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A Fight With Many Winners

By Thomas H. Maugh
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How much difference can one set of parents make when their child is diagnosed with a fatal genetic illness? In the case of Ryan Dant, all the difference in the world.

Ryan was an apparently healthy 4-year-old undergoing a preschool physical when his doctor noticed that his liver was enlarged. A trip to Children's Medical Center in Dallas revealed that the boy had Hurler/Scheie syndrome, a devastating disease in which his body was missing a crucial enzyme for processing sugar polymers. Physicians said Ryan would be lucky to survive until age 10.

Initially, Ryan's course was all downhill. Although he loved baseball, by age 5 he had difficulty holding a bat. His father gave him a bat and gloves equipped with Velcro. When Ryan got a hit, he would race to first base with the bat still stuck to his gloves.

By age 9, his hands were too stiff to swing a bat and he couldn't fully extend his arms. His father would drive out of his way to avoid parks, so Ryan wouldn't see other children playing ball. Ryan would get severe headaches, vomit and pass out, sleeping for 18 hours or longer.

But while Ryan was deteriorating, his parents--police detective Mark and airline reservationist Jeanne--were energized, as was the small town of Carrollton, Texas, where they lived.

Working late into the night, the Dants organized golf tournaments, bake sales and fund-raising drives that ultimately raised more than \$1 million for research into the disorder.

That's not unusual. Many parents of afflicted children undertake similar efforts. But what sets the Dants apart is that their efforts had an immediate effect--and that Ryan was one of the first to benefit from their hard work.

For while they were raising money, a young researcher at Harbor/UCLA Medical Center, Dr. Emil Kakkis, had encountered a funding crisis in his efforts to develop a therapy for the disorder. His goal was to artificially replace the enzyme that children like Ryan were missing. "We had a lot of information that this would work, but we couldn't move much further ahead for lack of money," Kakkis said.

Mark Dant eventually heard about Kakkis' research and began supporting it. "They funded us and got us moving in the direction of making it work," Kakkis said.

Two weeks ago, Kakkis and his colleagues reported in the New England Journal of Medicine that the replacement therapy was highly successful in 10 children and young adults with Hurler/Scheie. The Food and Drug Administration is requiring a clinical trial of the treatment against a placebo before it will approve the therapy. That trial is underway and the enzymes could be approved as soon as next year.

Ryan was one of the 10 treated, and his improvement has been remarkable, his father says.

"Ryan is now a normal, active sixth-grader," Dant said in a telephone interview. "To look at him, you would have no idea that he has such a serious genetic disease."

Disorder Affects 1 in 25,000

Hurler/Scheie, also called mucopolysaccharidosis-1 or MPS-1, is a disorder of the metabolism of mucopolysaccharides, long chains of sugar molecules used in building connective tissues in the body. Children with the disorder--about one in every 25,000 born in the United States--are missing an enzyme called alpha-L-iduronidase that breaks down mucopolysaccharides.

The improperly cleaved sugar polymers build up in tissues throughout the body, enlarging and producing severe damage in the kidneys, liver, brain and heart. Connective tissue is also damaged, making movement difficult.

MPS-1 is divided into three broad groups, depending on the severity of the symptoms. Children who are severely disabled, both mentally and physically, have Hurler syndrome, named after Dr. Gertrud Hurler, who first described it in 1919. Those who have normal intelligence and mild symptoms and who live into adulthood have Scheie syndrome, first observed by ophthalmologist Hank Scheie (pronounced Shay) in 1962. "It took a while to realize that they were actually forms of the same disease," said Dr. Elizabeth Neufeld of UCLA.

And those like Ryan, who have normal or near-normal intelligence, but more severe symptoms, are said to have Hurler/Scheie syndrome.

The only current treatment for MPS-1 is a bone marrow transplant, and that is used primarily for Hurler patients younger than 2 when the disease is diagnosed, said Dr. Chester Whitley of the University of Minnesota. If the transplant is delayed until after brain damage has occurred, he said, there is little point in performing it.

Transplants are rarely performed in patients with Hurler/Scheie or Scheie because the side effects and the relatively high mortality rate outweigh the benefits, he added.

The idea of using enzyme replacement therapy for genetic diseases such as Hurler/Scheie has been around for a long time, "but we despaired of ever going to clinical trials because it costs a lot of money," said Neufeld, who discovered the mutated gene that causes MPS-1.

Money from the Ryan Dant Foundation got Kakkis through some key early testing. At that point, BioMarin Pharmaceuticals of Novato stepped in to provide the additional \$6 million needed for further testing.

BioMarin thinks it can make a small profit on the enzyme, even though the potential number of patients is small and the cost will be about \$100,000 per patient per year, said Kakkis, who is now a BioMarin vice president.

Perhaps more important, MPS-1 represents a demonstration of the feasibility of treating a variety of genetic diseases in which patients are missing key enzymes. "The model is there now," Neufeld said. "Enzyme replacement can work. These rare diseases are now going to be treated."

Other researchers, meanwhile, are looking at alternative approaches to therapy, many of them using a mouse model of MPS-1 developed by Neufeld. Whitley, for example, is attempting to develop gene therapy that would allow the victim's body to manufacture its own alpha-L-iduronidase. But that effort has been plagued by the same problem that has afflicted gene therapy for a variety of diseases--the inability to get sufficient copies of the gene into the patient to produce enough enzyme to be useful.

Dr. Pat Chang at McMaster University in Canada has genetically engineered a line of laboratory-grown cells to produce the enzyme. The capsule protects the cells from the recipient's immune system, so that any type of cell can be used.

Chang has successfully treated MPS-1 in mice and dogs by implanting the capsules in muscle, and may begin studies in humans this year.

Ryan Dant, meanwhile, has undergone a marked change since he started the weekly infusions of alpha-L-iduronidase three years ago. After the second treatment, "he was standing naked in front of a mirror and was able to tell that his stomach had gotten flatter," Mark Dant said. After eight weeks, his liver and spleen were back to normal size.

Today, Ryan has grown four inches and gained 30 pounds. "He has started talking again about getting a driver's license, getting dates, and what college he will attend," Dant said. "He has the same dreams as people without the illness, and now he has a chance to realize them."

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