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INTERNATIONAL
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FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

CHRONIC
GRANULOMATOUS DISEASE

ABBREVIATIONS

CGD	Chronic granulomatous disease
DHR	Dihydrorhodamine 123
HSCT	Haematopoietic stem cell transplantation
NADPH	Nicotinamide adenine dinucleotide phosphate
NBT	Nitroblue tetrazolium
PID	Primary immunodeficiency
ROS	Reactive oxygen species
TNF-α	Tumour necrosis factor alpha

Chronic Granulomatous Disease (2nd edition)

IPOPI wishes to thank the patients and families who shared their pictures to illustrate this leaflet.

Front page: **Andrea, Italy** and **Alberto, Portugal.**

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INTRODUCTION

This booklet explains what chronic granulomatous disease (CGD) is, what the main symptoms are, how it is diagnosed and how it is treated.

Chronic granulomatous disease (CGD) is a genetic disorder in which white blood cells called phagocytes are unable to produce the reactive oxygen species (ROS) needed to kill certain bacteria and fungi. CGD is a primary immunodeficiency (PID) that affects five to fifteen individuals in every million people worldwide. People with CGD are highly susceptible to frequent and sometimes life-threatening bacterial and fungal infections that mainly affect the skin, lungs, lymph nodes and bones. They may develop abscesses in their lungs, liver, spleen, lymph nodes, bones or skin, and also masses (or clumps) of cells, called granulomas, due to dysregulated inflammatory responses as well as inflammation of the colon (colitis) and other inflammatory manifestations. CGD is diagnosed by specific blood tests, which is usually followed by genetic testing to determine the specific type of CGD. CGD is managed using a combination of antibiotics and antifungal prophylaxis therapies and the immunostimulatory protein interferon-γ to reduce infections, risk avoidance by eliminating exposure to potential sources of infection, and bone marrow or haematopoietic stem cell transplants have proven to be successful in some affected individuals with CGD. With proper medical care and treatment, many people with CGD can live healthy and independent lives.

Francis, China

WHAT IS CGD?

Chronic granulomatous disease (CGD) is a genetic disorder in which particular white blood cells, called phagocytes, are unable to produce hydrogen peroxide and other ROS that are needed to kill certain bacteria and fungi. A genetic mutation in any one of six different genes can cause a defect in the function of an enzyme called phagocyte NADPH oxidase, which affects the production of ROS necessary to destroy some microorganisms.

SYMPTOMS

People with CGD are highly susceptible to frequent and sometimes life-threatening bacterial and fungal infections that usually affect the lungs (pneumonia), lymph nodes (lymphadenitis), liver (abscess), bone (osteomyelitis) and skin (abscesses or cellulitis) (**Table**). Symptoms usually first appear in infancy or early childhood. However, individuals with mild forms of the disorder may not develop symptoms until the teenage years or adulthood. People with CGD may develop abscesses in their lungs, liver, spleen, bones or skin, and masses (or clumps) of cells, called granulomas, that can obstruct the bowel or urinary tract. In some people, the inflammation and granulomas associated with CGD can cause an inflammatory bowel disease that is similar to Crohn's disease; this manifestation is more common in the X-linked form of CGD (occurring in up to 50% of cases). In countries with tuberculosis vaccination, severe infection caused by the live-attenuated virus can be the first sign suggestive for CGD. In addition, heart or kidney problems, diabetes and autoimmune disease may occur in people with CGD, but this varies depending on the specific mutation. Abnormal enlargement of the liver and spleen (hepatosplenomegaly) may also occur. In the X-linked form of CGD chorioretinal lesions might be observed, which may affect vision.

[1] Leiding JW, Holland SM. Chronic Granulomatous Disease. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. Updated 2022 Apr 21]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK99496/.

TABLE. Infections in CGD: Common Pathogens and Sites of Involvement[1]

PATHOGEN	PRESENTATION
BACTERIAL INFECTIONS	
Staphylococcus aureus	Soft-tissue infection; lymphadenitis; liver abscess; osteomyelitis; pneumonia; sepsis
Burkholderia species	Pneumonia; lymphadenitis; sepsis
Serratia marcescens	More common: Osteomyelitis; soft-tissue infection Less common: Pneumonia; sepsis
Nocardia species	Pneumonia; osteomyelitis; brain abscess; lymphadenitis
Granulibacter bethesdensis	Necrotizing lymphadenitis; sepsis; meningitis
Chromobacterium violaceum	Sepsis
Francisella philomiragia	Sepsis
Mycobacteria *M tuberculosis* *BCG*	Pneumonia; osteomyelitis; brain abscess; lymphadenitis; digestive abscess
FUNGAL INFECTIONS	
Aspergillus species	Pneumonia; osteomyelitis; brain abscess; lymphadenitis
Paecilomyces species	Pneumonia; soft-tissue infection; osteomyelitis
Other molds	Pneumonia; soft-tissue infection
YEAST INFECTIONS	
Candida	Sepsis; soft-tissue infection; liver abscess
Trichosporon	Pneumonia; soft-tissue infection

WHO IS SUSCEPTIBLE TO CGD?

CGD is a genetic disorder with an incidence that is estimated at approximately 1/200,000 live births in the United States, and a highest incidence estimated to be 1.5/100,000 in the Israel Arab population, which corresponds to 5 to 15 individuals in every million people worldwide.[2]

Mutations in the *CYBA, CYBB, CYBC1, NCF1, NCF2,* or *NCF4* gene can cause CGD. These mutations result in the production of proteins with little or no function, or the production of no protein at all, that are part of NADPH oxidase, which is primarily active in immune system cells called phagocytes. There are six types of this condition that are distinguished by the gene that is involved. However, some individuals with CGD do not have an identified mutation in any of these genes. The cause of the condition in these individuals is unknown.

There are two forms of the disease, an X-linked recessive form that primarily affects males and an autosomal recessive form, which can affect both males and females. X-linked genetic disorders are conditions caused by an abnormal gene on the X chromosome and manifest mostly in males. Females that have a defective gene present on one of their X chromosomes are “carriers” for that disorder. Males have one X chromosome that is inherited from their mother and if a male inherits an X chromosome that contains a defective gene, he will develop the disease (**Figure 1**).

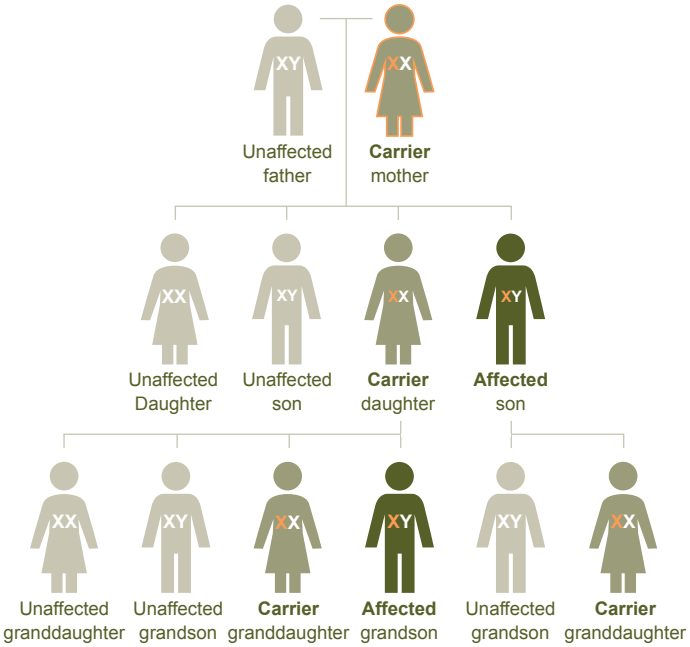

FIGURE 1. Inheritance pattern of X-linked CGD with carrier mother

WHAT IS THE RISK OF PASSING THE DISEASE ON TO THE CHILDREN OF PEOPLE WITH CGD?

Women who are carriers of the X-linked form of CGD do not usually display any symptoms as they have two X chromosomes and only one carries the defective gene. However, some X-linked CGD carriers may experience inflammatory conditions involving the skin, gastrointestinal tract, or less commonly, lupus or other autoimmune disorders. As can be seen from the above figure, women who are carriers of an X-linked disorder have a 1 in 4 chance of having a carrier daughter, a 1 in 4 chance of having a non-carrier daughter, a 1 in 4 chance of having an affected son and a 1 in 4 chance of having an unaffected son (**Figure 1**).

If a male with an X-linked disorder has children, his daughters will be carriers while none of his sons will. An affected male cannot pass an X-linked gene to his sons because males always pass their Y chromosome to male offspring (**Figure 2**). Genetic counselling is recommended for affected individuals and their families.

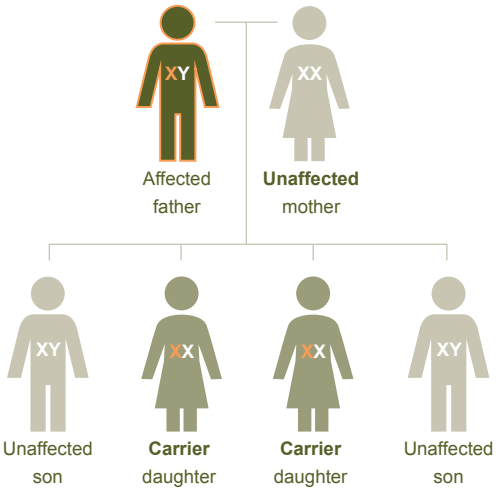

FIGURE 2.Inheritance pattern of X-linked CGD with affected father

[2] Yu HH, et al. Chronic Granulomatous Disease: a Comprehensive Review. Clin Rev Allergy Immunol 2021;61(2):101-113. doi: 10.1007/s12016-020-08800-x.

HOW IS CGD DIAGNOSED?

CGD is diagnosed by specific blood tests that show how well phagocytes produce hydrogen peroxide, an indicator that they are functioning properly. The most accurate test for CGD uses a molecule called dihydrorhodamine 123 (DHR) to determine whether or not phagocytes are making oxidants, including hydrogen peroxide, normally after several stimuli. Oxidants cause DHR to fluoresce and can be measured by flow-cytometry, thus for people with CGD the fluorescence is markedly reduced or absent in phagocytes.

Another historical blood test for CGD is the yellow dye nitroblue tetrazolium (NBT) slide test. In this test, NBT is mixed with the phagocytes, which are then activated to produce oxidants that react with NBT, turning it a deep blue colour. If this reaction does not occur, then these important oxidants are not being produced by an individual's phagocytes.

If CGD is diagnosed based on defects in blood cell oxidant production, genetic testing and counselling is typically recommended to determine the specific type of CGD. There are clinical diagnostic criteria of the European Society for Immunodeficiencies (ESID) working definitions. In addition, there is a need for microbiological studies for the early diagnosis of infection to direct the most appropriate therapy.

WHAT TREATMENTS ARE AVAILABLE FOR CGD?

People with CGD often need to take lifelong daily regimens of antibiotics and antifungals to prevent infections. These may include trimethoprim/sulfamethoxazole to protect against bacterial infections, and itraconazole for anti-fungal protection. There are new antibiotics and antifungals becoming available; carbapenems or fluoroquinolones for bacterial infections and azole drugs as voriconazole, posaconazole, or isovuconazole for fungal infections. Injections of interferon-γ, a protein that improves the activity of phagocytes, also may help reduce the number and severity of infections. Abscesses need aggressive care that may include percutaneous drainage or surgery. Granulomas and abscesses may require combined steroid therapy.

TREATMENT OF ACUTE INFECTIONS

Prompt, aggressive use of appropriate antibiotics is the best way to treat CGD infections. Rates of cure for infections in people with CGD are very high and are greatly improved by early diagnosis and therapy. Intravenous antibiotics may be needed for serious CGD infections. Phagocyte transfusions are rarely used and only when an infection is especially life threatening or for refractory fungal infections.

STEM CELL THERAPY

Allogeneic haematopoietic stem cell transplantation (HSCT) is the only known cure for CGD. Recent reports show excellent overall survival and event-free survival, especially when HSCT is performed with matched donors and at a younger age.

HSCT involves taking (harvesting) stem cells from a closely matched individual. The stem cells of the donor are put into the patient's bloodstream. The transplanted stem cells find their way to the bone marrow where they begin to produce new, healthy cells. When transplantation is successful, the immune system of the CGD patient can fight off infections.

INVESTIGATIONAL THERAPIES

Gene therapy is being investigated in early-stage clinical trials as a possible treatment for CGD because the disease results from a single-gene defect that affects almost exclusively blood cells. Gene therapy uses a patient's own stem cells to replace mutated genes with healthy copies by efficient virus-based methods in the laboratory and re-infusing them back into the patient.

A recent study has been able to repair the defective gene in stem cells in X-linked CGD. After transplantation into mice, the repaired stem cells developed into normally functioning white blood cells, suggesting the strategy could potentially be used to treat people with this disease.[3]

TREATMENT FOR BOWEL PROBLEMS

One of the most difficult aspects of CGD is the bowel problems. About 40–50% of people 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 but does respond to most of the same treatments as Crohn's disease (antibiotics, steroids, other immune suppressive drugs). However, injectable drugs that block the inflammatory molecule tumour 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.

[3] De Ravin SS, et al. CRISPR-Cas9 gene repair of hematopoietic stem cells from patients with X-linked chronic granulomatous disease. Science Translational Medicine 2017. DOI: 10.1126/scitranslmed.aah3480.

TREATMENT FOR LUNG PROBLEMS

Pneumonia is a recurrent and common problem in patients with CGD. Almost 50% of pneumonias in CGD patients are caused by fungi, particularly Aspergillus. Other organisms such as *Burkholderia cepacia, Serratia marcescens, Klebsiella pneumoniae* and Nocardia also commonly cause pneumonia. Fungal pneumonias often come on very slowly, initially only causing general fatigue and only later causing cough or chest pain. In 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 some of the lung tissue. Since pneumonias can be caused by many different organisms, it is important to catch these infections early and treat them aggressively for a long period of time with one or more antibiotics.

Recurrent lung infections can result in chronic respiratory disease. Bronchiectasis, obliterative bronchiolitis, and chronic fibrosis may occur in patients with CGD but are not as common as in some other PIDs.

LIVING WITH CGD

With appropriate everyday hygiene and prevention measures, many people with CGD can live healthy and independent lives. Skin hygiene is very important and should involve gentle washing with hypoallergenic, additive-free and soap-/fragrance-free products, and similarly caring for fingernails. People with CGD have normal immunity to most viruses and can range from partial to full immunity to many types of bacteria and fungi naturally found on their skin, in their bowel or in the environment, which is why they are not infected all of the time. Individuals may go from months to years without infections and then experience a severe one. However, people with CGD remain at significantly increased risk of infection throughout their lives. They must take their prophylactic medication, remain cautious, and get early diagnosis and treatment for possible infections – these can include apparently minor infections such as ‘colds’ (without fever), which can cause a problem for patients if they face physicians who are not aware of this fact (such as in an emergency ward). This emphasizes the importance of close follow-up of patients to aid in the early detection and treatment of infections.

Children with CGD should receive routine childhood vaccinations. People with CGD do not have any defect in immunity to viruses, so they are able to receive live virus vaccines without adverse effects. However, children with CGD should never receive the BCG live bacterial vaccine as it can result in a severe life-threatening systemic BCG infection. Live Salmonella vaccine should also be avoided. Please consult your specialist about this topic because in some cases vaccines are not a good option for patients with CGD.

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. The fungus Aspergillus is present in many samples of marijuana, so patients with CGD should avoid smoking marijuana and smoking in general. Aspergillus can also be found in pepper, flour, and in decaying plant matter. Hence, people with CGD 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, hayrides and barns.

All males with the X-linked form of CGD should be tested for antigens of the Kell blood group (present in most blood products) to avoid potential transfusional reactions should they require transfusion of blood products.

SELF-CARE

Staying fit and healthy is especially important if you have CGD. Along with taking preventative medication every day, other ways to help keep well are having a balanced diet, including vitamin and mineral supplements if needed, taking regular exercise, and getting an appropriate amount of rest.

With proper medical care and treatment combined with everyday hygiene and prevention measures, many people with CGD can live healthy and independent lives.

FURTHER INFORMATION AND SUPPORT

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 worldwide, please visit **IPOPI.org**.

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