

Chronic Granulomatous Disease

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Chronic granulomatous disease is a disorder that causes the immune system to malfunction, resulting in a form of immunodeficiency.

Keywords: genetic conditions

1. Introduction

Immunodeficiencies are conditions in which the immune system is not able to protect the body from foreign invaders such as bacteria and fungi. Individuals with chronic granulomatous disease may have recurrent bacterial and fungal infections. People with this condition may also have areas of inflammation (granulomas) in various tissues that can result in damage to those tissues. The features of chronic granulomatous disease usually first appear in childhood, although some individuals do not show symptoms until later in life.

People with chronic granulomatous disease typically have at least one serious bacterial or fungal infection every 3 to 4 years. The lungs are the most frequent area of infection; pneumonia is a common feature of this condition. Individuals with chronic granulomatous disease may develop a type of fungal pneumonia, called mulch pneumonitis, which causes fever and shortness of breath after exposure to decaying organic materials such as mulch, hay, or dead leaves. Exposure to these organic materials and the numerous fungi involved in their decomposition causes people with chronic granulomatous disease to develop fungal infections in their lungs. Other common areas of infection in people with chronic granulomatous disease include the skin, liver, and lymph nodes.

Inflammation can occur in many different areas of the body in people with chronic granulomatous disease. Most commonly, granulomas occur in the gastrointestinal tract and the genitourinary tract. In many cases the intestinal wall is inflamed, causing a form of inflammatory bowel disease that varies in severity but can lead to stomach pain, diarrhea, bloody stool, nausea, and vomiting. Other common areas of inflammation in people with chronic granulomatous disease include the stomach, colon, and rectum, as well as the mouth, throat, and skin. Additionally, granulomas within the gastrointestinal tract can lead to tissue breakdown and pus production (abscesses). Inflammation in the stomach can prevent food from passing through to the intestines (gastric outlet obstruction), leading to an inability to digest food. These digestive problems cause vomiting after eating and weight loss. In the genitourinary tract, inflammation can occur in the kidneys and bladder. Inflammation of the lymph nodes (lymphadenitis) and bone marrow (osteomyelitis), which both produce immune cells, can lead to further impairment of the immune system.

Rarely, people with chronic granulomatous disease develop autoimmune disorders, which occur when the immune system malfunctions and attacks the body's own tissues and organs.

Repeated episodes of infection and inflammation reduce the life expectancy of individuals with chronic granulomatous disease; however, with treatment, most affected individuals live into mid- to late adulthood.

2. Frequency

Chronic granulomatous disease is estimated to occur in 1 in 200,000 to 250,000 people worldwide.

3. Causes

Mutations in the *CYBA*, *CYBB*, *NCF1*, *NCF2*, or *NCF4* gene can cause chronic granulomatous disease. There are five types of this condition that are distinguished by the gene that is involved. The proteins produced from the affected genes are parts (subunits) of an enzyme complex called NADPH oxidase, which plays an essential role in the immune system. Specifically, NADPH oxidase is primarily active in immune system cells called phagocytes. These cells catch and destroy foreign invaders such as bacteria and fungi. Within phagocytes, NADPH oxidase is involved in the production of a toxic

molecule called superoxide. Superoxide is used to generate other toxic substances, which play a role in killing foreign invaders and preventing them from reproducing in the body and causing illness. NADPH oxidase is also thought to regulate the activity of immune cells called neutrophils. These cells play a role in adjusting the inflammatory response to optimize healing and reduce injury to the body.

Mutations in the *CYBA*, *CYBB*, *NCF1*, *NCF2*, and *NCF4* genes result in the production of proteins with little or no function or the production of no protein at all. Mutations in the genes that cause chronic granulomatous disease that prevent the production of any functional protein are designated "0". For example, mutations in the *CYBB* gene that lead to no functional beta chain are designated *CYBB*⁰. Mutations that lead to a reduction of the amount of protein produced are designated "-", for example, *CYBB*⁻.

Without any one of its subunit proteins, NADPH oxidase cannot assemble or function properly. As a result, phagocytes are unable to kill foreign invaders and neutrophil activity is not regulated. A lack of NADPH oxidase leaves affected individuals vulnerable to many types of infection and excessive inflammation.

Some people with chronic granulomatous disease do not have an identified mutation in any of these genes. The cause of the condition in these individuals is unknown.

3.1. The Genes Associated with Chronic Granulomatous Disease

- *CYBA*
- *CYBB*
- *NCF1*
- *NCF2*
- *NCF4*

4. Inheritance

When chronic granulomatous disease is caused by mutations in the *CYBB* gene, the condition is inherited in an X-linked recessive pattern. The *CYBB* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons. Rarely, females with one altered copy of the *CYBB* gene have mild symptoms of chronic granulomatous disease, such as an increased frequency of bacterial or fungal infections.

When chronic granulomatous disease is caused by *CYBA*, *NCF1*, *NCF2*, or *NCF4* gene mutations, the condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Men and women are affected by autosomal recessive conditions equally.

5. Other Names for This Condition

- autosomal recessive chronic granulomatous disease
- CGD
- granulomatous disease, chronic
- X-linked chronic granulomatous disease

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