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AN UPDATED REVIEW ON CHRONIC GRANULOMATOUS DISEASE

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ABSTRACT

Chronic granulomatous disease (CGD) is a genetic disorder in which certain immune system cells are unable to kill some types of bacteria and fungi. The disorder leads to long term and repeated infections. The condition is often discovered in very early childhood. Milder forms may be diagnosed during the teen years or even in adulthood. This Review has basic information about research work of CGD for further development in this field.

INTRODUCTION

Chronic granulomatous disease (CGD) (also known as Bridges–Good syndrome, Chronic granulomatous disorder, and Quie syndrome) is a diverse group of hereditary diseases in which certain cells of the immune system have difficulty forming the reactive oxygen compounds (most importantly, the superoxide radical) used to kill certain ingested pathogens. This leads to the formation of granulomata in many organs. CGD affects about 1 in 200,000 people in the United States, with about 20 new cases diagnosed each year.The word "granulomatous" relates to granulomas - scabs or scars which form in the tissues in response to infection.[1]

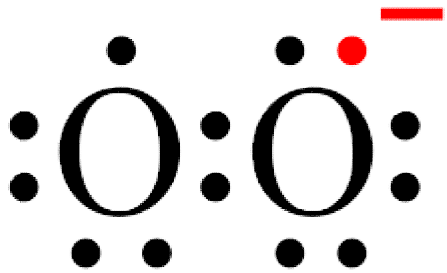
In 1954, at an annual meeting of the Society for Pediatric Research, Janeway and colleagues first reported five cases of children with elevated serum gamma globulin levels that suffered from recurrent infections. At this time, the basis for their susceptibility was not identified. Three years later, four boys with hypergammaglobulinemia, suffering recurrent infections of the lungs, lymph nodes, and skin, with a presence of granulomatous lesions were described by Bridges *et al.* Over the next ten years little more was known about the disease. Treatments using erythromycin and novobiocin antibiotics, along with regular surgical drainage, increased the survival rate of 4 years to one of 12 years. The use of the word 'fatal' was subsequently dropped from the clinical synonym as patient life expectancy increased with improved medicines and diagnostics, and was classified as the more commonly known chronic granulomatous disease (CGD).[2]

CAUSES, INCIDENCE, AND RISK FACTORS

Impetigo, skin abscesses and furuncles, and perianal and rectal abscesses are common in people with this disorder. Pneumonia that keeps coming back, and is caused by bacteria not typical of most pneumonia, is a significant problem. Chronic swelling of the lymph nodes in the neck, with the formation of abscesses, is common. Risk factors include a family history of recurrent or chronic infections. About half of CGD cases are transmitted as a recessive, sex-linked trait. This means that boys are more likely to inherit the disorder than are girls. Boys have an X and a Y chromosome. Girls have two X chromosomes. The defective gene is carried on the X chromosome. So, if a girl has one X chromosome with the defective gene, the other X chromosome may have a working gene to make up for it. A girl has to inherit the defective gene from both parents in order to have the disease. About 1 in a million people have CGD.[3]

CLASSIFICATION

Chronic granulomatous disease is the name for a genetically heterogeneous group of immunodeficiencies. The core defect is a failure of phagocytic cells to kill organisms that they have engulfed because of defects in a system of enzymes that produce free radicals and other toxic small molecules. There are several types, including chronic X-linked disease, chronic b-negative disease, X-linked cytochrome b-positive disease, x-linked variant disease, and atypical granulomatous disease.[1]



Superoxide

ICD-10	D71
ICD-9	288.1
OMIM	306400 233690 233700
DiseasesDB	2633
MedlinePlus	001239
eMedicine	ped/1590 derm/719
MeSH	D006105

SYMPTOMS

- Bone infections
- Frequent and difficult-to-clear skin infections
  - Abscesses
  - Chronic infection inside the nose
  - Furuncles
  - Impetiginized eczema (eczema complicated by an infection)
  - Impetigo
  - Perianal abscesses (abscesses around the anus)
- Joint infections

- Persistent diarrhea
- Pneumonia
    - Occurs frequently
    - Difficult to cure
- Swollen lymph nodes in the neck; those develop early in life, and stay swollen or occur frequently. The lymph nodes may form abscesses that require surgical drainage.

Signs and tests

Physical examination may show an enlarged liver (hepatomegaly), enlarged spleen (splenomegaly), and swelling of multiple lymph nodes all over the body (generalized adenopathy). There may be signs of a bone infection (osteomyelitis), sometimes affecting multiple bones.

A tissue biopsy may show granulomas (groups of abnormal phagocytes).

Other tests may include:

- Bone scan
- Chest x-ray
- Complete blood count (CBC)
- Flow cytometry tests
- Nitroblue tetrazolium test (NBT) to confirm the disease and detect that the mother is a carrier [3]

ATYPICAL INFECTIONS

Aspergillus fumigatus, an organism that commonly causes disease in people with chronic granulomatous disease.

People with CGD are sometimes infected with organisms that usually do not cause disease in people with normal immune systems. Among the most common organisms that cause disease in CGD patients are:

- bacteria (particularly those that are catalase-positive)
    - *Staphylococcus aureus.*
    - *Serratia marcescens.*
    - *Salmonella species.*
    - *Klebsiella species.*

- *Pseudomonas cepacia, a.k.a. Burkholderia cepacia*
- *Nocardia*.

- fungi
  - *Aspergillus species. Aspergillus has a propensity to cause infection in people with CGD and of the Aspergillus species, Aspergillus fumigatus seems to be most common in CGD.*
  - Candida species.

Patients with CGD can usually resist infections of catalase-negative bacteria. Catalase is an enzyme that catalyzes the breakdown of hydrogen peroxide in many organisms. In organisms that lack catalase (catalase-negative), normal metabolic functions will cause an accumulation of hydrogen peroxide which the host's immune system can use to fight off the infection. In organisms that have catalase (catalase-positive), the enzyme breaks down any hydrogen peroxide that was produced through normal metabolism. Therefore hydrogen peroxide will not accumulate, leaving the patient vulnerable to catalase-positive bacteria.[1]

PATHOPHYSIOLOGY

Phagocytes (i.e., neutrophils, monocytes, and macrophages) require an enzyme to produce reactive oxygen species to destroy bacteria after they ingest the bacteria in a process called phagocytosis, a process known as the respiratory burst. This enzyme is termed "phagocyte NADPH oxidase" (PHOX). The initial step in this process involves the one-electron reduction of molecular oxygen to produce superoxide anion, a free radical. Superoxide then undergoes a further series of reactions to produce products such as hydrogen peroxide (through the action of superoxide dismutase), hydroxyl radical and hypochlorite (bleach - through the action of myeloperoxidase on hydrogen peroxide). The reactive oxygen species this enzyme produces are toxic to bacteria and help the phagocyte kill them once they are ingested. Defects in one of the four essential subunits of this enzyme can all cause CGD of varying severity, dependent on the defect. There are over 410 known possible defects in the PHOX enzyme complex that can lead to chronic granulomatous disease.[1]

GENETICS

In the 1960s, studies on patient blood confirmed CGD to be a disease of impaired phagocytes. Holmes *et al.* suggested that the cellular defect was 'a deficiency in one enzyme, either located

within polymorph lysosomes or among those responsible for metabolic adaptations necessary for the normal function of the lysosomes or lysosomal enzymes'. This caused skepticism from some scientists who thought a deficiency of a single enzyme of this type was unlikely and that a less specific factor in the phagocytic process was responsible . It was also thought that because the disease occurred in boys and was familial that the defect was X-linked. However, reports of the disease in females began to emerge, thereby revealing an autosomal recessive inheritance of the same phenotype. It was then that Nathan and Baehner showed that leukocytes from CGD patients, unlike normal human leukocytes, did not reduce nitroblue tetrazolium (NBT), a compound that converts to insoluble blue formazan product upon reduction by the superoxide anion ($O^{2-.}$). This phenomenon was rapidly established as a sensitive clinical screening test for CGD that is still used today.

Over the next twenty years, over 150 scientific papers had been published reporting cases of patients with CGD describing their symptoms and similarities to other granuloma forming diseases. It was observed that CGD leucocytes could ingest micro-organisms but failed to kill the organisms responsible for the infections. Phagocytosis is normally accompanied by a marked increase in oxidative metabolism and studies had shown that NADPH oxidase was the respiratory enzyme responsible for bactericidal activity. The hexose monophosphate shunt is responsible for generating reduced NADPH . The critical deficiency in CGD cells is to generate $O^{2-.}$ and other reactive oxygen species such as hydrogen peroxide (H_2O_2) .The importance of H_2O_2 was illustrated by the fact that some bacterial species, such as *Streptococci*, that produces its own H_2O_2, could be killed by CGD leucocytes. Following further corroboration that the deficiency in CGD was caused by a defect in the NADPH oxidase system in CGD patients, scientists began to research the formation of the free radical form of oxygen, $O^{2-.}$, produced by NADPH oxidase during its respiratory burst, and showed that whereas normal leucocytes generated $O^{2-.}$ during phagocytosis, CGD phagocytes were not able to do this . Speculation that a b-type cytochrome may also be involved in this $O^{2-.}$ Generating activity began in 1979 from observations that a cytochrome-b associated with a particulate fraction of normal neutrophils, was absent from the neutrophils from some, but not all, patients with CGD. Described as the heme-containing protein, cytochrome-b_{558} was proposed as a primary component of the microbicidal oxidase system of phagocytes. A multicenter European evaluation of its incidence

and relevance was conducted in London where it was found to be undetectable in all 19 of the men studied in whom the defect appeared to be located on the X chromosome. Thus cytochrome-b_{558} was hailed an important component of the microbicidal NADPH oxidase system and provided insight into its role in the enzyme complex. Borregaard and colleagues [18] demonstrated that approximately 90% of the cytochrome-b_{558} resides in the membrane of the specific granules of unstimulated human neutrophils and that the cytochrome-b_{558} translocates to the plasma membrane when the cells are stimulated. The authors speculated that the observed translocation was essential to the formation of an electron transport chain which generates $O^{2-\cdot}$ the single precursor from which all microbicidal oxidants ultimately arise.[2]

TREATMENT

Management of chronic granulomatous disease revolves around two goals: 1) diagnose the disease early so that antibiotic prophylaxis can be given to keep an infection from occurring, and 2) educate the patient about his or her condition so that prompt treatment can be given if an infection occurs.

ANTIBIOTICS

Physicians often prescribe the antibiotic trimethoprim-sulfamethoxazole to prevent bacterial infections. This drug also has the benefit of sparing the normal bacteria of the digestive tract. Fungal infection is commonly prevented with itraconazole, although a newer drug of the same type called voriconazole may be more effective. The use of this drug for this purpose is still under scientific investigation.[1]

IMMUNOMODULATION

Interferon, in the form of interferon gamma-1b (Actimmune) is approved by the Food and Drug Administration for the prevention of infection in CGD. It has been shown to prevent infections in CGD patients by 70% and to reduce their severity. Although its exact mechanism is still not entirely understood, it has the ability to give CGD patients more immune function and therefore, greater ability to fight off infections. This therapy has been standard treatment for CGD for several years. Hematopoietic stem cell transplantation (HSCT) Hematopoietic stem cell transplantation from a matched donor is curative although not without significant risk.[1]

PROGNOSIS

There are currently no studies detailing the long term outcome of chronic granulomatous disease with modern treatment. Without treatment, children often die in the first decade of life. The increased severity of X-linked CGD results in a decreased survival rate of patients, as 20% of X-link patients die of CGD-related causes by the age of 10, in contrast to an approximate age of 35 in autosomal recessive patients.[1]

Gene therapy involves the permanent genetic correction of hematopoietic stem cells in which a vector is used to carry the corrective gene into the cells which are then re-introduced to the body. CGD is a particularly good candidate for gene therapy because low levels of functional phagocytes are expected to provide significant activity against pathogenic microbes. In 1992, Thrasher and colleagues used cell lines from patients with defective p47phox as targets for reconstitution using retrovirus-mediated gene transfer, thus creating an in vitro model of gene therapy for this disease. This was shortly followed by retrovirus-mediated gene transfer of gp91phox cDNA from patients with X-linked CGD to reconstitute functional NADPH oxidase activity in B-cell lines. The reconstitution of NADPH oxidase activity in cell lines from three unrelated patients, each of which had a different molecular defect in the gene, suggested that X-CGD would be a suitable disease for treatment by gene therapy. CGD mouse models have been developed by gene disruption, and preclinical studies on these animals using recombinant retroviral vectors have demonstrated reconstitution of functionally normal neutrophils and increased resistance to pathogens such as *Aspergillus fumigatus*, *Burkholderia cepacia* and *Staphylococcus aureus.* These studies were extended to human cell lines, where retroviral vectors to restore NADPH oxidase activity was tested in human myeloid leukemic cell lines defective in superoxide production, as well as in primary $CD34^{+}$ cells obtained from X-CGD patients. It was shown that the level of $O2^{-}$ production in phagocytes derived from transduced cells was 69% of normal levels. In the US, CGD gene therapy clinical trials targeted both the most common X-linked form of CGD as well as the autosomal recessive forms of this disease. Malech and colleagues isolated hematopoietic stem cells from four X-CGD patients, infected the cells with a retrovirus containing the normal gp91phox gene, grew the transfected cells in culture, and infused them back into the original patients from which the cells were derived. Three of the four patients had sustained and continuous production of low levels of reconstituted

neutrophils for 6 to 14 months. Of even greater interest, although still not understood, is the finding that two of the patients who had liver infections that resisted cure by conventional methods resolved during the course of treatment. This suggests that the gene therapy approach could also be effective in treating CGD patients with severe intractable infections, although more targeted and longer term studies are needed.

Gene therapy trials for CGD in Europe began in 2004 through the collaborative efforts in Frankfurt and London. So far, two patients have been treated with retroviral vector and encouraging results show that both patients have significant levels of gene corrected cells and are clinically well (personal communication). Gene therapy holds great promise as an alternative treatment for patients without suitable marrow donors or where BMT is not a viable treatment option.[2]

COMPLICATIONS

- Bone damage
- Chronic pneumonia
- Lung damage
- Skin damage[3]

RESEARCH

Gene therapy is currently being studied as a possible treatment for chronic granulomatous disease. CGD is well-suited for gene therapy since it is caused by a mutation in single gene which only affects one body system (the hematopoietic system). Viruses have been used to deliver a normal gp91 gene to rats with a mutation in this gene, and subsequently the phagocytes in these rats were able to produce oxygen radicals.

In 2006, two human patients with X-linked chronic granulomatous disease underwent gene therapy and blood cell precursor stem cell transplantation to their bone marrow. Both patients recovered from their CGD, clearing pre-existing infections and demonstrating increased oxidase activity in their neutrophils. However, long-term complications and efficacy of this therapy are unknown.[1]

Orofacial findings in chronic granulomatous Disease

Patients with chronic granulomatous disease may develop oral lesions reflecting susceptibility to infect and inflammation. It is also possible that social and genetic factors may influence the

development of this complication. Therefore, oral hygiene must be kept at an optimum level to prevent infections that can be difficult to manage.[4]

MODERN MANAGEMENT OF CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder of phagocytic cells resulting in failure to kill a characteristic spectrum of bacteria and fungi and in defective degradation of inflammatory mediators with concomitant granuloma formation. The prognosis for CGD patients has markedly improved over the past 10 years. Nevertheless the prophylactic and therapeutical approaches routinely employed are only supportive, still imperfect, and demand lifelong patient compliance. CGD thus remains a lethal disease, nowadays at an adult age. The ultimate goal is to develop curative approaches. Allogeneic stem cell transplantation and, possibly, gene-replacement therapy are such options. Two major obstacles immanent to CGD have been identified and might be overcome in a not too distant future. More patients would be treated using HSCT, if the inflammatory complications (graft-versus-host disease and inflammatory flare-up) triggered by heavy conditioning and pre-existing infection in a CGD recipient, could be prevented (Yang et al, 2002). RIC combined with moderate in vivo depletion of inflammatory cells is worth pursuing, taking care to preserve some donor T cells needed for engraftment of unrelated grafts. Gene therapy would advance, if the missing selective survival advantage of CGD-corrected cells could be substituted in a safe and efficient manner. Submyeloablative conditioning might pave the way to engraftment, perhaps combined with a system for on-demand in vivo selection of the gene-corrected cells using a non-mutagenic drug (Rappa et al, 2007).[5]

Chronic Granulomatous Disease Presenting With Hypogammaglobulinemia

Chronic granulomatous disease (CGD) is a primary immunodefi ciency disorder caused by inherited defects in the nicotinamide adenine dinucleotide phosphate oxidase complex. The neutrophils of patients with CGD can ingest bacteria normally, but the oxidative processes that lead to superoxide anion formation, hydrogen peroxide production, nonoxidative pathway activation, and bacterial killing are impaired. Serious infections result from microorganisms that produce catalase. Immunoglobulin levels of patients with CGD are usually normal or elevated.[6]

Enhanced inflammatory responses of chronic granulomatous disease leukocytes involve ROS independent activation of NF-B

Reactive oxygen species (ROS) generated by the cellular NADPH-oxidase are crucial for phagocytic killing of ingested microbes and have been implicated as signaling molecules in various processes. For example, ROS are thought to be involved in activation of the transcription factor NF-□B, central for mediating production of proinflammatory cytokines in response to inflammatory stimuli. Several studies have demonstrated that inhibitors of the NADPH-oxidase interfere with NF-□B activation and production of proinflammatory cytokines. Curiously, patients with chronic granulomatous disease (CGD), an immunodeficiency characterized by an inability to produce ROS, are not only predisposed to severe infections, but also frequently develop various inflammatory complications indicative of exaggerated inflammatory responses. Here, we show that human CGD leukocytes display a hyperinflammatory phenotype with increased production of proinflammatory cytokines in response to stimulation with Toll-like receptor agonists. The hyperinflammatory phenotype was also evident in mononuclear cells from CGD mice (gp91phox–/–), but not in control cells in the presence of NADPHoxidase inhibitor diphenyleneiodonium, probably reflecting NADPH-oxidase-independent effects of the inhibitor. Furthermore, we show that the major steps involved in NF□B activation were intact in human CGD cells. These data indicate that ROS were nonessential for activation of NF-□B and their production may even attenuate inflammation.[7]

Clinical and Radiological Aspects of Chronic Granulomatous Disease in Children: A case Series from Iran

CGD is a disease that is transmitted genetically by X-linked and autosomal recessive form. X-linked form of disease includes about 70% of the patients.In this research the male population included 2/3 (76%) of the total population which would include the genetic transmission (X-linked) in this group. Since not all of the female patients are AR, evaluation of the patients genotype is not possible without genetic investigations. Different studies have shown that 70% of patients are affected with at least one infection before 2-years of age. Similarly as demonstrated in our research 77% of the patients displayed serious clinical manifestations before 2-years of age. In neonates with CGD despite the transmission of maternal antibodies, the phagocytic system of the patient remain disturbed face acute infections in the first few months of life.[8]

Chronic Granulomatous Disease Presenting With Disseminated Intracranial Aspergillosis

Chronic granulomatous disease (CGD) is an uncommon congenital phagocyte disorder characterized by recurrent life-threatening infections. In this disorder, phagocytes are unable to catalytically convert oxygen to free-radical superoxide. Superoxide normally dismutates to hydrogen peroxide, which plays a key role in the killing of pathogenic microorganisms. The enzyme important in this process, NADPH oxidase, consists of five subunits, and mutations of any of these components can lead to CGD. Mutations in the Cytochrome b(_245) beta subunit (CYBB) are responsible for the X-linked form of the disease, accounting for 65% of cases of CGD. Mutations of the other four components account for the remainder of CGD cases, and these are inherited in an autosomal recessive manner. Inflammasome activation in NADPH oxidase defective mononuclear phagocytes from patients with chronic granulomatous disease.

Chronic granulomatous disease (CGD) is an inherited disorder characterized by recurrent infections and deregulated inflammatory responses. CGD is caused by mutations in subunits of the NADPH oxidase, an enzyme that generates reactive oxygen species in phagocytes. To elucidate the contribution of the proinflammatory protease caspase-1 to aberrant inflammatory reactions in CGD, we analyzed cells isolated from patients with defects in the phagocyte oxidase subunits p22phox, p47phox or gp91phox. We report that mononuclear phagocytes from CGD patients activated caspase-1 and produced biologically active interleukin-1_ (IL-1_) in response to danger signals. Notably, caspase-1 activation and IL-1_ secretion from CGD monocytes was elevated in asymptomatic patients and strongly increased in patients with noninfectious inflammatory conditions. Treatment with IL-1 receptor antagonist reduced IL-1 production in monocytes ex vivo and during medical therapy.[9]

Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Patients with chronic granulomatous disease and modest residual production of ROI have significantly less severe illness and a greater likelihood of long-term survival than patients with little residual ROI production. The production of residual ROI is predicted by the specific NADPH oxidase mutation, regardless of the specific gene affected, and it is a predictor of survival in patients with chronic granulomatous disease.[10]

Bone Findings in Chronic Granulomatous Disease of Childhood: A Genetic Abnormality of Leukocyte Function

Granulomatous disease of childhood is a chronic and eventually fatal, genetically transmitted syndrome usually affecting male children. Recent investigations have shown that the polymorphonuclear leukocytes and monocytes of these patients phagocytize normally but are unable to kill certain organisms. As a result, these children manifest a granulomatous response in many organs. Typically they develop eczematoid eruption, lymphadenitis with suppuration, hepatosplenomegaly, and repeated, slowly resolving pneumonias. Eight of twenty-eight patients developed osteomyelitis with distinctive clinical and roentgenographic findings. Thus, clinical, general roentgenographic, and orthopaedic manifestations are typical of the disease. Definite diagnosis is readily established by one or more relatively simple laboratory studies. Because of the ease of diagnosis and the importance of recognizing chronic granulomatous disease, the orthopaedist should be aware of its manifestations.[11]

Cytochrome b Deficiency in an Autosomal Form of Chronic Granulomatous Disease: A Third Form of Chronic Granulomatous DiseaseRecognized by Monocyte Hybridization

Three patients (two sisters and a brother) in one family are described with chronic granulomatous disease. The granulocytes of these patients did not respond with a metabolic burst to various stimuli and failed to kill catalase-positive microorganisms. The magnitude of the cytochrome b signal in the optical spectrum of the patients' granulocytes was <4% of the normal value, whereas the amount of noncovalently bound flavin in these cells was normal. The mode of inheritance of the genetic defect in this family is autosomal because the granulocytes of both parents (first cousins) and a nonaffected sister of the patients expressed 70-80% of the normal cytochrome b signal, showed low-normal or subnormal oxidative reactions during stimulation, and did not display mosaicism in the stimulated nitroblue-tetrazolium slide test. Somatic cell hybridization was performed between the monocytes from the affected boy in this family with monocytes from either a cytochrome b-negative male patient with X-linked chronic granulomatous disease or a cytochrome b-positive male patient with the classic autosomal form of this disease.[12]

CONLUSION

Chronic granulomatous disease (CGD) is a very rare disease, which affects the way the immune system works. It is really not one single disease, but rather a group of related conditions. Some of the white blood cells do not work as well as they should, so children with CGD are prone to developing infections. CGD is a congenital disorder, It affects about one in a million children.

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