

Chapter 21

Chronic Granulomatous Disease (CGD) and Other Phagocyte Disorders, Leukocyte Adhesion Deficiency and Neutropenia

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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 superoxide, hydrogen peroxide, and other chemicals needed to kill certain bacteria and molds. As a result of this defect, individuals with CGD have severe infections from bacteria, molds, and other environmental pathogens that do not typically cause infections in healthy people. Individuals with CGD can also have difficulty with immune cells forming knots called granulomas, hence the name of the disease. Additionally, individuals with CGD can get excessive inflammation even when there is not an infection, and that inflammation can cause intestinal and urinary problems.

Definition

CGD is due to mutations in the NADPH oxidase complex. The NADPH complex is made up of a group of molecules inside certain types of white blood cells known as phagocytes (from Greek, phagein, to eat). The NADPH complex usually functions to make chemicals that kill invaders and control inflammation. Individuals with CGD typically get recurrent infections and inflammation. There are two main types of phagocytes, neutrophils and monocytes, that travel from the bloodstream to sites of infection. They surround invading microorganisms and then ingest them into tiny compartments within the cells. These compartments, known as phagosomes, generate high levels of oxygen free radical chemicals (also called superoxides), such as hydrogen peroxide and bleach, that help kill the microorganisms. Phagocytes from individuals with CGD go to the sites of infection and ingest the microorganisms normally. However, once the microorganisms are ingested, phagocytes in those with CGD cannot effectively kill the microorganisms because they are missing key proteins required to make the necessary chemicals.

The production of superoxide inside the cell is required for killing of a specific set of invaders known as bacteria and fungi, which explains why individuals with CGD are susceptible to only those specific infections (*Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* and *Aspergillus*). However, individuals with CGD have normal defense against many common infections, which is why the infections in CGD are so specific and unusual. Individuals with CGD make normal antibodies, so unlike individuals with lymphocyte problems, they are not particularly susceptible to viruses (such as, common cold, flu, chicken pox, measles, etc). Individuals may go months or years without infections and then have a severe one.

Clinical Presentation

Children with CGD usually appear healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria *Serratia marcescens*, so any infant with this particular infection 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 (infection of the lungs) 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 with fever and cough. *Nocardia*, in particular, can cause high fevers and lung abscesses that can destroy parts of the lung. It is important to identify the presence and specific cause of infections early and to treat the infection completely, usually for long periods of time, to ensure infection stops and prevent relapse. Chest X-rays and computerized tomography (CT) scans of the chest are the best ways to look for lung infections. When they are seen, it is very important to figure out exactly which infection it is and that may require a biopsy (usually done with a needle or a bronchoscope) or sometimes even surgery. Treatment may require many weeks.

Liver abscesses occur in about one third of individuals with CGD. A liver abscess can start out as fever and fatigue, but it may also cause pain over the right upper abdomen. Some sort of scan is required for diagnosis, such as magnetic resonance imaging (MRI), CT scan, or ultrasound, and needle biopsy is necessary to determine the specific cause of the infection. *Staphylococcus aureus* causes most liver abscesses in CGD. Liver abscesses are hard to drain and may need surgery, but treatment with a combination antibiotics and steroids reduces the inflammation and lets the antibiotics work better even without surgery.

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

Newer antibiotics and antifungals are very active when administered by mouth. Managing infections and improving quality of life in individuals with CGD can be greatly improved with early diagnosis and appropriate therapy.

Inflammation is also a significant problem in people with CGD, both with and without infection. Granulomas can cause trouble with intestinal or urinary function, and can also form in the lung, the eye, or the skin.

One of the most difficult aspects of living with CGD is bowel inflammation. About 40 to 50% of individuals with CGD develop inflammation in the intestine that is not clearly due to a specific infection. Individuals with CGD can have severe abdominal pain, diarrhea, weight loss, and sometimes abnormal narrowing in parts of the intestines. Inflammation in the gastrointestinal (GI) tract can present as colitis (inflammation and ulcers of the bowl wall of the colon) (See Immune Dysregulation, Enteropathy, and Colitis Chapter). Commonly called inflammatory bowel disease (IBD), this inflammation is similar in clinical appearance to Crohn's disease. In addition, mouth sores, frequent vomiting, problems with urination and sometimes damage to the kidneys can be seen due to the inflammation associated with CGD. Treatment of this is similar to that applied to other forms of IBD, with steroids having good effect to control symptoms, but other immunosuppressive drugs are often used as steroid sparing agents. It is important to note that, injectable drugs that block the action of inflammatory molecule tumor necrosis factor alpha (TNF α), although very effective to reduce the IBD symptoms, can lead to severe infections in individuals with CGD and are not recommended.

Diagnosis

There are five different genetic kinds of CGD. The most common form in North America is called X-linked because the affected gene for part of the NADPH complex is on the X chromosome (70% of cases in the U.S.) and affects almost only males. The other types of CGD are due to autosomal recessive mutations where two abnormal copies of the gene for other parts of the NADPH complex lead to symptoms of CGD, therefore males and females are equally affected. In addition, girls carrying the X-linked gene may have autoimmune problems, like lupus of the skin, and sometimes may have serious infections. It is important to follow the neutrophil function in females carrying the abnormal x-linked gene, since this can change over time and lead to increased risk of CGD symptoms including infections and IBD. (See Inheritance Chapter.)

Usually infections begin in childhood leading to the diagnosis. However, some individuals with CGD may not have infections until late adolescence or adulthood. Pediatricians and internists must consider the possibility of CGD in any person with pneumonia with a characteristic CGD organism, such as *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* and *Aspergillus*.

The most accurate test for CGD, called the dihydrorhodamine reduction (DHR), measures the ability of phagocytes to produce oxygen free radicals in phagocytes using a chemical called dihydrorhodamine. In the past, the Nitroblue Tetrazolium (NBT) slide test was used to diagnose CGD, but this is less commonly used now since it is more prone to incorrect reading.

Once the diagnosis of CGD is made, it is valuable to determine the specific gene and mutation involved for purposes of prognosis and genetic counseling. The severity of CGD can partly be determined from the specific mutation in the gene and its impact on the DHR result.

Treatment

All individuals with CGD should be on antibiotics for prevention (prophylaxis) of bacterial infection. The first line therapy is usually trimethoprim/sulfamethoxazole, also known as cotrimoxazole and septrin. In addition, itraconazole, voriconazole, or posaconazole should be used for prevention of fungal infections. Use of these medications reduces infections dramatically. Interferon gamma is an injectable pro-inflammatory molecule that can be used together with antibacterial and antifungal prophylaxis to reduce infection. Since the infections that are important in CGD are found in the environment and not carried in our bodies normally, the effect of prophylaxis is to build a wall around the individual: it can still be jumped over but prophylaxis makes it harder for infections to get in. Maximum infection prophylaxis for CGD involves treatment with twice-daily oral doses of cotrimoxazole and once daily itraconazole, plus three times weekly injections of interferon gamma. With these prophylactic treatments, the average incidence of severe infections in CGD is less than once every four years.

Early diagnosis of infection and prompt, aggressive use of appropriate antibiotics and antifungal agents are the best ways to treat acute CGD infections. Initial therapy with antibiotics aimed at the usual

suspects makes sense while waiting for results of infection test results, 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 or slow to resolve such as can be the case with deep tissue fungal infections.

Steroid medications, such as prednisone or methylprednisolone, may sometimes be required to control inflammation. Individuals on steroids need close monitoring for side effects such as high blood pressure and high sugar levels.

Side effects of both antibiotics and antifungals may include nausea, vomiting, diarrhea, loss of appetite, or rash. Interferon gamma injections may cause fever, fatigue, and depression. Acetaminophen taken before the injection may help. Flu-like side effects are usually related to the dose and may be decreased by lowering the dose or how often it is given. Even doses lower than the standard recommendation may provide some protection against infection. Individuals with CGD should consult their healthcare provider if they experience side effects. The risks and benefits of any treatment should be carefully considered.

Managing Exposures

Fungal and bacterial exposures are prevalent in every day life, but there are some precautions that can be taken to avoid exposures and reduce infection risk.

Many physicians suggest that swimming should be confined to well-chlorinated pools. Brackish water in particular, like bays and rivers near the ocean, may contain organisms that are specifically dangerous in CGD, such as *Francisella philomiragia*, *Chromobacterium violaceum*.

Individuals with CGD should avoid handling of dirt, as well as grass cuttings, decaying leaves, garden mulch (shredded moldy tree bark), and potting soil because they contain high levels of fungi and bacteria. These exposures can cause severe pneumonias. Individuals 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 individuals with CGD. Individuals with CGD should also 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. *Aspergillus* is also present in marijuana, so individuals with CGD should avoid smoking it. Individuals should see their doctors about even minor infections and colds to avoid life-threatening infections.

Hematopoietic Stem Cell Transplantation and Gene Therapy

Individuals with CGD can be treated with hematopoietic stem cell transplantation (HSCT), which, in those with CGD, essentially replaces the defective phagocytes with working ones. HSCT outcomes are generally good for people with CGD. HSCT has been associated with improved long-term survival, approximately greater than 90%, and improved quality of life, particularly in individuals with X-linked CGD when compared to those individuals who are managed with medications. HSCT is also quite effective for the treatment of inflammatory colitis associated with CGD. HSCT is not indicated for all individuals with CGD, as many do well on medical management. The risks and benefits of the procedure must always be carefully weighed. (See Hematopoietic Stem Cell Transplantation Chapter.)

Replacement of only the defective gene, called gene therapy, is currently available in clinical trials for X-linked CGD. In this therapy, some of the individual's own hematopoietic stem cells are harvested (removed) from the individual, and a healthy copy of the abnormal gene is added to the individual's own stem cells. These corrected cells are then transfused back into the individual, similar to the procedure used for HSCT. As with HSCT and any treatment, the risks and benefits of the procedure must always be carefully weighed. (See Gene Therapy Chapter.)

Expectations

The long-term outcome for individuals with CGD is highly dependent upon how much superoxide the phagocytes are able to make. Particularly for individuals with X-linked CGD and minimal superoxide production, the survival after 20 years of age is poor with medical management alone. In contrast, survival is better for individuals with autosomal recessive forms of CGD or X-linked CGD associated with higher levels of residual superoxide

production. Individuals should talk with their immunologist to understand the predicted long-term outcome based on their genetic testing and DHR results.

Hospitalizations may be required for individuals 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 individuals reach adulthood, when serious infections tend to occur less frequently.

Leukocyte Adhesion Deficiencies

The chief phagocytic white blood cell is the polymorphonuclear granulocyte (PMN), also known as neutrophil. The neutrophil's job is to move to sites of infection, ingest the invader and kill it. (See The Immune System and Primary Immunodeficiency Diseases Chapter.)

In order for neutrophils to remove invaders, they must be able to get into the tissues. To do this they need to stick to the walls of the blood vessel and squeeze their way between the vessel cells to get out into the tissues. There are several specific defects that impair this process, all grouped together as Leukocyte Adhesion Deficiencies (LADs). LADs are characterized by recurrent life-threatening infections, delayed separation of the belly button (umbilical) stump, infection of the umbilical stump, skin infections without pus formation, and elevated white blood cell counts. LAD type 1 (LAD1) is due to mutations that cause failure of the tight sticking of neutrophils to the blood vessel, which allows the neutrophil to go out into the tissue. LAD1 is by far the most common cause of LAD and, it is usually corrected by HSCT. However, milder forms of LAD1 can sometimes be managed with antibiotics alone. LAD type 2 (LAD2) causes trouble with the gentle sticking of neutrophils to the vessel wall. LAD type 3 (LAD3) causes problems with how neutrophils sense when attachment is happening.

Neutropenias

Neutropenias are disorders with less than 500 neutrophils/microliter; normal is more than 2,000 cells/microliter. Depending on its severity and duration, neutropenia can lead to serious infections or intermittent infections of the skin or other tissues. Therefore, not all neutropenias are severe and some do not require therapy (benign neutropenia).

Neutropenia can be recognized at birth or later and can be either chronic and constant or intermittent. One form, termed severe congenital neutropenia (Kostmann syndrome), is an autosomal recessive disorder due to mutations in the gene *HAX1*. These individuals require treatment with granulocyte colony stimulating factor (G-CSF), a medication that stimulates the body's production of granulocytes, and HSCT should be considered since there are risks associated with long term use of G-CSF.

The intermittent form of neutropenia is called cyclic neutropenia, an autosomal dominant disorder in which the neutropenia occurs every two to four weeks and lasts about a week. In between periods of neutropenia, the individual typically has a low normal neutrophil count. Cyclic neutropenia is caused by mutations in a gene termed *ELANE*.

Autoimmune neutropenia can present at any time of life. In this condition, an antibody against the neutrophils causes their destruction. This can occur on its own but may also be one of the first symptoms of Common Variable Immune Deficiency (CVID). (See Common Variable Immune Deficiency Chapter.) In children autoimmune neutropenia most commonly resolves on its own.

Treatment for neutropenias may include antibiotics for infections, prophylactic antibiotics, immunoglobulin (Ig) replacement therapy, G-CSF injections or HSCT.

Several other forms of primary immunodeficiency diseases (PI) may have associated neutropenia. These include X-linked Hyper IgM Syndrome (CD40 ligand deficiency), CVID, X-linked Agammaglobulinemia (XLA), WHIM Syndrome, Wiskott-Aldrich Syndrome, and GATA2 deficiency. Not all neutropenias result from genetic defects. Neutropenia can be acquired secondary to severe infections as well as treatment with certain medications and is seen in lupus.

Other Neutrophil Disorders

Specific Granule Deficiency: Specific granule deficiency is extremely rare and is associated with decreased granules within the neutrophils that help with killing of invaders. Individuals with this condition are at risk for bacterial infections.

Glycogen Storage Disease Type Ib: Glycogen storage disease type Ib is a disorder with neutropenia, poor neutrophil killing of invaders, 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. Individuals with this condition are at risk for bacterial infections and are often treated with G-CSF.

Beta-actin Deficiency: Beta-actin Deficiency is associated with poor granulocyte movement (chemotaxis) and recurrent infections. Other chemotactic disorders which are associated with severe periodontitis and early tooth loss include Papillon-Lefebvre syndrome, prepubertal periodontitis, and juvenile periodontitis.

Chediak Higashi: Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder in which granules in the neutrophil inappropriately fuse causing impaired bacterial killing. People with CHS have partial albinism (light skin and silvery hair), and they have problems with sun sensitivity and photophobia. These individuals also have problems with lymphocytes and may develop an accelerated phase, in which fever and cell destruction can require chemotherapy treatments. Progressive peripheral nerve damage neuropathy are common and increase with age. Bacterial infections involve mucous membranes, skin, and the respiratory tract. Infections are treated with antibiotics and abscesses are surgically drained when appropriate. HSCT fixes the accelerated phase and the infections but does not change the neuropathy.

Griscelli Syndrome: Griscelli syndrome (GS) is a rare autosomal recessive disorder that results in low amounts of pigment in the skin and hair. There are three different forms of GS and only GS type 2 (caused by mutation in the *RAB27A* gene) is a form of PI. Individuals have partial albinism, frequent bacterial infections, and neutropenia, and low platelets. Individuals also have low immunoglobulins. Individuals with GS2, like those with CHS can develop the accelerated phase, which is fatal if not treated aggressively. Early HSCT is strongly recommended for GS2.

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