

Chronic Granulomatous Disease and Other Phagocytic Cell Disorders



Chapter 15

Chronic Granulomatous Disease (CGD) is a genetic (inherited) disease in which the body's cells that eat certain invaders (also called phagocytes) do not make hydrogen peroxide and other chemicals needed to kill certain bacteria and molds. As a result of this defect, patients with CGD get more infections, and they also get too many immune cells forming "knots" called granulomas, hence the name of the disease. Another problem in CGD is that patients can get excessive inflammation even when there is not an infection, and that inflammation can cause diarrhea, and bladder and kidney problems.

Definition of Chronic Granulomatous Disease

Phagocytes (from the Greek, phagein, "to eat") are white blood cells that can surround and ingest microorganisms into tiny compartments in the cell. These compartments, called phagosomes, are filled with chemicals that help kill bacteria and fungi. These chemicals include hydrogen peroxide and bleach, which are made in these compartments and reach high levels there. There are two main types of phagocytes, neutrophils and monocytes. They crawl out of blood vessels and head directly for where there is infection. When they get to the infection site, they seek out the bacteria or fungus and ingest it into the phagosomes. Then the normal phagocyte pumps hydrogen peroxide, bleach and other toxins into the compartment to kill the infecting organism.

CGD phagocytes go normally to sites of infection, where they ingest infecting microbes. However, they cannot make the hydrogen peroxide and bleach that

normal cells do because they are missing key proteins that help generate the bleach. It is very remarkable that the phagocytes of patients with CGD can defend against most infections, but not all. Patients with CGD have normal immunity to most viruses and some bacteria and fungi, which is why they are not infected all the time. They may go months to years without infections and then have a severe one. Patients with CGD make normal antibodies, so unlike patients with lymphocyte problems, patients with CGD are not particularly susceptible to viruses.

In summary, CGD phagocytes fail to make hydrogen peroxide and bleach, leading to infections with only a few bacteria and fungi including *Staphylococcus aureus*, *Burkholderia cepacia complex*, *Serratia marcescens*, *Nocardia* and *Aspergillus*. Much of the rest of their immune system is normal.

Clinical Presentation of Chronic Granulomatous Disease

Children with CGD are usually healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria *Serratia marcescens*, and any infant with an infection with this particular organism should be tested for CGD. In fact, any infant or child with a significant infection with any of the organisms previously listed should be tested for CGD.

Infections in CGD may involve any organ or tissue, but the skin, lungs, lymph nodes, liver and bones are the usual sites of infection. Infections may rupture and drain with delayed healing and residual scarring. Infection of lymph nodes (under the arm, in the groin, in the neck) is a common problem in CGD, often requiring drainage or surgery along with antibiotics.

Pneumonia is a common problem in CGD. Pneumonias due to the fungus *Aspergillus* may come on very slowly, initially only causing fatigue, and only later causing cough or chest pain. Fungal pneumonias often do not cause fever. In contrast, bacterial infections (*Staphylococcus aureus*, *Burkholderia cepacia complex*, *Serratia marcescens*, *Nocardia*) usually come on very quickly with fever and cough. *Nocardia* in particular, causes high fevers and lung abscesses that can destroy parts of the lung. It is important to identify infections and the causative pathogen early and treat the infection completely, usually for a long period of time, so it is critical to seek medical attention early. Chest X-rays and computerized tomography (CT) scans of the chest are very helpful. However, if pneumonia is seen, it is very important to figure out exactly which microbe is causing it, which may require a biopsy usually done with a needle or a bronchoscope and not surgery. Treatment may require many weeks.

Liver abscesses occur in about a third of patients with CGD. An abscess can present as fever and fatigue, but it may also cause mild pain over the right upper

abdomen. Some sort of scan is required for diagnosis (magnetic resonance imaging or MRI, CT scan, ultrasound), and needle biopsy are necessary to determine the specific cause of the infection.

Staphylococcus aureus causes most liver abscesses in patients with CGD. Often the liver abscesses are hard to drain and may need surgery. Sometimes abscesses can be treated with antibiotics and steroids, which reduce the inflammation and let the antibiotics work better.

Bone infection (osteomyelitis) can involve the hands and feet, but can also involve the spine, particularly if a fungal infection in the lungs spreads to the spine.

There are new antibiotics and antifungals becoming available, many very active by mouth. Rates of cure for infections in patients with CGD are very high and are greatly improved by early diagnosis and therapy.

One of the most difficult aspects of CGD is the bowel problems. About 40-50% of patients with CGD develop inflammation in the intestine that is not clearly due to a specific infection. This inflammation can be mistakenly diagnosed as Crohn's disease, and it does look a lot like it. It also responds to most of the same treatments (antibiotics, steroids, other immune suppression drugs). However, injectable drugs that block the inflammatory molecule tumor necrosis factor alpha (TNF α), which are very effective in Crohn's disease, lead to severe infections in patients with CGD and should be avoided. Similar problems can occur in the bladder or ureters, causing problems with urination.

Diagnosis of Chronic Granulomatous Disease

There are five different genetic kinds of CGD. The most common form is called X-linked, because it is on the X chromosome (70% of cases in the U.S) and affects almost only boys. However, the other four types are located on other chromosomes and have autosomal recessive inheritance. These forms affect boys and girls equally, so around 15% of cases are in girls. For the X-linked form, boys get disease while girls are relatively asymptomatic carriers. (*See chapter titled "Inheritance."*)

The severity of CGD can partly be determined from the specific mutation in the gene. Usually infections begin in childhood leading to the diagnosis. However, some patients with CGD may not have infections until late adolescence or adulthood. Pediatricians and internists cannot ignore the possibility of CGD in an adult with pneumonia with a characteristic CGD organism.

Therefore, any patient of any age with a CGD type infection (*Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* and *Aspergillus*) should be tested for CGD unless there is a good reason not to.

The most accurate test for CGD measures hydrogen peroxide in phagocytes using a chemical called dihydrorhodamine. The test is called dihydrorhodamine reduction or DHR. There are other types of tests still used to diagnose CGD, such as the Nitroblue Tetrazolium (NBT) slide test. The NBT test is still valuable but more prone to incorrect reading.

Once the diagnosis of CGD is made, it is useful to confirm the genetic sub-type of CGD for genetic counseling and because some types of CGD need bone marrow transplantation more than others.

Treatment of Chronic Granulomatous Disease

Early diagnosis of infection and prompt, aggressive use of appropriate antibiotics is the best way to treat CGD infections. Initial therapy with antibiotics aimed at the usual suspects makes sense while waiting for results of cultures, but it is important to try to identify the specific infection and not just guess all the way along. Intravenous antibiotics may be needed for serious CGD infections. Phagocyte transfusions are sometimes used when an infection is especially life threatening.

All patients with CGD should receive antibiotic prophylaxis (prevention), usually with trimethoprim/sulfamethoxazole (*cotrimoxazole*, *Bactrim* or *Sepra*) and itraconazole. These reduce infections by almost 70%. Since the infections that are important in CGD are in the environment and not carried in our bodies normally, the effect of prophylaxis is to build a wall around the patient: it can still be jumped over, but

prophylaxis makes it harder for infections to get in. This also means that the organisms that are an issue are not usually seeing the antibiotics, so they do not develop resistance.

Daily doses of the oral antifungal drug itraconazole reduce fungal infections in CGD. Maximum infection prophylaxis for CGD involves treatment with twice-daily oral doses of cotrimoxazole and once daily itraconazole, plus three times weekly injections of gamma interferon. With these prophylactic treatments, the average incidence of severe infections in CGD is less than once every four years. Of course, individual factors will influence this frequency as well.

Interferon gamma is made normally by the body, but it can also be given by injection to boost immunity. Patients with CGD who receive interferon gamma (under the skin three times a week) have 70% fewer infections, and

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when infections do occur, they may be less serious. Interferon gamma is not a cure for CGD. It may cause fever, fatigue and depression. Acetaminophen (Tylenol) taken before the injection may help. Some patients choose not to take interferon gamma because they do not like injections, because of the cost or because of the side effects. Even doses lower than the standard recommendation may provide some protection against infection. Side effects are usually related to the dose and may be decreased by lowering the dose or how often it is given.

CGD can be cured by bone marrow transplantation, but this is complex and not yet widely available. Patients may lack a fully matched normal sibling or may be doing well enough with normal treatment that they do not want a transplant. However, some patients with CGD have good transplant options and may want to explore this. With the right donor and a healthy patient, bone marrow transplantation can be highly effective. Gene therapy is not yet an option to cure CGD. However, some laboratories are working on this new therapy, and gene therapy might be an option in the future.

Many physicians suggest that swimming should be confined to well-chlorinated pools. Brackish water in particular may expose patients to organisms that are specifically dangerous in CGD (*Francisella philomiragia*, *Chromobacterium violaceum*). Aspergillus is present in many samples of marijuana, so patients with CGD should avoid it.

A major risk to patients with CGD is the handling of garden mulch (shredded moldy tree bark) or potting soil. This type of exposure can cause a severe life-threatening pneumonia due to inhalation of the fungus Aspergillus, which likes to live in decaying plant matter. Patients with CGD should remain indoors during mulching in neighboring yards. Once the mulch is settled firmly on the ground and is not being spread or raked, it is much less of a danger to patients with CGD. Patients should avoid turning manure or compost piles, repotting house plants, cleaning cellars or garages, removing carpets, performing demolition, digging in dirt, dusty conditions, cutting grass, raking leaves, hay rides and barns. Patients should see their doctors about even minor infections.

Expectations for Patients with Chronic Granulomatous Disease

The quality of life and longevity for patients with CGD has improved dramatically over the last 50 years. The great majority of children with CGD can expect to live well into adulthood, and many adult patients with CGD have jobs, get married and have children. However, patients with CGD remain at significant risk for infection throughout life. They must take their prophylaxis, remain cautious, and get early diagnosis and treatment for possible infections.

Hospitalizations may be required for patients with CGD to locate sites and causes of infections. Intravenous antibiotics may be needed for serious infections. Prophylactic antibiotics and treatment with interferon gamma increase healthy periods. The vast majority of patients reach adulthood, when serious infections tend to occur less frequently.

Other Phagocytic Cell Disorders

The chief phagocytic white blood cell is the polymorphonuclear granulocyte (PMN, also known as neutrophil). To be effective, the neutrophil must move to a site of infection, ingest the organism and then kill the organism. (See chapter titled “*The Immune System and Primary Immunodeficiency Diseases.*”)

Neutropenias

Neutropenias are disorders characterized by low numbers of granulocytes, usually defined as a neutrophil count of less than 500 cells/ul (normal is more than 2,000 cells/ul). Depending on its severity and duration, neutropenia can lead to serious and fatal infection or intermittent infection of the skin, mucus membranes, bones, lymph nodes, liver, spleen or blood stream (sepsis).

Neutropenia can occur at birth and can be life-long. One form, termed severe congenital neutropenia (Kostmann syndrome), is an autosomal recessive disorder. This disorder is associated with a gene abnormality of a gene called *HAX1*. These infants require treatment with granulocyte colony stimulating factor (G-CSF) and may be candidates for bone marrow transplantation.

Another form of neutropenia is cyclic neutropenia, which is an autosomal dominant disorder in which the neutropenia occurs every two to four weeks and lasts about a week. It is associated with a gene defect termed *ELA2*.

A third form, benign chronic neutropenia, has low, but not life threatening, neutropenia and is often asymptomatic. A final form is immune neutropenia, usually present at birth but sometimes presents later. In this condition, there is an antibody to the neutrophils that causes their destruction. Treatment for all of these disorders may include antibiotics for infections, prophylactic antibiotics, intravenous immunoglobulin, G-CSF injections or bone marrow transplantation.

Several primary immunodeficiencies may have an associated neutropenia. These immunodeficiencies include X-linked hyper-IgM syndrome (CD40 ligand deficiency), Common Variable Immune Deficiency (CVID), X-linked Agammaglobulinemia (XLA), WHIM syndrome, Wiskott-Aldrich Syndrome and GATA2 deficiency. Some of these patients acquire an autoimmune antibody to their own neutrophils. This antibody causes autoimmune neutropenia due to accelerated destruction of the neutrophils. All of these diseases are discussed in more detail in other chapters in this Handbook.

Phagocyte Killing Defects

Several rare phagocyte defects involve an inability to kill organisms similar to patients with CGD. They should be suspected in patients who seem to have CGD, but tests for that disorder are normal. These include enzyme defects or deficiencies of glucose-6-phosphate dehydrogenase, myeloperoxidase, glutathione reductase and glutathione synthetase.

Leukocyte Adhesion Deficiencies

For neutrophils to go into the tissue and remove invaders, they must be able to exit blood vessels and enter tissues. This process is complex and there are several specific defects that impair it. Leukocyte adhesion deficiency type I (LAD1) is the result of mutations in a gene called CD18. LAD1 is by far the most common cause of leukocyte adhesion deficiency and it is usually corrected by bone marrow transplantation. However, milder forms of LAD1 can sometimes be managed with antibiotics alone. Leukocyte adhesion deficiency type II (LAD2) is due to mutations in an enzyme that attaches fucose (a type of sugar) to proteins. These patients can be treated by eating large amounts of fucose. Leukocyte adhesion deficiency type III (LAD3) is caused by mutations in a gene called *FERMT3*.

(Other Phagocytic Cell Disorders continued)

Specific Granule Deficiency

Specific granule deficiency is extremely rare and is associated with killing defects and decreased granules within the neutrophils. Patients are at risk for bacterial and fungal infections.

Glycogen Storage Disease Type Ib

Glycogen storage disease type Ib is a disorder with neutropenia, poor granulocyte killing, a large liver and low blood sugar. It is due to a defect of the enzyme glucose-6 phosphate transporter 1 with accumulation of glycogen in the liver.

β -actin Deficiency

β -actin Deficiency is associated with poor granulocyte movement (chemotaxis) and recurrent infection. β -actin is a structural protein that allows cell movement. Some patients with chemotactic disorders have severe periodontitis and early tooth loss. Three of these syndromes are termed Papillon-Lefebvre syndrome, prepubertal periodontitis and juvenile periodontitis.

Chediak Higashi

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder that arises from a microtubule polymerization defect. CHS is a disease causing impaired bacterial killing due to failure of phagolysosome formation. There is impaired lysosome degranulation within phagosomes, so phagocytosed bacteria are not destroyed by the lysosome's enzymes. Giant granules within the neutrophils are characteristic. In addition, secretion of lytic secretory granules by cytotoxic T-cells is affected. People with CHS have partial albinism (light skin and silvery hair) and have problems with sun sensitivity and photophobia. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous

membranes, skin and the respiratory tract. Affected children are susceptible to infection by Gram-positive and Gram-negative bacteria and fungi, with *Staphylococcus aureus* being prominent. Most children with CHS ultimately reach a stage known as the accelerated phase, also known as the lymphoma-like-syndrome. This severe phase of the disease may be triggered by a viral infection, usually the Epstein-Barr virus (EBV). In the accelerated phase, defective white blood cells divide uncontrollably and invade many of the body's organs. The accelerated phase is associated with fever, episodes of abnormal bleeding, overwhelming infections and organ failure. These medical problems are usually life threatening in childhood. There is no specific treatment for CHS. Bone marrow transplants appear to have been successful in several patients. Infections are treated with antibiotics and abscesses are surgically drained when appropriate.

Griscelli Syndrome

Griscelli syndrome (GS) is a rare autosomal recessive disorder that results in pigmentary dilution of the skin and hair, the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes. There are three different forms of GS, each caused by a different gene defect, and only GS type 2 (caused by mutation in the RAB27A gene) is a primary immunodeficiency disease. Griscelli described children with a disorder resembling CHS. Features were partial albinism, frequent pyogenic infections, and acute episodes of fever, neutropenia, and thrombocytopenia. Despite an adequate number of T- and B-lymphocytes, the patients were hypogammaglobulinemic, deficient in antibody production, and incapable of delayed skin hypersensitivity and skin graft rejection. Differences from CHS were morphologic normality of polymorphonuclear leukocytes; the giant granules of CHS were not found. The morphologic characteristics

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of the hypopigmentation also distinguished the disorder from CHS, as well as from other pigmentary anomalies of man. Another difference was normal leukocyte specific protease activity, which is very low in CHS. GS with partial albinism and immune impairment (now called GS type 2) is a serious immunodeficiency disorder with many patients developing a hemophagocytic syndrome potentially leading to death in the absence of bone marrow transplantation. Because the prognosis is poor, early bone marrow transplantation is strongly recommended for GS-2.

The three forms are Griscelli syndrome type 1 (GS1) which represents hypomelanosis with a primary neurologic deficit but without immunologic impairment or manifestations of hemophagocytic syndrome (associated with a defect in the MYO5A gene). Griscelli syndrome with immune impairment, or Griscelli syndrome type 2, is caused by mutation in the RAB27A gene. Griscelli syndrome type 3, characterized by hypomelanosis with no immunologic or neurologic manifestations, is caused by mutation in the melanophilin (MLPH gene).