



X-Linked Agammaglobulinemia

CHAPTER

3

The basic defect in X-Linked 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 immunoglobulins.

Definition of X-Linked Agammaglobulinemia

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, 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 microorganisms (e.g. bacteria, viruses). Antibodies are important in the recovery from infections and also protect against getting certain infections more than once. There are antibodies specifically designed to combine with each and every microorganism—much like a lock and key. When microorganisms, such as bacteria, land on a mucus membrane or enter the body, antibody molecules specific for that microorganism stick to the surface of the microorganism. Antibody bound to the surface of a microorganism can have one or more effects that are beneficial to the person. For example, some microorganisms must attach to body cells before they can cause an infection and antibody prevents the microorganism from “sticking” to the cells. Antibody attached to the surface of some microorganisms will also cause the activation of 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 bacteria which are not coated with antibody. All of these actions prevent microorganisms 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 proteins that are produced by specialized cells in the body, called the plasma cells (see chapter titled *The Immune System and Primary Immunodeficiency Diseases*). The development of plasma cells proceeds in an orderly fashion from stem cells located in the bone marrow. The stem cells give rise to immature lymphocytes called pro-B-lymphocytes. Pro-B-lymphocytes give rise to Pre-B-lymphocytes, which in turn give rise to B-lymphocytes. Each B-lymphocyte bears on its cell surface a sample of the immunoglobulin that it is able to produce. This cell surface immunoglobulin can bind foreign substances, called antigens. When the B-lymphocyte comes into contact with its specific antigen, like the pneumococcus or tetanus toxoid, it matures into an antibody secreting plasma cell. 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 B-lymphocyte precursors, but very few of these go on to become B-lymphocytes. As a result, the underlying defect in XLA is a failure of B-lymphocyte precursors to mature into B-cells. Patients with XLA have mutations in the gene that is necessary for the normal development of B-lymphocytes. This gene, discovered in 1993, is named *BTK*, or Bruton's Tyrosine Kinase, in honor of the discoverer of the disorder, Dr. Ogden Bruton. As the name of the disorder suggests, the *BTK* gene is located on the X chromosome.

Clinical Presentation of X-Linked Agammaglobulinemia

Patients with X-Linked Agammaglobulinemia (XLA) 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, sinuses and lungs, but in some instances can also involve the bloodstream or internal organs. As a result, patients with XLA may have infections that involve the sinuses (sinusitis), the eyes (conjunctivitis), the ears (otitis), the nose (rhinitis), the airways to the lung (bronchitis) or the lung itself (pneumonia). Gastrointestinal infections can also be a problem, especially with the parasite *Giardia*. *Giardia* may cause abdominal pain, diarrhea, poor growth or loss of serum proteins like gamma globulin. Some patients with XLA 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 patients are usually caused by microorganisms that are killed or inactivated very effectively by antibodies in normal people. The most common bacteria that cause infection are the pneumococcus, the streptococcus, the staphylococcus and *Hemophilus influenzae*. Some specific kinds of viruses may also cause serious infections in these patients.

On physical examination, most patients with XLA 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

The diagnosis of XLA should be considered in any boy with recurrent or severe bacterial infections, particularly if he has small or absent tonsils and lymph nodes.

The first screening test should be an evaluation of serum immunoglobulins. In most patients with XLA all of the immunoglobulins (IgG, IgM and IgA) are markedly reduced or absent. However, there are exceptions; some patients make some IgM or IgG. In addition, unaffected babies make only small quantities of immunoglobulins in the first few months of life, making it difficult to distinguish an unaffected baby with a normal delay in immunoglobulin production from a baby with a true immunodeficiency. If the serum immunoglobulins are low or if the physician strongly suspects the diagnosis of XLA, the number of B-cells in the peripheral blood should be tested. A low percentage of B-cells (nearly absent) in the blood is the most characteristic and reliable laboratory finding in patients with XLA.

If a baby boy has a brother, maternal cousin or maternal uncle with XLA, the newborn baby is at risk to have XLA and his family and his 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.

Inheritance of X-Linked Agammaglobulinemia

X-Linked Agammaglobulinemia (XLA) is a genetic disease and can be *inherited* or passed on in a family. It is inherited as an X-linked recessive trait. (For more information on how X-Linked recessive traits are inherited, see chapter titled *Inheritance*.) 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 have a 50% chance of transmitting the disease to each of their sons (see chapter titled *Inheritance*). 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.

Treatment for X-Linked Agammaglobulinemia

At this time, there is no way to cure patients who have X-Linked Agammaglobulinemia (XLA). The defective gene cannot be repaired or replaced, nor can the maturation of B-lymphocyte precursors to B-lymphocytes and plasma cells be induced. However, patients with XLA 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 *Specific Medical Therapy*). The immunoglobulin preparations contain antibodies that substitute for the antibodies that the XLA patient can not make himself. They 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 benefit from the use of oral antibiotics every day to protect them from infection or to treat chronic sinusitis or chronic bronchitis.

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

Expectations for X-Linked Agammaglobulinemia Patients

Most X-Linked Agammaglobulinemia (XLA) patients 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 XLA 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.