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Gene therapy offers a family hope

At Jefferson, experiments into a fatal disorder may have broad implications.

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Ilyce and Michael Randell trade off holding and comforting their only child, Max, 31/2, as they sit on a bed at Thomas Jefferson University Hospital. They carefully support his shaved head, freshly scarred from a highly experimental gene-therapy treatment he had two days earlier - a treatment they hope will slow the relentless progression of his fatal disorder.

Whether the gene therapy will help Max is unknown. But the Randells say it was their only choice other than simply watching their son degenerate further and die, probably before his 10th birthday.

Max has Canavan disease, a rare condition in which defective genes do not produce a substance that protects neurons in the brain, leaving them to erode rapidly. He is mentally alert but unable to communicate, locked in a body he can barely move. He is unlikely ever to speak or walk.

Although gene therapy - the infusion of healthy genes into cells to replace or supplement defective ones - has been studied for more than a decade, this trial is among the first to introduce the new genetic material into the brain.

"The implications of this go far beyond Canavan disease," said Andy Freese, the Jefferson neurosurgeon who performed the gene-transfer operation. If the experiments work, researchers may learn techniques they can apply to treating Parkinson's disease, Alzheimer's, and a number of lesser-known inherited diseases of the brain and nervous system.

In the next year, the Jefferson team will work with 15 children dying from Canavan disease. Max was the second patient in the trial.

Max was a beautiful, normal baby at birth, his parents said, but stopped developing after about four months. He never learned to turn himself over, crawl, or talk.

Canavan disease, which can be hard to diagnose, was not confirmed until Max was 11 months old. At first, his mother said, "I was in denial. . . . I thought he would need special ed."

Ilyce Randell, 34, imagined that Max would walk and talk - that perhaps he would be mildly disabled. As reality set in, she and her husband, Michael, 38, searched the Internet and found just one group doing human experiments for Canavan disease - the Jefferson group, which was then at Yale University.

Neurosurgeon Freese and gene-therapy researchers Matthew During and Paola Leone, who heads the trial, had started a small-scale experiment to infuse new genetic material into the brain cells

of their patients. Once seen as a possible miracle treatment for dozens of diseases, by 1998 gene therapy had not produced any major successes among the several hundred experiments going on around the country.

Still, the Randells felt it was their only hope.

"But we were told it was parent-funded," said Ilyce Randell, who traveled from her home outside Chicago to New Haven, Conn., and, later, to Philadelphia for Max's treatments. The researchers told the Randells they should try to raise \$50,000, she said, and even then they couldn't guarantee that Max would get into the experimental trial.

She got out their wedding-guest list and sent everyone a card with an old picture of Max, who had curly blond hair, soft blue eyes, and an angelic smile.

"We had gone on a crusade," she said. "This was the main focus of our lives." They raised \$65,000, and Max got into the early trial. The therapy was designed to correct - not merely treat - the genetic defect that gave Max the disease. About one in 37 people with Eastern European or Ashkenazi ancestry carry a damaged, scrambled copy of this gene, but only when a child inherits a copy of that defective gene from each parent does the condition lead to illness.

Those born with two defective copies of the Canavan gene cannot produce a key enzyme needed to break down an acid called NAA. The acid builds up in the brain and destroys the substance that coats the neurons, called myelin, eventually destroying the brain's ability to function.

In theory, the gene therapy would deliver the correct version of the gene to cells in the brain. Then the cells would make that key enzyme on their own.

To get the gene into the cells, most gene-therapy experiments have used some kind of modified virus. In nature, viruses reproduce by inserting their own genes into the cells of other creatures. Genetic-engineering technology allowed researchers to take out some of a virus' own genes and add strands of genetic material carrying healthy versions of the damaged or defective genes they wanted to replace for various diseases.

This first Canavan experiment used a synthetic version of a virus, which researcher Leone said would be safer but probably less effective. Max was treated with this early form of gene therapy in November 1998.

The Randells said they thought Max showed signs of improvement - he seemed more alert and able to track people with his eyes - and they were looking forward to the second treatment planned for a few months later. The researchers, however, had decided to stop using synthetic virus and move to a real virus, which they believed had more promise.

Federal and university approvals for that change were expected to take about a year. But in late 1999, an 18-year-old subject died during a gene-therapy treatment at the University of Pennsylvania. His death made national news and eventually led to the shutdown of all gene-

therapy experiments at Penn, which until then had been one of the leading centers of gene-therapy research in the world.

Jefferson's researchers - and Max - got caught up in the spotlight that the federal government shined on gene-therapy experiments nationwide. A review board in Washington told Leone that her group would have to do more animal experiments before proceeding with the human trial using real viruses.

Meanwhile, the Randells watched Max get worse. He used to be able to wave hello and goodbye, his father said, but by then his motor control had degenerated to the point that he could not raise his own arm.

Tests show that if Max is allowed to answer questions by blinking or pointing with his eyes, he can demonstrate that he recognizes colors and pictures of objects as well as healthy children his age, his mother said. But he is having increasing difficulty communicating anything.

He still responds to words for his favorite foods - chocolate pudding and McDonald's fish sandwiches - by blinking and smiling weakly.

"It's not just that our children are dying," said Ilyce Randell, whose fund-raising efforts spawned a foundation that involves other desperate parents of children with Canavan. "Our children are getting worse by the hour. Their brains are dissolving and turning into a spongy mass - their heads are expanding. We don't have the luxury of time to wait for a review process.

"Their prognosis is 100 percent death."

The Food and Drug Administration finally gave its approval for the experiment in March, and the university review board followed in May.

The first patient, Lindsay Karlin, 7, traveled from Connecticut for the therapy on June 5.

The treatment was part of a protocol used in clinical trials of virtually all new drugs, called Phase I, that is supposed to merely test the safety of the therapy. In most Phase I studies, patients are given doses too small to have any effect on their illness.

In this case, however, Leone, who holds the title of associate director of Jefferson's center for central nervous system gene therapy, said the researchers chose a dose large enough to have a possible effect, although it was lower than what they had given their animal subjects. They decided they needed to look at the risk/benefit ratio, Leone said. To justify the risk of the brain surgery, she said, the researchers believed they should give their patients enough of the genetic material to deliver a benefit. The FDA agreed.

On June 17, Ilyce and Michael Randell handed Max over to the surgeons. Though he doesn't speak, Max can understand people and had picked up enough emotion from his parents to know something scary was about to happen.

"He was shaking like crazy when we took him in," Leone said.

Max was put under general anesthesia and six holes were drilled into his skull. The neurosurgeon used an optical fiber, thinner than a human hair, to slowly pump a solution with the virus into his brain.

About three hours later, when the doctors handed Max back to Ilyce Randell, seeing him with his head shaved made her think of the day he was born. "I mean, he's huge now," she said. "But in a way this does represent a new start."

Later in the afternoon, Leone stopped by. She greeted Max by playfully picking up a stuffed white rabbit - a new toy he had acquired on this trip. "I didn't sleep for two nights before," she said. If Max had had a bad reaction, he could have developed a fever that could lead to seizures, or he could have suffered brain swelling or some other unexpected reaction could have cropped up - as in the Penn research.

Later this month, Leone's team will treat their third patient, age 4. They also will evaluate the first two, Lindsay and Max. They will get a battery of tests to measure Max's responsiveness, motor skills and cognitive function.

Ilyce Randell said that since the procedure, she had seen subtle signs that Max is improving incrementally. Any progress at all would make her happy, she said. "If this is all it does, it's still worth it."

Please note - This promising Canavan Gene Therapy Trial (described in the article above) is currently at Cooper Health System, a division of Robert Wood Johnson Hospitals, Camden, N.J.