Understanding Chronic Granulomatous Disease

Different from other immunodeficiencies, CGD is becoming better understood with improvement in diagnosis and treatment.

By Bob Geng, MD

DR. CHARLES JANEWAY first described chronic granulomatous disease (CGD) in 1954. At the time, immunodeficiency was characterized by recurrent infections due to low immunoglobulin levels. However, Dr. Janeway described several male patients who had recurrent infections and an enlarged liver and spleen, but elevated immunoglobulin levels. Over the next several years, more cases similar to these, along with granuloma formation and severe inflammation, were reported. In the late 1960s, Staphylococcus bacteria was discovered to be the predominant form of infection in CGD patients, and while neutrophils (white blood cells) in CGD patients could ingest these bacteria without difficulty, they could not digest them. Then, from the 1970s through the 1990s, other genetic discoveries of specific defects leading to CGD were made, which greatly improved our understanding of the disease.

What Causes CGD?

CGD results from the inability of cells in the innate immune system (neutrophils and monocytes) to make superoxide compounds that could effectively kill bacteria or fungus that they ingest. Neutrophils are the main cells of the innate immune system, and they respond quickly to bacterial or fungal infections. Normally, neutrophils are able to produce an "oxidative burst" from the production of hydrogen peroxide from superoxide, which kills the bacteria. An enzyme called nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is made up of six different proteins, accomplishes this process. These six components are gp91phox, p22phox, p47phox, p67phox, p49phox and Rac2. Mutations in the first five of the six components can lead to CGD. A mutation in the sixth component causes a different disease.

When the neutrophil is in a resting state before encountering any bacteria or fungus, these components are separate. Once a normal neutrophil is activated through encountering bacteria or fungus, these components combine together to initiate the "oxidative burst" process that kills the ingested organism. Mutations in any one of the components will lead to a defective NADPH oxidase that is incapable of producing the necessary compounds to kill the ingested invading organism.

Since neutrophils cannot effectively clear out the bacterial or fungal infections in CGD, the immune system forms granulomas to wall off the infections and contain them. The formation of the granulomas is the phenomenon that gives rise to the name CGD.

How Common Is CGD?

The prevalence of CGD is estimated to be around one in 200,000 live births. But, this statistic may be an underestimate because the disease is not systematically screened like severe combined immunodeficiency. The diagnosis can occur at any age because of different times of symptom manifestation, but generally the majority of diagnoses are made in children. However, autosomal recessive forms of the disease may present with a milder phenotype with delayed diagnosis into adulthood.

The most common form of CGD is the X-linked type, meaning that the defect is located on the X chromosome, and the condition is only seen in males. The X-linked form (gp91phox) accounts for 65 percent of CGD. There are three major autosomal recessive forms (requiring two copies of the same defect in order to manifest clinical presentation of disease), with the defect on chromosome 7 (p47phox) accounting for 25 percent of all known CGD cases. The remaining two forms of autosomal recessive CGD (p22phox and p67phox) each account for less than 5 percent of the known cases. There are no known autosomal dominant forms of the disease.

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Signs and Symptoms of CGD

Most CGD patients present with symptoms in early childhood, but presentations later in adulthood also occur. As previously mentioned, later onset of disease can be the result of the autosomal recessive mutation. But, delayed diagnosis may also occur because symptoms are better controlled in developed countries with lower levels of bacterial/fungal exposure, as well as use of strong antibiotics for infections.

The predominant presentations of CGD are infections that can occur in the liver, skin, lungs and lymph nodes. In the U.S., CGD-related infections are generally from Staphylococcus aureus, Nocardia species, Serratia marcescens, Burkholderia cepacia and Aspergillus. In many other places in the world, tuberculosis, Bacillus Calmette-Guerin (BCG from vaccination) and Salmonella are common causes of infections in CGD patients. Other uncommon but CGD-defining bacterial infections are those from Chromobacterium violaceum and Francisella philomiragia. With the exception of Staphylococcus aureus, all

the other pathogens rarely cause disease in non-CGD patients. Fungal agents such as Aspergillus cause common infections in CGD patients, and initial presentation can be difficult to appreciate, leading to a delay in diagnosis.

Staphylococcal liver abscesses occur in a significant number of CGD patients, and they can be difficult to manage. The abscesses cause increases in liver enzymes and, over time, lead to structural complications such as elevation of pressures in the portal veins and abnormal enlargement of the liver and spleen. These complications are often associated with lower platelet counts that, coupled with worsening liver function, often lead to significant morbidity and mortality.

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Symptoms of both urinary and gastrointestinal obstruction can also be prominent in CGD patients due to the presence of granulomas. Formation of granulomas in the stomach can lead to gastric outlet obstruction resulting in early satiety (fullness after eating), nausea, decreased gastric emptying and severe vomiting. Blockage from granulomas can occur anywhere along the gastrointestinal tract, such as the esophagus, stomach, small intestines, large intestines and rectum, leading to signs and symptoms of obstruction. Granulomas in the bladder can lead to obstruction in the urinary tract leading to complications of chronic kidney disease, as well as difficulty urinating.

Aside from severe infectious complications and structural blockage from granulomas, another significant clinical manifestation seen in CGD is from severe inflammation. The infectious agents that are exposed to the compromised innate immune system of CGD patients lead to excessive inflammation. This poorly controlled inflammatory response can directly impact the function of the lungs, bladder and gastrointestinal tract leading to severe illness and disability. Excessive inflammation can also lead to signs and symptoms of skin disease and poor wound healing, as well as complications in oral health such as gum disease and ulcer formation.

Female carriers of the X-linked form of CGD usually do not present with infections unless the level of normal neutrophils falls below 5 percent to 10 percent. Females can develop autoimmune complications of disease due to excessive inflammation such as discoid lupus (a chronic skin condition), oral ulcers and rashes caused by sunlight.

Diagnosing CGD

There are three main ways to test for CGD. The oldest and most well-known test is the nitroblue tetrazolium test (NBT) in which a special dye is used to stain neutrophils on a microscope slide. The cells that have normal reducing capacity to form superoxides form an insoluble bluish black compound, whereas the abnormal cells that have abnormal capacity to produce superoxides will not develop a color change. Therefore, a CGD patient's neutrophils will not stain normally, leading to the diagnosis. However, this test is rarely performed today due to its inability to detect more subtle forms of disease and its difficulty in quantifying degree of disease severity.

The NBT has been largely replaced by the dihydrorhodamine test (DHR), which functions by testing the amount of hydrogen peroxide produced by neutrophils. The DHR is a flow cytometry test, meaning that it is a quantitative test based on the counting of response of individual cells. This test relies on the measurement of fluorescence (emission of light) following the oxidation of dihydrorhodamine by activated neutrophils. Inability to generate this fluorescence leads to the diagnosis of inadequate oxidative capacity of the neutrophil. In addition to diagnosing CGD, the DHR can also distinguish between the X-linked form and the autosomal recessive forms. The DHR can also detect female carriers of the X-linked form.

With the DHR test, neutrophils from normal individuals will have a low level of fluorescence in the resting state and a significantly elevated level of fluorescence following stimulation. Neutrophils from classic X-linked CGD will demonstrate no change in degree of fluorescence following stimulation. Neutrophils from autosomal recessive CGD will result in a wider variation and lower degree of fluorescence compared with neutrophils from normal individuals following stimulation. Neutrophils from carriers of X-linked CGD will demonstrate two peaks following stimulation, showing that these individuals possess both normal cells and abnormal cells.

The third method of detection of CGD is through direct genetic testing. For the X-linked form, the defect is in the CYBB gene on chromosome Xp21. The most common form of autosomal recessive form is from a defect in the NCF1 gene on chromo-

some 7. The other remaining autosomal recessive types are the result of defects of the CYBA gene on chromosome 16 and the NCF2 gene on chromosome 1q42.

Treating CGD

There are several approaches to treating CGD. Acute infectious and inflammatory complications need to be managed with the appropriate antimicrobials and immunosuppressive medications. Antimicrobials need to be selected based on their activity against the particular offending bacteria or fungus. Immunosuppressive medications need to be used to manage autoimmune complications. Liver abscesses in CGD need to be managed by a combination of both antibiotics and steroids for inflammation reduction. In general, steroids can help reduce the complications associated with the formation of granulomas, as well as the hyperinflammation seen in CGD following exposure to infectious agents. Biologic immunosuppressive medications should be avoided in CGD patients due to concern for increased risk of serious infections.

The cornerstone of CGD management is prevention. The recommended prevention regimen includes the use of antibiotics, namely trimethoprim-sulfamethoxazole (TMP-SMX), antifungal (itraconazole) and interferon gamma for immunomodulation. TMP-SMX should be administered at 5 mg/kg/day up to 320 mg in two divided doses. If the patient is allergic to sulfa drugs, then TMP, fluoroquinolones or a cephalosporin can be considered instead. Itraconazole should be administered at 100 mg/day for children under 13 years or less than 50 kg, and 200 mg/day for those older than 13 years or greater than 50 kg. Interferon gamma should be administered subcutaneously at 50 micrograms per meter-squared body surface area three times a week.

An additional therapy used in prophylaxis in CGD is interferon-gamma (Actimmune by Horizon Pharmaceutical). CGD is one of the first diseases to be treated with cytokine therapy in its routine management. Interferon gamma has been shown in a multicenter, international, double-blind, placebo-controlled study to reduce development of infections by 70 percent. It is believed that interferon gamma works because it increases superoxide production in neutrophils and macrophages to improve killing ingested bacteria. The benefit is most significant for young patients with the X-linked form of disease.

Immune globulin (IG) therapy is not typically used for the treatment of CGD. Historically, CGD was first described as recurrent infections in the setting of hypergammaglobulinemia. The defect is not in the adaptive immune system or the production of antibodies. There have been rare case reports of some CGD patients with hypogammaglobulinemia, but it is uncertain whether those cases really represent two different deficiencies in the same patient. Some experts have used high-dose intravenous IG for the management of the severe inflammatory response seen in CGD patients, but again, the usage is rare, and there is no definitive evidence of efficacy.

CGD patients should receive all routine vaccinations, including live virus vaccines because the disease does not reduce the body's immune response against viruses. However, CGD patients should never receive the BCG vaccine due to the potential of developing life-threatening BCG infection. This can be a concern in most countries around the world due to routine policies of BCG vaccination; however, it is usually not a concern in the U.S. because BCG vaccines are not generally administered.

The only approved form of curative therapy for CGD is hematopoietic stem cell transplantation. While transplant is a curative option, the majority of CGD patients have not been transplanted, and there are significant risks associated with stem cell transplant. Since each type of CGD arises from a single gene defect, there is significant research interest in the possibility of gene therapy as a potential cure.

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CGD Prognosis

The survival in CGD has been shown to correlate with residual oxidative ability of the neutrophils. Therefore, patients with a higher amount of residual oxidative capability will generally have better outcomes. This is consistent with the fact that autosomal recessive forms (higher residual oxidative capability) have better survival than the X-linked type. The overall survival of CGD has been improving, and is currently around 90 percent in 10 years. ■

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