Chronic Granulomatous Disease

Chronic Granulomatous Disease (CGD) is an X-linked recessive disorder (some forms are autosomal recessive) that results in defective NADPH oxidase. The defective NADPH oxidase leads to decreased superoxide and hydrogen peroxide, which means there is impaired intracellular microbe killing in phagocytes. Patients with CGD have recurrent purulent skin and lung infections, especially with catalase positive organisms. Diagnosis is made with the nitroblue tetrazolium test and DHR flow cytometry and confirmed with genetic testing. Treatment consists of antimicrobial prophylaxis with TMP- SMX and itraconazole. Interferon- gamma can be used in severe cases as well.



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Pathophysiology

Most Commonly X-linked Recessive

#1 Foam-finger X-suit with Recessive-chocolates

This disease is commonly X- linked recessive, although some forms are autosomal recessive.

Defective NADPH Oxidase (Enzyme Complex)

Broken NADPH-cigarette with Ox-daisy

Under normal circumstances, phagocytes (i.e. neutrophils, monocytes and macrophages) use NADPH oxidase to generate reactive oxygen compounds, which are used to kill ingested pathogens. Chronic granulomatous disease arises from mutations that result in defective subunits of the NADPH oxidase complex, which leads to the inability of phagocytes to destroy certain microbes.

Decreased Hydrogen Peroxide

Down-arrow Hydrogen Peroxide

Under normal circumstances, after NADPH has formed, an electron is taken from NADPH and donated to molecular oxygen, leading to the formation of superoxide. Superoxide is then converted to hydrogen peroxide by superoxide dismutase. Hydrogen peroxide is then converted to hypochlorous acid, also known as bleach. The production of these reactive oxygen species leads to destruction of ingested microbes. This process is called the respiratory burst. Patients with Chronic Granulomatous Disease have defective NADPH oxidase, which leads to decreased superoxide, hydrogen peroxide and bleach. Therefore, there is impaired intracellular killing in phagocytes.

Impaired Intracellular Killing in Phagocytes

Can't Kill inside Fang-ocytes

Due to a lack of NADPH oxidase, there is impaired intracellular killing in phagocytes in patients with Chronic Granulomatous Disease (CGD). Phagocytes (neutrophils, monocytes and macrophages) can still ingest pathogens, but they are unable to destroy them. This results in the formation of granulomas in many organs. It is important to note that the quantity of leukocytes, platelets, B cells and T cells is unaffected in CGD.

Signs and Symptoms

Recurrent Purulent Skin and Lung Infections

Puss-pile with Skin-suit and Lungs

The most common sites of infection are the skin, lungs, lymph nodes and liver. Patients present with purulent infections such as abscesses, pneumonia, aphthous ulcers, inflammation of the nares and suppurative adenitis. The most common pulmonary infection is pneumonia, but patients can present with lung abscesses, empyema and hilar lymphadenopathy.

Catalase Positive Organisms

Cat Positive

Patients with Chronic Granulomatous Disease (CGD) have recurrent infection and granuloma formation with bacterial and fungal pathogens. They are especially susceptible to catalase- positive organisms, including Staphylococcus aureus, Burkholderia (Pseudomonas) cepacia, Serratia marcescens, Nocardia and Aspergillus. Catalase is an enzyme that inactivates hydrogen peroxide. Since catalase positive organisms destroy any hydrogen peroxide that was produced, this leaves patients with CGD vulnerable to infection with catalase positive organisms.

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Diagnosis

Negative Nitroblue Tetrazolium Test

Negative Nitro-blue tank

The nitroblue tetrazolium test is used to screen for Chronic Granulomatous Disease (CGD) by measuring the ability of NADPH oxidase to convert oxygen to superoxide. In this test, leukocytes are incubated with NBT (nitroblue tetrazolium) dye. In patients with neutrophils that have normally functioning NADPH oxidase, the yellow/colorless tetrazolium is converted into the blue-colored formazan. This is a reactive/positive test. However, CGD patients have a defective NADPH oxidase complex so the dye remains yellow/colorless. This is considered a non-reactive/negative test and indicates the cells are unable to produce reactive oxygen species.

DHR (Dihydrorhodamine) Flow Cytometry

Die-hydrants-rodent

In this test, DHR is taken up by phagocytes and oxidized to a green fluorescent compound by the products of NADPH oxidase. In patients with CGD and defective NADPH oxidase, there is decreased green fluorescence. Flow cytometry is preferred as the NBT test is falling out of favor.

Treatment

Antimicrobial Prophylaxis

Microbe Purple-axes

Patients with Chronic Granulomatous Disease (CGD) are treated with antimicrobial prophylaxis to protect against bacterial and fungal infections. The most common therapies in the United States include Trimethoprim- sulfamethoxazole (TMP- SMX) and Itraconazole with or without interferon- gamma (INF-gamma).

TMP-SMX

Tampon on SMX-snowmobile

Trimethoprim- sulfamethoxazole (TMP- SMX) is used as prophylaxis against bacterial infections.

Itraconazole

I-truck-nozzle

Itraconazole is used as prophylaxis against fungal infections.

Interferon-Gamma

Interferon-ray-gun Grandma

Immune modulatory therapy has become part of the prophylactic and treatment regimen, especially in severe cases of CGD. Studies have shown this drug can reduce infections by 70% and decrease their severity.

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