

Understanding **Agammaglobulinemia**

By Bob Geng, MD

The inability to naturally produce immunoglobulins in the body is the hallmark of agammaglobulinemia, but with immune globulin therapy and vigilance regarding their health, patients' prognosis is good.

AGAMMAGLOBULINEMIA is a condition in which the body cannot produce immunoglobulins (antibodies that fight infection). The exact incidence of this condition is unknown, but it is estimated to be in the range of one in 300,000. In 1952, it was the first primary immunodeficiency to be discovered by Colonel Ogden Bruton who described a young boy with recurrent respiratory infections who could not make specific antibodies, but was successfully treated by immune globulin (IG) replacement therapy. The condition was named in honor of Colonel Bruton, and Bruton's agammaglobulinemia became the name of the X-linked type of agammaglobulinemia (XLA), which comprises the majority of all agammaglobulinemia cases.

In 1993, it was discovered that XLA is caused by a defect in the Bruton tyrosine kinase (BTK) gene, which is crucial for B-cell maturation and development. The BTK gene is located on the long arm of the X chromosome. Therefore, females are only carriers, and males are only affected. In the absence of normal BTK expression, B-cell development cannot proceed, and B cells cannot evolve to become plasma cells that produce immunoglobulin.

Not all cases of agammaglobulinemia are XLA. Since the discovery of the BTK gene, only 85 percent of agammaglobulinemia cases were identified to have a mutation in BTK. Furthermore, by definition, an X-linked disease affects only boys, and for some time, there have been reports of girls with the same clinical presentation of XLA. Therefore, over the past two decades, further investigations have revealed several additional genetic defects of proteins that work along with BTK in the process of B-cell development. When any of these genes and the proteins they encode are defective, B-cell maturation does not occur, and immunoglobulins are not produced. These identified defects are the mu heavy chain of immunoglobulin molecule, lambda 5, Ig-alpha, Ig-beta and BLNK. All these proteins help to support the maturation of pro-B cells into pre-B cells, which is a crucial step in B-cell development. The inheritance pattern of these gene defects is autosomal recessive, meaning that a person needs both copies of the gene to be defective in order to have the disease. Therefore, since these defects are not found on the X chromosome, females can be affected as much as males.

The inability for B-cell maturation to take place leads to an inability to produce antibodies against various invading pathogens (bacteria, viruses, fungi, etc.). Antibodies are very important in the body's defense against invading pathogens for two main reasons: 1) when they bind to bacteria, it creates a docking site for additional inflammatory molecules such as complements to bind and destroy the bacteria; and 2) antibodies

help to defend the body by facilitating the process in which other cells clear out bacteria. The main workhorse of the immune system is the phagocyte (neutrophils, macrophages, dendritic cells, etc.), which defends the body by engulfing or ingesting the invading bacteria so it can be destroyed inside the cell. When antibodies bind the surface of bacteria, it makes it easier for the phagocyte to recognize and engulf them. This process is called opsonization. Without antibody binding, bacteria do not appear as "attractive" to the phagocyte, and they do not ingest bacteria as efficiently.

Clinical Presentation

The main clinical features of agammaglobulinemia are recurrent upper and lower respiratory tract infections. These infections start at a very young age, in general, but often start after maternal antibody stores in the infant are depleted, since maternal antibodies protect the infant for the first several months of life. Respiratory tract infections are most often caused by bacteria in which antibody binding is crucial for clearance. These bacteria include, but are not limited to, *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Streptococcus pyogenes* and *Pseudomonas* species. Recurrent respiratory tract infections not only cause significant morbidity during the actual episode of illness, but also predispose patients to developing chronic lung disease. Repeated courses of pneumonia will lead to chronic inflammatory changes in the airways, which may lead to scarring and bronchiectasis (abnormal dilation of the airways leading to signs and symptoms of chronic airway obstruction).

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Beyond respiratory tract infections, other bacteria such as *Campylobacter* and *Salmonella* can lead to infections in the gastrointestinal tract. In addition, patients may develop more serious giardia (parasite) infections if they are exposed.

If any bacterial infections are left untreated, they can progress to bacteremia (presence of bacteria in the bloodstream), sepsis



(infection of the blood stream) and invasion of other vital organ systems such as the central nervous system (meningitis or encephalitis), bones (osteomyelitis) and joints (infectious arthritis). While the spread of bacterial infection can happen in all patients, agammaglobulinemia patients are much more susceptible due to the absence of antibodies.

In addition to bacterial infections, agammaglobulinemia patients are susceptible to certain viral infection, namely the enteroviruses, which include coxsackie virus and echovirus. These viruses can lead to chronic infection of the central nervous system, skin, muscle and liver. The most well-known enterovirus is poliovirus, and in the past when live-attenuated vaccines were used, agammaglobulinemia patients developed debilitating polio infections. Since the advent of the inactivated polio vaccine in the U.S., that issue has resolved; however, for areas in the world where the live-attenuated vaccine is still used, this remains an issue.

Aside from infectious complications, agammaglobulinemia patients are also more susceptible to the development of certain autoimmune complications. The mechanisms in which these complications develop are not completely understood. While patients cannot make autoimmune antibodies due to deficient B cells, the phenomenon of autoimmune disease can still occur. Autoimmune conditions often seen include cytopenias (low counts of various blood cells), inflammatory skin conditions, arthritis (inflammation of the joints) and chronic gastrointestinal inflammation.

Diagnosis

Agammaglobulinemia is diagnosed through both clinical recognition of signs/symptoms and laboratory findings. Clinical presentation may include poor growth, failure to thrive, recurrent

sinopulmonary infections, recurrent gastrointestinal infections and absence of tonsils (due to absence of B cells).

The main laboratory finding is the absence of all classes of serum immunoglobulin. The serum levels of IgA, IgM and IgG are all extremely low, often below the point of detection. In addition to low immunoglobulins, the cellular immune panel is abnormal because B cells are often absent as well. On the flow cytometry (cell counter) of the immune cells of the blood, the number of CD-19 or CD-20 cells (markers on the surface of B cells) is greatly diminished or often absent. Generally, according to expert guidelines, presence of less than 2 percent B cells is considered a necessary criteria for a diagnosis. Furthermore, patients have virtually no antibody response to vaccinations. Specific antibody levels (i.e., tetanus, diphtheria, streptococcus pneumonia, etc.) following those vaccinations are absent or extremely low. In addition, around 25 percent of patients have low neutrophil counts, which may be due to the persistent presence of recurrent systemic infections.

The definitive diagnosis of agammaglobulinemia is made with genetic testing. For Bruton's XLA, a definitive diagnosis is made by the absence of the BTK gene expression (such as by messenger RNA detection), a specific BTK gene mutation by genetic sequencing, or by lack of detection of BTK protein in cells. While on a therapeutic basis, treatment can be initiated for probable diagnosis, a definitive diagnosis is important for genetic counseling purposes due to the known pattern of both Bruton's and autosomal recessive agammaglobulinemia. When patients receive a definitive diagnosis, there are genetic testing options that exist for parents to receive carrier status evaluation.

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Because infants have residual levels of maternal antibodies in the first 6 months of their lives, diagnosis of agammaglobulinemia is often not made until after that time. On average, only half of Bruton's cases are diagnosed by 1 year of age, but almost all cases are generally diagnosed by 5 years of age.

While a swift diagnosis is important, it is equally important to recognize that other conditions can appear similar to agammaglobulinemia. The differential diagnosis of agammaglobulinemia can include common variable immune deficiency, transient hypogammaglobulinemia of infancy, Wiskott-Aldrich syndrome and combined immune deficiencies such as severe combined immune deficiency with B-cell defects.

Management

The main treatment for agammaglobulinemia is IG replacement therapy. Replacement can be achieved by either the intravenous (IV) or subcutaneous (SC) route. IVIG is generally administered every three to four weeks, and SCIG is generally administered weekly, but can be given multiple times a week or every other week. While there is no established dosing regimen for IG replacement, the general guideline consensus is between 400 mg/kg/month and 600 mg/kg/month. Many practitioners will start at that level, and will titrate the dose according to clinical presentation (i.e., frequency/severity of infections and tolerability) and laboratory parameters (i.e., serum IgG trough level).

There is a dose-dependent relationship between dose and serum IgG trough level. According to a study by Orange et al., there is, on average, an increase of 121 mg/dL of serum IgG for every 100 mg/kg increase in dose of IG replacement. There is also a relationship between the serum IgG trough level and infection frequency. According to a study by Lucas et al., a serum IgG level of greater than 800 mg/dL is necessary to be infection-free in XLA patients. IG replacement therapy has led to significant reductions in infection frequency, severity and hospitalizations for agammaglobulinemia patients. In addition, due to the decrease in acute infections, the number of chronic lung diseases has decreased.

While replacement therapy has led to significant advances in the treatment of agammaglobulinemia, antibiotic therapy is still often necessary. First, IVIG and SCIG only replace the IgG, but not the IgM or IgA that are also deficient. Those two other classes of immunoglobulins play important roles in host defense against pathogens. Second, unlike naturally produced antibodies, replacement immunoglobulins do not fluctuate appropriately with the presence of invading pathogens. During active infection, the body often needs more antibodies to be present to fight off the infection than it does when a person is not sick. Therefore, patients and caregivers still need to be vigilant about infections, and they need to seek medical attention and have a low threshold for using antimicrobials to combat infections even if they are being adequately treated with IG replacement therapy.

Patients with agammaglobulinemia should not receive live-attenuated vaccines since they have a compromised immune system. The exposure to live-attenuated vaccines may predispose them to develop serious systemic infections of the pathogen

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to which they are exposed. These include the measles/mumps/rubella, rotavirus and chickenpox vaccines. Because most patients with agammaglobulinemia are on IG replacement therapy, they are already receiving passive immunity to these diseases, and typically do not need the vaccinations. Furthermore, one of the hallmarks of agammaglobulinemia is that these patients cannot make antibodies following stimulation from vaccines. However, there are some immunologists who still feel agammaglobulinemia patients may benefit from inactivated (killed) vaccines to elicit a T-cell immune response. This is because agammaglobulinemia patients generally have intact T-cell function, and the body responds to many infections via a combination of T-cell and antibody responses.

A Healthy Prognosis

Overall, the prognosis is good for patients with agammaglobulinemia who are treated with IG replacement therapy. IVIG and SCIG have dramatically reduced the morbidity and mortality of disease. With proper follow-up, strict adherence to IG replacement therapy and surveillance for infectious and autoimmune complications, most patients lead a normal and productive life. ■

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