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Sending genes to save a child

Pa. parents gamble on an unproven therapy to give their infant daughter a normal life.

By Rory Sweeney
Inquirer Staff Writer

On Wednesday, little Ariel Coover lay with her chin tucked to her chest in a bright, white operating room at Cooper University Hospital in Camden. The only visible part of the 31/2-month-old was the top of her bald head, where six catheters protruded like shiny strands of hair.

Through those tubes flowed her only chance for a normal life: 900 billion viral particles carrying the one gene that could keep her brain from slowly eroding into a spongy mass.

Ariel is the latest and youngest patient in the first clinical gene-transfer study of its kind to receive funding from the National Institutes of Health.

Combining computer-assisted imagery, an ultra-pure viral delivery system, and an extremely young patient, researchers hope to have found a way to combat Canavan disease, a degenerative genetic disorder that leads to seizures, paralysis and death.

Since 2001, only 10 other patients have participated in the study, which is still in Phase One safety trials. The results have been promising. Researchers found that all of the patients' brains have stopped atrophying. None of the patients have died, and at least one has lived past the average life expectancy of 10 years.

But the treatment doesn't reverse the disease; it only stops it. None of the patients are able to walk unassisted or talk.

What makes Ariel special is that she is too young to have been affected. Well before she was born, parents Walter and Peggy Coover knew what they were in for. Through genetic testing during pregnancy, doctors confirmed Ariel had Canavan.

This wasn't new ground for the family from Shippensburg, Pa. Their daughter Amber would have turned 13 in August, but in 2000, she died from the disease.

"We were a lot younger then," said Peggy, who gave birth to Amber at 19. "We grew up because of her. We learned to ask more questions and not listen to everything they say."

What they said was that Canavan has no cure, that parents are doomed to watch their thriving children devolve to where communication consists of faint smiles and eye blinks. Eventually, they said, the children die.

But Amber taught the Coovers to "take more chances because it's final," Walter said. "When it's done, it's done."

That's what sent the Coovers to Cooper. Since 1995, neuroscientist Paola Leone, director of the Cell and Gene Therapy Center there, has been developing a gene-therapy treatment for Canavan.

Gene therapy, once a wide-open medical frontier, hit a major setback in 1999 when teenager Jesse Gelsinger died while participating in a gene-transfer study at the University of Pennsylvania. Since then, advances have been cautious, but recent successes have

revived the field.

Canavan is one of 40 to 60 disorders caused by a defect in a single gene, according to Dan Tagle, program director for neurogenetics at the National Institute of Neurological Disorders and Stroke, which is part of the NIH and provided \$2.3 million for Leone's research.

This defect prevents the production of aspartoacyclase, a brain enzyme that breaks down N-acetylaspartate acid, or NAA, into some of the elements needed to create myelin. Myelin is a fatty covering that protects nerve cells in the brain and spinal cord. Without aspartoacyclase, NAA builds up and causes the destruction of the myelin, which, in turn, causes the spongy atrophy of the brain.

Leone's treatment pumps in billions of correct copies of the gene, each housed in an adeno-associated virus approved by the Food and Drug Administration. The viruses diffuse in the brain and insert the gene into the DNA of every cell they contact.

However, the viruses have an affinity for neurons and, because the gene requires a specific cellular promoter, it will only turn on in neurons, Leone said.

By last night, all the viral vectors had inserted the new gene, Leone said, and it would take two or three weeks for the cells to produce a stable amount of aspartoacyclase. The production will decrease slightly after 12 to 24 months but will continue for the life of the cell. Because brain cells don't split, there is no chance of the gene's being replicated. The success of the procedure will not be known for one to three months, but the doctors involved are optimistic.

"Ariel is an amazing miracle," Leone said. "She was diagnosed in utero. That's not usually the case. Usually, when they call me, they're 10 months old. She's so young and unaffected."

The procedure shows promise for other single-gene disorders but remains unproven, Tagle said.

"We don't know what to expect," he said. "Is the vector system the right delivery system to use? Will the brain tolerate the virus? It's still research in some ways, because we're still trying to figure it out."

The study is not designed to test effectiveness, he said. The treatment's safety is the main question, and the surgery includes serious risks. But, for the Coovers, the potential benefit was too great to pass up.

"The biggest risk is she could die," Walter said. "And she was going to die anyway."

The Coovers say Ariel acts differently from Amber. Ariel is a cooperative eater, while Amber was not, and Ariel tries to hold her head up. They hope she is the little sister their 5-year-old son, Dylan, has been asking for.

Dylan, who was just 7 months old when Amber died, did not inherit Canavan. It is an autosomal recessive disease, meaning it is not sex-linked, both parents must be carriers and, even then, there is only a 25 percent chance of inheritance.

Before having Dylan, the Coovers decided to terminate the pregnancy if Canavan was detected, but it was not.

And after birth, Dylan showed the normal signs of development, such as rolling over and holding his head, well before expected.

Ariel's conception came as a surprise and, after testing, the Coovers had four days to make a decision. They had an appointment at an abortion clinic scheduled for the final day.

"We wrestled with it. We cried a lot," Peggy said.

They canceled the appointment the night before. Not until after Ariel was born did they learn of Leone's research.

Now Peggy wears a bracelet inscribed with "Miracles," a reference to the Coovers' new foundation, Ariel's Miracle. They are preparing a fund-raiser in Shippensburg for next Saturday, and plan to donate the proceeds to Leone for research. They already have raised about \$4,000.

"I want to be able to say when this is over there's a cure for Canavan," Walter said. "I want my daughter to be a shining example."