Trace amounts of microbe-killing molecules predict chronic granulomatous disease survival

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Investigators at the National Institutes of Health have observed that the survival rate of people with a rare immunodeficiency disease called chronic granulomatous disease (CGD) is greatly improved when even very low levels of microbe-killing molecules are present. Because production of these molecules, made by an enzyme called NADPH oxidase, can be predicted from genetic analysis, a patient's risk for severe CGD could be assessed very early in life, allowing for more personalized treatment, say the researchers.

The study was conducted at the NIH Clinical Center and led by researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, and their associated contract labs at SAIC-Frederick Inc. The study is available online in the New England Journal of Medicine.

"Advances in treatment of CGD have made it possible for people with this once-fatal disease of early childhood to survive into adulthood; however, the disease remains difficult to manage," says NIAID Director Anthony S. Fauci, M.D. "Having a marker to help predict disease prognosis will enable physicians to recommend treatment options that are more tailored to the needs of individual patients."

People with CGD have increased susceptibility to infections caused by certain bacteria, such as Staphylococcus aureus, and fungi, such as

Aspergillus. They can have abscesses in the lungs, liver, spleen, bones or skin. Those with severe disease also can have tissue masses, called granulomas, which can obstruct the bowel or urinary tract. CGD affects an estimated 1,200 people in the United States and approximately 25,000 people worldwide.

The disease is caused by inherited mutations in any one of five different genes required by immune cells to make the NADPH oxidase enzyme, which in turn makes superoxide, an oxygen-derived molecule that immune cells use to destroy harmful bacteria and fungi. All CGD patients have impaired superoxide production. Some make a little superoxide, while others make none. The research team found that the level of superoxide production was linked to the type of mutation in the NADPH oxidase gene, and that the more superoxide a patient with CGD can make, the less severe the disease and the greater the life expectancy.

Until now, the severity of CGD has been linked only to how people inherit the NADPH oxidase gene mutation. If people inherit the mutation as an autosomal recessive trait, meaning that two copies of the abnormal gene, one from each parent, are present, the disease has generally been less severe than in those who inherit the mutation as an X-linked trait, meaning that the abnormal gene is located on the female sex chromosome. The majority of people with CGD inherit the mutation as an X-linked trait.

For their study, the NIH team tested the level of superoxide production by immune cells isolated from blood samples taken from 287 people with CGD, aged 1 to 64 years old, compared with superoxide production in healthy people. Some tests dated back to 1993, though patients and families affected by CGD have come to the NIH Clinical Center for treatment since the 1970s.

The NIH researchers used methods that could detect even trace amounts

of superoxide, and grouped people with CGD based on the amount of superoxide made by the immune cells. The patients who produced the highest levels of superoxide had the highest survival rates, whereas those who produced the lowest levels of superoxide had the lowest survival rates.

"By precisely measuring superoxide production, we observed that even tiny residual amounts, at levels below what doctors paid attention to in the past, had a significant impact on patient survival," says John Gallin, M.D., director of the NIH Clinical Center, chief of the Clinical Pathophysiology Section of the NIAID Laboratory of Host Defenses, and senior author on the paper.

Treatment of CGD consists of lifelong antibiotics and antifungal medications. Some people also receive injections with interferon-gamma, a protein that can stimulate the immune cells to fight infections. For people with the most severe forms of CGD, bone marrow transplantation is a treatment option, but it carries potential complications that can make patients and their families reluctant to elect this therapy.

Based on the research team's observations, doctors should be able to use DNA gene-typing results to help identify those patients who are candidates for more aggressive treatments, including possible bone marrow transplantation. Bone marrow transplantation replaces the immune cells of people with CGD, which produce no or reduced amounts of microbe-killing superoxide, with healthy immune cells. In addition, therapies designed to promote NADPH oxidase function might reduce CGD severity. Therapies exist to stimulate NADPH oxidase but none are used to treat CGD.

"This study is a great example of the special strengths of the Clinical Center," comments Dr. Gallin. "We have worked for over three decades

with patients with CGD, which at one time was almost entirely fatal, and have seen vast improvements in care and treatment. This work now gives us another tool to help individuals fight this disease."

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