CONDITION

Agammaglobulinemia

Learn how agammaglobulinemia affects antibody production, including its symptoms, inherited causes, diagnosis, immunoglobulin replacement, and follow-up care.

WHAT IT IS
Rare inherited antibody deficiency

BODY SYSTEM
Immune system

MAIN SYMPTOMS
Repeated ear or sinus infections, pneumonia or bronchitis, persistent cough, diarrhea

WHAT CAUSES IT
Inherited genetic changes

HOW IT IS DIAGNOSED
Immunoglobulin blood tests, B-cell flow cytometry, genetic testing

MAIN TREATMENT
Lifelong immunoglobulin replacement therapy

CAN IT BE CURED?
No, treatment cannot correct genetic cause

IS IT AN EMERGENCY?
Sometimes, with difficulty breathing

LONG-TERM OUTLOOK
Lifelong condition with fewer infections on treatment

Overview

Agammaglobulinemia is a rare immune system disorder in which the body makes very few or no effective antibodies. Antibodies, also called immunoglobulins, are proteins that recognize germs and help protect against infection.

The condition develops when immune cells called B lymphocytes, or B cells, do not mature normally. Mature B cells can become plasma cells, which produce antibodies. Without enough working B cells and antibodies, a person is especially vulnerable to certain bacterial infections.

The most common inherited form is X-linked agammaglobulinemia, often shortened to XLA. It is caused by changes in the BTK gene on the X chromosome. Because of the way XLA is inherited, it mainly affects boys and men. Less common genetic forms can affect people of any sex.

Babies with agammaglobulinemia may seem healthy during their first few months. Antibodies transferred from the mother during pregnancy provide temporary protection. Infections often become more noticeable after these antibodies decline, usually during infancy or early childhood. The timing varies, and some people are diagnosed later.

Agammaglobulinemia is a lifelong condition, but treatment can replace missing antibodies and reduce infections. Early diagnosis and regular care are important because repeated infections can damage the lungs, ears, sinuses, and other organs.

Symptoms

The main feature of agammaglobulinemia is a pattern of repeated, unusually severe, or hard-to-clear infections. Symptoms depend on the part of the body affected.

Common problems include:

Bacterial infections are often caused by organisms that have an outer capsule, including Streptococcus pneumoniae and Haemophilus influenzae . Antibodies normally play an important role in controlling these bacteria.

People may also be vulnerable to Giardia , a parasite that can cause prolonged diarrhea, stomach cramps, bloating, and weight loss. Some enteroviruses can cause serious infections involving the brain, spinal cord, muscles, or joints, although these complications are less common.

The tonsils and lymph nodes may be very small or difficult to feel because these tissues normally contain many mature B cells. However, this finding alone cannot confirm or rule out the condition.

Some people develop joint swelling or pain. Others have low numbers of neutrophils, a type of white blood cell that helps fight bacteria, especially around the time of diagnosis. Symptoms vary widely, including among relatives with the same genetic change.

- Repeated ear or sinus infections
- Pneumonia or bronchitis
- Persistent cough or nasal drainage
- Skin and soft-tissue infections
- Eye infections
- Diarrhea or other intestinal symptoms
- Poor growth or difficulty gaining weight in children

- Infections that return soon after antibiotics like amoxicillin or doxycycline are stopped
- A need for intravenous antibiotics or hospital treatment

Causes and risk factors

X-linked agammaglobulinemia is caused by a harmful change in the BTK gene. This gene provides instructions for making Bruton tyrosine kinase, a protein needed for early B cells to mature. When the protein does not work properly, B-cell development stops before the cells can produce antibodies.

The altered gene is carried on the X chromosome. Boys and men have one X chromosome, so one altered copy can cause XLA. Women with one altered copy are usually carriers and generally do not have the condition, although rare exceptions can occur.

A carrier has a chance of passing the altered gene to each child. Genetic counseling can explain the inheritance pattern for a specific family and discuss testing options without assuming that any relative is affected.

Much less commonly, agammaglobulinemia results from changes in other genes involved in B-cell development. These forms may follow different inheritance patterns and can affect both males and females.

Factors that raise the possibility of an inherited form include:

Some medicines, cancers, kidney or intestinal diseases, and other medical conditions can also lower antibody levels. These are secondary, or acquired, antibody deficiencies rather than inherited agammaglobulinemia. Distinguishing between inherited and acquired causes is an important part of the evaluation.

- A close relative with XLA or another antibody deficiency
- Maternal male relatives who had severe infections or died from infection at a young age
- Repeated bacterial infections beginning in infancy or childhood
- Very low immunoglobulin levels together with very few mature B cells

Diagnosis

Diagnosis usually involves a clinical history, physical examination, blood tests, and sometimes genetic testing. An allergist-immunologist, often called an immunologist, typically directs the evaluation.

The clinician will ask about the number, type, and severity of infections. They may review which organisms were found, how well antibiotics worked, whether growth has been affected, and whether relatives have had similar problems.

Blood testing usually measures the major immunoglobulin classes, including IgG, IgA, and IgM. Results must be compared with normal ranges for the person's age because antibody levels change during infancy and childhood.

Flow cytometry is a laboratory test that counts different types of immune cells. People with classic XLA usually have very few mature B cells. Other white blood cells may be measured to help distinguish agammaglobulinemia from other immune disorders.

Clinicians may also consider:

Genetic testing can identify a disease-causing change in BTK or another relevant gene. A confirmed result can support the diagnosis, guide testing of relatives, and provide information for genetic counseling. However, a negative genetic test does not always exclude an immune disorder.

Starting immunoglobulin treatment can affect later antibody measurements. When possible, diagnostic blood samples are collected before replacement therapy begins, but necessary treatment should not be delayed when there is a serious infection.

- Blood counts to evaluate neutrophils and other cells
- Tests for previous responses to vaccines, when these results can be interpreted reliably
- Cultures or molecular tests to identify an active infection
- Imaging or lung function tests if there has been repeated pneumonia or a chronic cough
- Tests for protein loss, medication effects, cancer, or other acquired causes of low antibodies

Treatment and management

The main treatment is lifelong immunoglobulin replacement therapy. This treatment provides IgG antibodies collected from screened human plasma donors. It lowers the risk of many infections but does not restore normal B-cell development or cure the underlying genetic condition.

Immunoglobulin can be given in two main ways. Intravenous immunoglobulin, or IVIG, is infused into a vein at regular intervals. Subcutaneous immunoglobulin, or SCIG, is delivered under the skin in smaller, more frequent infusions. Some people receive SCIG at home after training. The best approach depends on age, health, preferences, vein access, side effects, and

insurance or local availability.

Headache, tiredness, chills, muscle aches, and reactions around an infusion site can occur. Serious reactions are uncommon but require prompt medical assessment. The care team may adjust the infusion method or schedule when reactions occur.

Immunoglobulin therapy is monitored using infection history, clinical health, and blood IgG levels. The goal is not simply to reach one laboratory number. Treatment is adjusted by the specialist according to how well infections are controlled and whether complications are present.

Bacterial infections should be assessed and treated promptly. Antibiotics may sometimes be needed for longer than they would be in a person with a typical immune response. Preventive antibiotics may be considered for selected people who continue to have infections, but this requires an individualized decision.

Additional management may include airway-clearance therapy for chronic mucus, treatment for asthma-like symptoms, nutritional support, hearing evaluation, or care from lung, ear, or digestive specialists.

Live vaccines may cause infection in people with severe antibody deficiency. A person with agammaglobulinemia should speak with their immunology team before receiving any vaccine, particularly live vaccines. Inactivated vaccines cannot reproduce in the body, but they may provide limited protection when antibody production is absent. Family members should also ask about vaccine precautions, especially in countries where oral polio vaccine is used.

Stem cell transplantation is not routine treatment for classic XLA. It may be considered only in unusual circumstances at highly specialized centers. Gene-based treatments remain an area of research.

Complications

Repeated respiratory infections can injure the airways. Over time, this may cause bronchiectasis, a permanent widening and scarring of the breathing tubes that makes it harder to clear mucus. Bronchiectasis can lead to chronic cough, shortness of breath, and further infections.

Other possible complications include chronic sinus disease, hearing loss after repeated ear infections, persistent intestinal infection, poor growth, and inflammatory joint problems. Rare enterovirus infections can affect the brain and nervous system.

Complications are not inevitable. Regular immunoglobulin replacement, early treatment of infections, and monitoring for changes in lung or digestive health can reduce risk.

Follow up

Routine follow-up with an immunologist is needed even when infections are well controlled. Visits may review infusion tolerance, IgG levels, antibiotic use, missed school or work, growth in children, and any new breathing, hearing, joint, or digestive symptoms.

People with a history of lung infections may need periodic lung function testing or imaging. A persistent wet cough, falling exercise tolerance, or repeated pneumonia should be reported rather than saved for the next routine visit.

Contact the medical team promptly for fever, worsening cough, ear pain, persistent diarrhea, an infected wound, or other signs of infection. Early assessment is especially important if symptoms are not improving as expected.

Seek urgent or emergency care for difficulty breathing, blue or gray lips, severe dehydration, confusion, a seizure, a stiff neck with severe illness, fainting, or rapidly worsening symptoms. An emergency medical identification card or phone record can help inform clinicians about the immune disorder and current treatment.

Sources

- GeneReviews: X-Linked Agammaglobulinemia . GeneReviews®, University of Washington, Seattle; available through the National Center for Biotechnology Information Bookshelf.
- Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency . Journal of Allergy and Clinical Immunology . 2015;136(5):1186-1205.e78.
- Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence . Journal of Allergy and Clinical Immunology . 2017;139(3 Suppl):S1-S46.
- Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee . Journal of Clinical Immunology . 2022;42:1473-1507.
- X-Linked Agammaglobulinemia . Immune Deficiency Foundation.
- Altered Immunocompetence: General Best Practice Guidelines for Immunization . Centers for Disease Control and Prevention.