Carolina scientists use virus to deliver genetic material to slow kids' illness

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Even if the patients hadn't been as young as 4 months old, the surgery would have been harrowing: six holes bored into the skull, six tiny tubes inserted directly into targeted parts of the brain, then a solution containing hundreds of millions of viruses pumped in.

But the rare degenerative illness it fights is even scarier. Canavan disease strikes infants, essentially making the brain attack itself with a toxic chemical, stopping and reversing development. It then kills, usually before age 10.

The procedure used in the study though, slowed Canavan's progress and improves - and may even help extend - their lives, according to a study that appeared last month in the online journal *Science Translational Medicine*. It does that by using viruses as microscopic trucks to deliver missing genetic material precisely where it's needed in the kids' brains.

This form of gene therapy was created at the University of North Carolina-Chapel Hill, and the viral vehicle and genetic cargo used in the study were developed there at the medical school's Gene Therapy Center. Center director R. Jude Samulski was a senior author of the study, which began in 2001 and tracked 13 children who received the treatment.

The youngest was 4 months old, the oldest 83 months when they got the operation. After the procedure the researchers, led by Paola Leone, an associate professor of cell biology at the University of Medicine and

Dentistry of New Jersey, then followed them to see how the therapy affected their illness.

To an outsider, the results might not even be noticeable. To the families, though, the changes began quickly and were nothing short of dramatic.

"Right away, we saw a significant change in his eyes," said Jordana Holovach of Rye, N.Y., whose son Jacob participated in the study. "He then was able to regain some of the strength he had lost in grasping, improved his head control, his immune system clearly got better and he was even with some assistance able to take steps, something we never thought we'd be able to see."

Jacob, who had the operation in 2001, will be 17 years old in February. He has grown so much that he doesn't have the strength to take steps now, but attends a mainstream high school, albeit with substantial help.

Ilyce Randell of Buffalo Grove, Ill., whose son Max was diagnosed when he was little more than 4 months old, said that he hadn't seemed to use his eyes at all before the operation, which he had when he was 3 years old. Not long after it, though, he clearly was focusing on things, and began using his arms.

To this day, his sight is improving and he barely needs glasses. "That's a huge thing, when you're trapped in your body," she said.

When he was diagnosed, experts then told her to expect little more than a short life for Max. There was no treatment, let alone a cure.

"Basically I was told, go home and look for a pediatric nursing home; there's nothing you can do," she said.

Now Max is 15. He is severely disabled and requires a wheelchair but

can hold conversations in his own way, attends school and has a healthy sense of humor. And he recently developed a keen eye for women with a certain look.

"I guess the best way to describe it is that Hooters thing," said his mother.

At his school, which is for kids with varying levels of disability, he greets classmates by name via a computerized device operated by blinking.

After the participants were treated, researchers followed their condition with regular checks involving behavioral tasks and brain imaging. They found that the gene therapy reduced the number of seizures and led to improvements in attention, sleep and in degree of movement when lying down and rolling. The best results were among children treated before they turned 2 years old.

The approvals required were elaborate, and the procedure was so experimental that the research and surgery team had to do one child, observe the effects carefully, then present them to an independent board before permission was granted to work on the next child, Samulski said.

Because the disease can reverse development of functions a child has already gained, it's crucial to treat it as early as possible. So the pressure on the team was intense to get approval to treat each successive child.

While surgery sounds scary, it was nothing compared to the stress of watching time pass without it and to the efforts it took to raise money for the research that made it possible and the lobbying to get permission for the procedure, said Rendell.

The virus had to be pumped directly into the kids' brains because an

elaborate barrier prevents such viruses from entering the brain via the bloodstream, said Samulski.

The center also has developed virus-borne approaches to fight other diseases, including hemophilia, Parkinson's disease and retinal disorders. The method was used for the first gene therapy clinical trial for muscular dystrophy in the United States.

Now Samulski's team is working on a promising new type of "delivery vehicle" that would make the daunting neurosurgery unnecessary. It was carefully designed to pass through the blood-brain barrier. So it could simply be administered via an IV tube in a simple outpatient procedure. It's being tested on monkeys.

One day, he said, the idea of having to use brain surgery for such therapies could seem almost laughably outmoded.

Canavan disease is thought to affect fewer that 1,000 people in the United States. Money for fighting rare illnesses can be scarce, and the battle against Canavan has been led to a great degree by charities created by parents of patients. Charities started by the Randells and Holovachs have raised several million dollars to support research.

They are hoping for even more sophisticated treatments, or even a cure.

The virus-based genetic therapy in the study was far from a cure, but clearly it was an important step, Randell said.

For Max, in regular conversation, a blink means "yes" and opening his eyes wide open means "no." The eyelid movements are more complex than that, though. For example, squeezing his eyes shut says he really, really means yes.

His mother says that his blinks are like the dozens of words Eskimos are said to use for snow. His family has learned to understand the nuances.

"I ask, and he says he has a very happy life," Randell said. "I was curious and asked if, in his dreams, he ever is walking, or whether he's always in the wheelchair, and he says always the chair.

"For this therapy to have preserved his brain so that we could have these kinds of conversations when he was 15 years old, that's something I would never have thought was possible," she said.

The goal now is to keep him healthy as long as possible and to keep raising money for more research.

"I just hope to have him doing well for as long as possible, but I don't know what that will mean," Randell said.

"He's good, he's smart and he's lovable," she added. "What more do you want in a kid?"

More information: Information on Canavan: www.canavan.org
The charities begun by the Randell and Holovach families can be seen at jacobscure.org and www.canavanresearch.org.
The study can be read here: stm.sciencemag.org/content/4/165/165ra163