Nervous system may be culprit in deadly muscle disease

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Brain may win out over brawn as the primary cause of breathing problems in children with a severe form of muscular dystrophy known as Pompe disease.

Researchers at the Powell Gene Therapy Center at the University of Florida have discovered that signals from the brain to the diaphragm — the muscle that controls breathing — are too weak to initiate healthy respiration in mouse models of the disease.

The discovery for the first time shifts responsibility to the nervous system for the severe breathing problems experienced by infants with Pompe disease, a rare genetic disorder that causes extreme muscle weakness. Children born with the disorder usually die before age 2.

"For years what we have thought is principally a muscle disease may actually be caused by problems with signaling between the spinal cord and the muscle," said Dr. Barry Byrne, a UF pediatric cardiologist, a member of the UF Genetics Institute and the director of the Powell Gene Therapy Center. "As we've treated children with this disease, we found many of them have become ventilator-dependent, so we went back to the laboratory and found that a significant part of the respiratory deficit is in the spinal cord and not in the diaphragm alone."

The findings, which will be published the week of May 25 in the online early edition of the Proceedings of the National Academy of Sciences, also have a bearing on motor neuron diseases, a group of incurable brain

disorders that destroy cells that influence essential muscle activity such as speaking, walking, breathing and swallowing. Notable among these is ALS, technically known as amyotrophic lateral sclerosis or, more commonly, Lou Gehrig's disease.

Although many laboratory discoveries never advance to the point where they can be confirmed in patients, scientists will be able to evaluate whether there is indeed a neural aspect to Pompe disease in a clinical safety study of a gene therapy in six infants with the disorder.

The clinical trial, which will begin this summer at UF, had previously advanced on its merits as a therapy for breathing problems in a group of patients who have very few treatment alternatives.

Children with Pompe disease cannot produce the enzyme acid alpha-glucosidase, or GAA. Without the enzyme, sugars and starches that are stored in the body as glycogen accumulate and destroy muscle cells, particularly those of the heart and respiratory muscles.

In this first-in-humans gene therapy for neuromuscular disease, scientists will incorporate the correct gene to produce GAA into an adeno-associated virus, which already exists in most people, and inject it into each patient's diaphragm. The intent is to "infect" cells of Pompe patients with the genetic machinery they have been missing since birth.

Now, in addition to testing the safety of the dosage and watching closely for signs of therapeutic effects, researchers will fortuitously be able to study the response of the phrenic nerve, which shuttles impulses from the brain to the diaphragm via the spinal cord.

In the PNAS study, UF researchers examined breathing in mice with a form of Pompe disease and in a line of mice genetically engineered to produce GAA only in muscle, not in the central nervous system. In both

models, phrenic nerve bursts to stimulate breathing were substantially weaker than in normal mice. As a backdrop, they considered a detailed analysis of a Pompe disease patient's nervous system, finding similar unhealthy glycogen buildup in the spinal cord and deficient neural output to the diaphragm.

"Treatments that target muscle alone may be ineffective," Byrne said. "Fortunately the gene transfer we are attempting also affects the phrenic nerve, and we know in mice we can restore phrenic nerve stimulation of the diaphragm. Ultimately we hope that by restoring the function of this gene in both muscle and nerve the patients may have improved respiratory function and possibly breathe independently."

In addition to Pompe disease, this finding has relevance for congenital and other forms of muscular dystrophy, according to Xiao Xiao, a distinguished professor of gene therapy at the University of North Carolina Eshelman School of Pharmacy at Chapel Hill who was not involved in the research.

"People did not realize there was nerve involvement in these diseases until this study," Xiao said. "It provides us with a new target for therapy, but it also gives us a new challenge. Not only do we have to deliver therapy to the muscle and heart, we now have to deliver it to the nerve. Fortunately Dr. Byrne is very well-qualified and positioned to take this therapy from the bench to the bedside."

The general therapy for children with Pompe disease involves intravenous infusions to replace the missing GAA enzyme, according to Dr. Robert D. Steiner, a professor of pediatrics and molecular and medical genetics and vice chair for pediatric research at Oregon Health & Science University and OHSU Doernbecher Children's Hospital. In a subset of patients, the enzyme replacement therapy helps initially, but becomes ineffective over time.

"I think this study begins to explain some of the difficulties we've had in treating patients," said Steiner, who did not participate in the research. "The findings are clear that central nervous system involvement is likely to be important in Pompe disease, and that treatments that do not take this into account will not be 100 percent effective in the long-term. It is very reasonable to pursue gene therapy for treatment of this disease, because gene therapy makes it possible to target the central nervous system."

Source: University of Florida (news : web)