idfa.org.au

Chronic Granulomatous Disease

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

Also available :

COMMON VARIABLE IMMUNODEFICIENCY

HYPER IgM SYNDROME

X-LINKED AGAMMAGLOBULINEMIA

SEVERE COMBINED IMMUNODEFICIENCY

WISKOTT-ALDRICH SYNDROME

Graphic Project & Printing: TIP. ALA snc (ITALY)
www.tipolito-ala.it

CHRONIC GRANULOMATOUS DISEASE

Chronic Granulomatous Disease (CGD) is a genetically determined (inherited) disease characterized by an inability of the body's phagocytic cells (also called phagocytes) to make hydrogen peroxide and other oxidants needed to kill certain microorganisms.

DEFINITION

Chronic Granulomatous Disease (CGD) is a genetically determined (inherited) disease characterized by an inability of the body's phagocytic cells (also called phagocytes) to make hydrogen peroxide and other oxidants needed to kill certain microorganisms. As a result of this defect in phagocytic cell killing, patients with CGD have an increased susceptibility to infections caused by certain bacteria and fungi. The condition is also associated with an excessive accumulation of immune cells into aggregates called granulomas (hence the name of the disease) at sites of infection or other inflammation.

The term "phagocytic" (from the Greek, phagein, "to eat") is a general term used to describe any white blood cell in the body that can surround and ingest microorganisms into tiny membrane packets in the cell. The membranes packets (also called phagosomes) are filled with digestive enzymes and other antimicrobial substances. In general, there are two main categories of phagocytic cells found in the blood, neutrophils and monocytes. Neutrophils (also called granulocytes or polymorphonuclear leukocytes [PMNs]) comprise 50-70% of all circulating white blood cells and are the first responders to bacterial or fungal infections. Neutrophils are short lived, lasting only about three days in the tissues after they kill microorganisms. Monocytes are the other type of phagocyte, making up about 1-5% of circulating white blood cells. Monocytes entering the tissues can live a long time, slowly changing into cells called macrophages or dendritic cells, which help to deal with infections.

Phagocytes look very much like amoeba in that they can easily change shape and crawl out of blood vessels and into tissues, easily squeezing between other cells. They can sense the presence of bacteria or fungus pathogens that cause an infection in the tissues and then, crawl rapidly to the site of infection. When the phagocytes arrive at the site of infection, they approach the microorganism and attempt to engulf it and contain it inside a pinched off piece of membrane that forms a sort of bubble, or membrane packet, inside the cell called a phagosome. The cell is then triggered to dump packets of digestive enzymes and other antimicrobial substances into the phagosome. The cell also produces hydrogen peroxide and other toxic oxidants that are secreted directly into the phagosome. The hydrogen peroxide works together with the other substances to kill and digest the infection microbe.

Although phagocytes from patients with CGD can migrate normally to sites of infection, ingest infecting microbes and even dump digestive enzymes and other antimicrobial substances into the phagosome, they lack the enzyme machinery to make hydrogen peroxide and other oxidants. Thus, CGD patients' phagocytes can defend against some types of infections, but not infections which specifically require hydrogen peroxide for control of the infection. Their defect in defense against infection is limited to only certain bacteria and fungi. CGD patients do have normal immunity to most viruses and to some kinds of bacteria and fungi. This is why CGD patients are not infected all the time. Instead they may go months to years without infections, and then experience episodes of severe life-threatening infections with microbes that especially require hydrogen peroxide for control. CGD patients make normal amounts and types of antibodies, so that unlike patients with inherited defects in lymphocyte function, CGD patients are not particularly susceptible to viruses.

In summary, the phagocytic cells of patients with CGD fail to produce hydrogen peroxide, but otherwise retain many other types of antimicrobial activities. This leads CGD patients to be susceptible to infections with a

special subset of bacteria and fungi. They have normal antibody production, normal T-cell function, and a normal complement system; in short, much of the rest of their immune system is normal.

CLINICAL PRESENTATION

Children with Chronic Granulomatous Disease (CGD) are usually healthy at birth. Then, sometime in their first few months or years of life, they may develop recurrent bacterial or fungal infections. The most common presentation of CGD in infancy is a skin or bone infection with bacteria called Serratia marcescens. In fact, any infant with a major soft tissue or bone infection with this particular organism is usually tested for CGD. Similarly, if an infant develops an infection with an unusual fungus called Aspergillis, this may result in testing for CGD.
The infections in CGD may involve any organ system or tissue of the body, but the skin, lungs, lymph nodes, liver, bones and occasionally brain are the usual sites of infection. Infected lesions may have prolonged drainage, delayed healing and residual scarring. Infection of a lymph node is a common problem in CGD, often requiring either drainage of the lymph node or in many cases surgical removal of the affected lymph node to achieve cure of the infection.

Pneumonia is a recurrent and common problem in patients with CGD. Almost 50% of pneumonias in CGD patients are caused by fungi, particular Aspergillus. Other organisms such as Burkholderia cepacia, Serratia marcescens, Klebsiella pneumoniae and Nocardia also commonly cause pneumonia. Fungal pneumonias may come on very slowly, initially only causing a general sense of fatigue, and only later causing cough or chest pain. Surprisingly, many fungal pneumonias do not cause fever in the early phases of the infection. By contrast bacterial infections usually present acutely with fever and cough. Nocardia in particular, causes high fevers and can also result in lung abscesses that can destroy parts of lung tissue. Since pneumonias can be caused by so many different organisms and it is important to catch these infections early and treat them aggressively for

a long period of time, it is critical to seek medical attention early. There should be a low threshold for getting a chest X-ray or even a computerized tomography (CAT) scan of the chest, followed by other diagnostic procedures to make a specific diagnosis. Treatment often requires more than one antibiotic and effective treatment to cure an infection may require many weeks of antibiotics.

Liver abscess can also occur in patients with CGD. This may present with generalized malaise, but often is associated with mild pain over the liver area of the abdomen. Imaging scans are required for diagnosis and needle biopsy is necessary to determine the organism causing the abscess. Staphylococcus causes about 90% of liver abscesses. Often the liver abscesses do not form a large easily drained pocket of pus, but instead forms a hard lump or granuloma and multiple tiny abscesses in the liver. This solid mass of infection may require surgical removal for cure.

Osteomyelitis (bone infections) frequently involves the small bones of the hands and feet, but can involve the spine, particularly in cases that spread from an infection in the lungs, such as with fungi such as Aspergillus.

There are many potent new antibacterial and antifungal antibiotics, many of them very active in oral form, which treat CGD infections. Due to this, there has been significant improvement in the rates of successful cure of infection without significant organ damage from the infection. However, this requires prompt diagnosis of the infection and prolonged administration of antibiotics.

Some infections may result in the formation of localized, swollen collections of infected tissue. In some instances, these swellings may cause obstruction of the intestine or urinary tract. They often contain microscopic groups of cells called granulomas. In fact, it is the granuloma formation that was the basis for the name of the disease. Granulomas can also form without any clear infection cause and may result in sudden blockage of the urinary

system in small children. In fact, about 20% of CGD patients develop some type of inflammatory bowel disease as a result of CGD granulomas and, in some cases, is indistinguishable from Crohn's Disease.

DIAGNOSIS

Because the most common genetic type of CGD affects only boys, it may be mistakenly assumed that CGD cannot affect girls. However, there are several genetic types of CGD, and some do affect girls. In fact, about 15% of all CGD patients are girls.

CGD can vary in its severity and there is a certain amount of chance as to when a patient with CGD develops a severe infection. For this reason there are some CGD patients that may not have an infection that draws attention to the disease until late adolescence or even adulthood. While it is more common to see infections that lead to diagnosis in early childhood, surprisingly, the average age of diagnosis of boys with CGD is about three years old and of girls, seven years old. It is important for pediatricians and internists caring for adolescents and young adults not to completely dismiss the possibility of a diagnosis of CGD in a young adult patient who gets pneumonia with an unusual organism like the Aspergillus fungus. Any patient of any age who presents with an Aspergillus, Nocardia or Burkholderia cepacia pneumonia, a staphylococcus liver abscess or pneumonia, or a bone infection with Serratia marcescens should be tested to rule out CGD. These are the usual combinations of organisms and sites of infection that commonly trigger testing for CGD. By contrast, merely having an occasional staphylococcal infection of the skin is not particularly a special sign of CGD, nor is recurrent middle ear infections, though CGD patients can also suffer from these problems.

The most accurate test for CGD measures the production of hydrogen peroxide in phagocytic cells. Hydrogen peroxide produced by normal phagocytes oxidizes a chemical called Dihydrorhodamine, making it fluorescent and the fluorescence is measured with a sophisticated machine.

In contrast, phagocytic cells from CGD patients cannot produce enough hydrogen peroxide to make the dihydrorhodamine fluoresce. There are other types of tests still used to diagnose CGD, such as the Nitroblue Tetrazolium (NBT) slide test. The NBT is a visual test in which phagocytes producing oxidants turn blue and are scored manually using a microscope. It is more prone to human subjective assessment and can lead to false negatives, occasionally missing the diagnosis of CGD in patients with mild forms of CGD, where cells may turn slightly blue, but actually are abnormal.

Once a diagnosis of CGD is made, there are a few specialized labs that can confirm the genetic sub-type of CGD.

INHERITANCE PATTERN

Chronic Granulomatous Disease (CGD) is a genetically determined disease and can be inherited or passed on in families. There are two patterns for transmission. One form of the disease affects about 75% of cases and is inherited in a sex-linked (or X-linked) recessive manner; i.e. it is carried on the "X" chromosome. Three other forms of the disease are inherited in an autosomal recessive fashion. They are carried on chromosomes other than the "X" chromosome. It is important to understand the type of inheritance so families can understand why a child has been affected, the risk that subsequent children may be affected, and the implications for other members of the family.

TREATMENT

A mainstay of therapy is the early diagnosis of infection and prompt, aggressive use of appropriate antibiotics. Initial therapy with antibiotics aimed at the most likely offending organisms may be necessary while waiting for results of cultures. A careful search for the cause of infection is important so that sensitivity of the microorganism to antibiotics can be determined. Intravenous antibiotics are usually necessary for treating serious infections in CGD patients and clinical improvement may not be

obvious for a number of days in spite of treatment with the appropriate antibiotics. In the past, granulocyte transfusions have been used for some CGD patients when aggressive antibiotic therapy fails and the infection is life-threatening. Fortunately, this is not commonly needed any more because of the availability of newer, more potent antibacterial and antifungal antibiotics.

Some patients with CGD have such frequent infections, especially as young children, that continuous daily administered oral antibiotics (prophylaxis) are often recommended. CGD patients who receive prophylactic antibiotics may have infection-free periods and prolonged intervals between serious infections. The most effective antibiotic to prevent bacterial infection in CGD is a formulation of the combination of trimethoprim and sulfamethoxasole, sometimes also called co-trimazole or under the trade names, Bactrim or Septra. This reduces frequency of bacterial infection by almost 70%. It is a safe and effective agent for CGD patients because it provides coverage for most of the bacterial pathogens that cause infection in CGD, but does not have much effect on normal bowel flora, leaving most of the normal protective bacterial ecology of the gut in place. The other important thing about co-trimazole prophylaxis is that it does not seem to wane in its effectiveness. This is because the bacteria that it protects against in CGD are not normally found in patients except in the setting of an actual infection. So, the antibiotic does not usually cause the organisms it is protecting against to become resistant.

A natural product of the immune system, gamma interferon, is also used to treat patients with CGD to boost their immune system. Patients with CGD who are treated with gamma interferon have been shown to have more than 70% fewer infections, and when infections do occur, they may be less serious. CGD patients are not deficient in gamma interferon, and gamma interferon is not a cure for CGD. It augments immunity in a number of general ways that partially compensate for the defect in hydrogen peroxide production. Gamma interferon may have side effects such as causing fever, nightmares, fatigue and problems with concentration.

Antipyretics such as Motrin or Advil may help. Some patients choose not to take gamma interferon because they do not like injections, because of the cost or because they have unacceptable side effects. There is some evidence that even doses of gamma interferon, lower than the standard recommendation, may provide some protection against infection. Due to this, a number of experts in the field have suggested that patients, who decide not to take gamma interferon for any of the above reasons, should at least first consider trying lower or less frequent dosing. In particular, side effects are usually dose dependent and may be decreased or eliminated by lowering the dose of gamma interferon which will likely still provide infection prophylaxis even at the lower dose or frequency of administration.

More recently it has been demonstrated that daily doses of the oral antifungal agent, Itraconazole, can reduce the frequency of fungal infections in CGD. Maximum infection prophylaxis for CGD involves treatment with daily oral doses of co-trimazole and itraconazole together, plus three times weekly injections of gamma interferon. On this regimen, the average rate of infection in CGD patients drops to an average of one severe infection approximately every four years. Of course individual genetic factors and chance result in some CGD patients having more frequent infections while others have infections even less frequently than every four years.

CGD can be cured by successful bone marrow transplant, but most CGD patients do not seek this option. This may be because they lack a fully tissue matched normal sibling, or because they are doing well enough with conventional therapy that it is inappropriate to assume the risks associated with transplantation. But it is important for that subset of CGD patients who do have constant problems with life threatening infections to know that bone marrow transplantation could be a treatment option. 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. Fresh water lakes, in particular, and even salt water swimming may expose patients to organisms which are not virulent (or infectious) for normal swimmers but may be infectious for CGD patients. Aspergillus is present in many samples of marijuana, so CGD patients should be discouraged from smoking marijuana. A major risk to CGD patients is the handling of garden mulch (shredded moldy tree bark); this type of exposure is the cause of a grave and life-threatening form of full lung acute inhalation Aspergillus pneumonia. Households with CGD patients should never use garden mulch at all if possible, and CGD patients should remain indoors during its application 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 CGD patients. Patients should also avoid turning manure or compost piles, repotting house plants, cleaning cellars or garages, performing demolition for construction, dusty conditions, and spoiled or moldy grass and hay (including avoiding "hay rides"). Since early treatment of infections is very important, patients are urged to consult their physicians about even minor infections.

EXPECTATIONS

The quality of life for many patients with Chronic Granulomatous Disease (CGD) has improved remarkably with knowledge of the phagocytic cell abnormality and appreciation of the need for early, aggressive antibiotic therapy when infections occur. Remarkable improvements in morbidity and mortality have occurred in the last 20 years. The great majority of CGD children can expect to live into adulthood, and many adult CGD patients hold responsible jobs, get married and have children. However, most CGD patients remain at significant risk for infections and must take their prophylaxis and be vigilant to seek early diagnosis and treatment for possible infection. Recurrent hospitalization may be required in CGD patients since multiple tests are often necessary to locate the exact site and cause of infections, and intravenous antibiotics are usually needed for treatment of serious infections. Disease-free intervals are increased

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

Other booklets are available in this series.

For further information and details of PID patient organisations in 63 countries worldwide please visit www.ipopi.org

www.idfa.org.au
1800 100 198
info@idfa.org.au
PO Box 742, Wollongong NSW 2520