitute for the antibodies that the individual cannot make themselves. These products contain antibodies to a wide variety of germs and is purified from the blood of healthy donors. Ig is particularly effective in preventing the spread of infections into the bloodstream and to deep body tissues or organs. Some people may also need daily oral antibiotics to protect them from infection or to treat chronic sinusitis or chronic bronchitis.

People with antibody deficiency with absent B cells should not receive any live viral vaccines, such as live polio, the measles, mumps, rubella (MMR) vaccine, the chicken pox vaccine, the rotavirus vaccine, yellow fever, live typhoid, or the live shingles vaccine. Although uncommon, it is possible that live vaccines, particularly the oral polio vaccine, in people with agammaglobulinemia can transmit the diseases that they were designed to prevent.

Individuals with antibody deficiency with absent B cells should receive the yearly influenza (flu) vaccine. Ig replacement therapy may interfere with the response to a vaccine; therefore, individuals should contact their healthcare provider prior to receiving any vaccination. It is also important for family members and close contacts of people with antibody deficiency with absent B cells to be vaccinated in order to provide them with a level of protection called herd immunity or community immunity.

Expectations

Most individuals with antibody deficiency with absent B cells, who receive Ig replacement therapy on a regular basis, will be able to lead relatively normal lives. They do not need to be isolated or limited in their activities. Children with agammaglobulinemia can participate in all regular school and

extracurricular activities, and active participation in team sports should be encouraged. Infections may require some extra attention from time to time, but many with antibody deficiency with absent B cells can go on to become adults with productive careers and families. A full active lifestyle is to be encouraged and expected.

Adapted from: Chapter 2 Agammaglobulinemia: X-Linked and Autosomal Recessive. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.