Gene therapy for muscular dystrophy shows promise beyond safety

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Researchers have cleared a safety hurdle in efforts to develop a gene therapy for a form of muscular dystrophy that disables patients by gradually weakening muscles near the hips and shoulders.

Described as the first gene therapy trial in muscular dystrophy demonstrating promising findings, researchers from the University of Florida (UF), Nationwide Children's Hospital in Columbus, Ohio, and The Ohio State University report how they safely transferred a gene to produce a protein necessary for healthy muscle fiber growth into three teenagers with limb-girdle muscular dystrophy.

The findings, which have relevance to genetic disorders beyond muscular dystrophy as well as conditions in which muscles atrophy, were published online today in the Annals of Neurology.

"We think this is an important milestone in establishing the successful use of gene therapy in muscular dystrophy," said Jerry Mendell, MD, director of the Center for Gene Therapy in The Research Institute at Nationwide Children's Hospital and the lead author of the study. "This trial sets the stage for moving forward with treatment for this group of diseases and we are very pleased with these promising initial results. In subsequent steps we plan to deliver the gene through the circulation in hopes of reaching multiple muscles. We also want to extend the trials over longer time periods to be sure of the body's reaction." Mendell is also a professor of Pediatrics and Pathology at The Ohio State University College of Medicine.

Limb-girdle muscular dystrophy actually describes more than 19 disorders that occur because patients have a faulty alpha-sarcoglycan gene. In each of the disorders, the muscle fails to produce a protein essential for muscle fibers to thrive. It can occur in children or adults, and it causes their muscles to get weaker throughout their lifetimes. The trial evaluated the safety of a modified adeno-associated virus — an apparently harmless virus known as AAV that already exists in most people — as a vector to deliver the alpha-SG gene to muscle tissue.

"The safety data is accumulating because this is the same type of vector that we and other research groups have successfully used in gene therapy trials for other diseases," said Barry Byrne, MD, a UF pediatric cardiologist who is a member of the UF Genetics Institute and director of the Powell Gene Therapy Center. "In this effort, although proof of safety was the main endpoint, the added benefit was that this was an effective gene transfer. Even though we were dealing with a small area of muscle, the effect was long-lasting, and that has never been observed before."

Research subjects received a dose of the gene on one side of the body and saline on the opposite side. Neither the researchers nor the patients knew which of the foot muscles received the actual treatment until the end of the experiment. The volunteers were evaluated at set intervals through 180 days, and therapy effectiveness was measured by assessing alpha-SG protein expression in the muscle, which was four to five times higher than in the muscles that received only the saline. The volunteers encountered no adverse health events, and the transferred genes continued to produce the needed protein for at least six months after treatment.

In addition, scientists actually saw that muscle-fiber size increased in the treated areas, suggesting that it may be possible to combat the so-called "dystrophic process" that causes muscles to waste away during the course

of the disease. Beyond muscular dystrophy, the discovery shows muscle tissue can be an effective avenue to deliver therapeutic genes for a variety of muscle disorders, including some that are resistant to treatment, such as inclusion body myositis, and in conditions where muscle is atrophied, such as in cancer and aging.

"These exciting results demonstrate the feasibility of gene therapy to treat limb-girdle muscular dystrophy," said Jane Larkindale, portfolio director with Muscular Dystrophy Association Venture Philanthropy, a program that moves basic research into treatment development. "The lack of adverse events seen in this trial not only supports gene therapy for this disease, but it also supports such therapies for many other diseases."

Source: Nationwide Children's Hospital (news : web)