Study: Gene therapy reverses effects of lethal childhood muscle disorder in mice

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Reversing a protein deficiency through gene therapy can correct motor function, restore nerve signals and improve survival in mice that serve as a model for the lethal childhood disorder spinal muscular atrophy, new research shows.

This muscle-wasting disease results when a child's motor neurons - nerve cells that send signals from the spinal cord to muscles - produce insufficient amounts of what is called survival motor neuron protein, or SMN. This reduced protein in motor neurons specifically - rather than in other cells throughout the body that contain the protein - is caused by the absence of a single gene.

The researchers used an altered virus to deliver a portion of DNA that makes the SMN protein into the veins of newborn mice ranging in age from 1 to 10 days old. The SMN-laced viral vector injected into the youngest mice reached almost half of their motor neurons, resulting in improved muscle coordination, properly working electrical signals to the muscles and longer survival than in untreated mice, scientists said.

"We're replacing what we know is lost. And we have shown that when you put the protein in postnatally, it will rescue the genetic defect," said Arthur Burghes, professor of molecular and cellular biochemistry at Ohio State University and a senior co-author of the study. "This technique corrects the mice considerably more than any drug cocktails being studied as a potential treatment in humans."

Spinal muscular atrophy (SMA) is a genetic disorder that strikes about one in every 6,000 babies born in the United States, and leads to death in some affected children before age 2. According to the National Institutes of Health, there are many types of SMA, and life expectancy depends on how the disease affects breathing. There is no cure, but medicines and physical therapy help treat symptoms.

The research is published online in the journal *Nature Biotechnology*.

The scientists used a special form of a virus to deliver the SMN protein to nerve cells in the mice. This virus still has the capability to infect cells but has been altered so it will not copy itself and cause illness in humans, said Brian Kaspar, an investigator in the Research Institute at Nationwide Children's Hospital and assistant professor of pediatrics at Ohio State, also a senior co-author of the study.

Kaspar's lab previously determined that this particular viral vector can cross the blood-brain barrier, a characteristic that is required to ensure this protein reaches nerve cells in the spinal cord.

The research group demonstrated that effect in this study, as well, by intravenously injecting some of the disease-model mice with a green fluorescent protein that functioned as a marker of where the virus traveled in the body. Ten days after the injection, 42 percent of spinal motor neurons in these mice showed that they contained the fluorescent protein.

Similarly, mice with spinal muscular atrophy that received the SMN protein via the viral vector when they were 1 day old showed increases of the protein in the brain, spinal cord and muscles within 10 days, though the levels remained lower than the levels of SMN in normal mice.

Those higher levels of the protein appeared to be sufficient to reverse effects of the disease, Burghes said. That is significant because, based on mouse data, the disease is believed to affect people with SMN levels below about 20 percent of normal. But people with only 50 percent of the expected amount of the protein in their motor neurons do not have the disorder.

In addition, a single gene therapy treatment appears to reverse the disease, as opposed to drug treatments under investigation that might elevate SMN protein levels but would require a lifetime of taking medication.

In this study, the researchers tested mice with SMA after the treatment with the protein for their ability to roll themselves upright and for the presence of electrical signals from nerve cells to muscles.

Within 13 days after the injection, 90 percent of the treated mice had the muscle coordination needed to right themselves as quickly as normal animals. By this time, untreated SMA mice already were suffering symptoms that left them unable to right themselves. The day-1 treated mice also were nearly identical to normal mice in their ability to run on a wheel.

In the case of restored nerve impulses, 90 days after the gene therapy, there was no difference in nerve pulses between the treated SMA mice and normal mice, which indicated that the nerves to muscle developed correctly.

The treated SMA mice also gained weight and lived substantially longer than untreated mice with the disease, and some mice were still alive when the paper was submitted 250 days after they received the treatment, Kaspar said.

Improvements this dramatic were seen only in the mice that received SMN on their first two days of life. Later delivery reduced the impact of correction.

"We don't yet know the exact window of when it is capable of getting into the right cells in a human. Is it a month after birth, or a week after birth? That's still a question," Kaspar said.

Complicating this issue is the fact that symptoms of spinal muscular atrophy aren't typically apparent in infants, and the only existing newborn screening technique has not been implemented because it is considered prohibitively expensive.

"So if you have a technique that needs to be delivered early, then you need a newborn screening," Burghes noted.

The researchers hope to progress to human clinical trials of this gene therapy technique as soon as the requisite toxicology experiments are in place and federal regulators will allow. This study should help move the process along because of its inclusion of a single viral vector treatment of a 1-day-old macaque with the green fluorescent protein. The experiment showed that the treatment crossed the blood-brain barrier in this species as well, and penetrated motor neurons.

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