

# Agammaglobulinemia: X-Linked and Autosomal Recessive



## Chapter 2

*The basic defect in both X-Linked Agammaglobulinemia and autosomal recessive agammaglobulinemia is a failure of B-lymphocyte precursors to mature into B-lymphocytes and ultimately plasma cells. Since they lack the cells that are responsible for producing immunoglobulins, these patients have severe deficiencies of all types of immunoglobulins.*

## Definition of X-Linked Agammaglobulinemia (XLA) and Autosomal Recessive Agammaglobulinemia (ARA)

X-Linked Agammaglobulinemia (XLA) was first described in 1952 by Dr. Ogden Bruton. This disease, sometimes called Bruton's Agammaglobulinemia or Congenital Agammaglobulinemia, was one of the first immunodeficiency diseases to be identified. XLA is an inherited immunodeficiency disease in which patients lack the ability to produce antibodies, the proteins that make up the gamma globulin or immunoglobulin fraction of blood plasma.

Antibodies are an integral part of the body's defense mechanism against certain types of microorganisms or germs, like bacteria or viruses. Antibodies are important in the recovery from infections and protect against getting certain infections more than once. There are antibodies specifically designed to combine with each and every microbe—much like a lock and key.

When a germ, such as bacteria, lands on a mucus membrane or enters the body, antibody molecules that recognize it stick to its surface. Antibody bound to the surface of a microorganism 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 antibody prevents the germs from “sticking” to the cells.

Antibody on the surface of some microbes 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 which

are not coated with antibody. All of these actions prevent germs from invading body tissues where they may cause serious infections. (See chapter titled “*The Immune System and Primary Immunodeficiency Diseases.*”)

The basic defect in XLA is an inability of the patient to produce antibodies. Antibodies are produced by specialized cells in the body, called plasma cells. Plasma cells develop in an orderly sequence of steps beginning with stem cells located in the bone marrow. The stem cells give rise to immature lymphocytes, called pro-B-lymphocytes. Pro-B-lymphocytes next develop into pre-B-cells, which then give rise to B-lymphocytes. Each B-lymphocyte bears on its cell surface a small amount of the immunoglobulin that it is able to produce. This cell surface immunoglobulin can bind foreign substances, (an antigen). When the B-lymphocyte comes into contact with its specific antigen, like pneumococcus or tetanus, it is triggered to mature into a plasma cell which is specialized in making and secreting large amounts of that specific antibody. Each B-cell makes a slightly different antibody, or immunoglobulin, to allow the body to respond to millions of different foreign substances.

Most patients with XLA have normal numbers of B-lymphocyte precursors, but very few of these go on to become B-lymphocytes. This is the underlying defect in XLA, a failure of B-lymphocyte precursors to mature into B-cells. Patients with XLA have mutations in a gene that is necessary for the normal development of

## (Definition of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia continued)

B-lymphocytes. This gene, discovered in 1993, is named Bruton's Tyrosine Kinase (BTK) in honor of the discoverer of the disorder, Colonel Ogden Bruton, MD. As the name of the disorder suggests, the BTK gene is located on the X chromosome.

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. Since XLA is an x-linked disorder, only boys are affected; however, it had been known for several years that there were girls who had an immunodeficiency that looked just like XLA and immunologists had suggested that there were forms of agammaglobulinemia with autosomal recessive inheritance (ARA).

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

- $\mu$  heavy chain (*IGHM*)
- $\lambda 5$  (*IGLL1*)
- Ig $\alpha$  (*CD79A*)
- Ig $\beta$  (*CD79B*)
- BLNK (*BLNK*)

All of these genes code for proteins that work with BTK to support the maturation of pro-B-cells into pre-B-cells. Patients with mutations in any of these genes have clinical and laboratory findings that are very similar to those seen in patients with mutations in BTK.

## Clinical Presentation of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

Patients with either XLA or ARA are prone to develop infections because they lack antibodies. The infections frequently occur at or near the surfaces of mucus membranes, such as the middle ear (otitis), sinuses (sinusitis) and lungs (pneumonia or bronchitis), but in some instances infections can involve the bloodstream or internal organs as well.

Gastrointestinal infections can also be a problem, especially those caused by the parasite, Giardia. Giardia may cause abdominal pain, diarrhea, poor growth or loss of serum proteins like gamma globulin. Some patients with agammaglobulinemia also have problems with skin infections.

In patients without antibodies, any of these infections may invade the bloodstream and spread to other organs deep within the body, such as the bones, joints or brain. Infections in XLA and ARA patients are usually caused by microorganisms that are killed or inactivated very

effectively by antibodies in normal people. The most common bacteria that cause infections are the pneumococcus, the streptococcus, the staphylococcus and *Hemophilus influenzae*. Some specific kinds of viruses may also cause serious infections in these patients.

The defect in B-cells is present at birth, and infections may begin at any age. However, infections often do not occur with unusual frequency until sometime between 6-18 months of age because, until then, infants are protected by antibodies acquired from the mother during the pregnancy.

On physical examination, most patients with agammaglobulinemia have very small tonsils and lymph nodes (the glands in your neck). This is because most of the bulk of tonsils and lymph nodes is made up of B-lymphocytes. In the absence of B-lymphocytes, these tissues are reduced in size.

## Diagnosis of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

The diagnosis of agammaglobulinemia should be considered in any child with recurrent or severe bacterial infections, particularly if the patient has small or absent tonsils and lymph nodes.

The first screening test should be an evaluation of serum immunoglobulins. In most patients with agammaglobulinemia, all of the immunoglobulins (IgG, IgM and IgA) are markedly reduced or absent. However, there are exceptions; some patients with XLA make some IgM or IgG. In addition, normal babies make only small quantities of immunoglobulins in the first few months of life, making it difficult to distinguish a normal baby with a normal delay in immunoglobulin production from a baby with true immunodeficiency.

If the serum immunoglobulins are low or if the physician strongly suspects the diagnosis of agammaglobulinemia, the number of B-cells in the peripheral blood should be

measured. A low percentage of B-cells (nearly absent) in the blood is the most characteristic and reliable laboratory finding in patients with either XLA or ARA.

If a newborn baby has a brother, sister, maternal cousin or maternal uncle with agammaglobulinemia, the baby is at risk to have a similar immunodeficiency and the family and physicians 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; however, members of the same family usually have the same mutation. The specific gene that causes ARA can be identified by DNA analysis.

## Inheritance of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

XLA and ARA are 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.

Now that the precise gene that causes XLA has been identified, it is possible to test the female siblings (sisters) of a patient with XLA, and other female relatives such as the child's maternal aunts, to determine if they

are carriers of the disease. Carriers of XLA have no symptoms, but they have a 50% chance of transmitting the disease to each of their sons.

In some instances, it is also possible to determine if a fetus of a carrier female will be born with XLA. Currently, these genetic tests are being performed in only a few laboratories. (*See the chapter titled "Inheritance."*)



## Treatment of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

At this time, there is no way to cure patients who have agammaglobulinemia. The defective genes cannot be repaired or replaced, nor can the maturation of B-lymphocyte precursors to B-lymphocytes and plasma cells be induced. However, patients with agammaglobulinemia can be given some of the antibodies that they are lacking. The antibodies are supplied in the form of immunoglobulins (or gamma globulins) and can be given directly into the blood stream (intravenously) or under the skin (subcutaneously). (See chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”)

Immunoglobulin preparations contain antibodies that substitute for the antibodies that the patients with agammaglobulinemia cannot make themselves. These

products contain antibodies to a wide variety of microorganisms. Immunoglobulin is particularly effective in preventing the spread of infections into the bloodstream and to deep body tissues or organs. Some patients may also benefit from the use of daily oral antibiotics to protect them from infection or to treat chronic sinusitis or chronic bronchitis.

Patients with either XLA or ARA should not receive any live viral vaccines, such as live polio, the measles, mumps, rubella (MMR) vaccine, the chicken pox vaccine (Varivax) or the rotavirus vaccine (Rota-teq). Although uncommon, it is possible that live vaccines, particularly the oral polio vaccine, in patients with agammaglobulinemia can transmit the diseases that they were designed to prevent.

## Expectations for Patients with X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

Most patients with XLA or ARA who receive immunoglobulin on a regular basis will be able to lead relatively normal lives. They do not need to be isolated or limited in their activities. Active participation in team sports should be encouraged. Infections may require some extra attention from time to time, but children with

agammaglobulinemia can participate in all regular school and extracurricular activities, and when they become adults can have productive careers and families. A full active lifestyle is to be encouraged and expected.