Treatment offers hope for one regional family that has suffered from a rare genetic disease for generations

BY JAMIE TALAN, SPECIAL TO THE TIMES-TRIBUNE / PUBLISHED: MARCH 29, 2020

Thomas Deater went off to fight the Civil War with ulcers on his feet. Over the next seven generations, a few dozen family members would go on to develop similar symptoms, including limb ulcers, numbness, tingling, nerve pain, muscle weakness, bone infections. Today, a map of the family — from the Stull area in Noxen Twp. — suggests that this clan has a rare genetic mutation that causes hereditary sensory and autonomic neuropathy type 1.

Scientists at Massachusetts General Hospital began showing up at the Deater family's legendary Pennsylvania reunions in 1986. By then, Larry Deater, who had spent about a dozen years with severe neuropathy, limb weakness and severe skin ulcerations that would lead to amputation of many digits on his hands and feet, had befriended Mass General neurologist Dr. Robert Brown. Brown and his colleagues set up shop in a camper at the reunion, held in a wooded area next to a creek in the Back Mountain area, and began drawing blood.

The collection paid off. They identified the genetic culprit and began using the mutation in test tubes and animal models to figure out what was going wrong in this family. Lipids were accumulating in the nerves of mice and immune cells were called to the scene.

The mutation in the family codes for two of three subunits of serine palmitoyltransferase (SPT). The mutant enzyme "misbehaves" and takes other partners than serine — namely alanine and glycine. This leads to the formation of neurotoxic lipids. It was a study collaborator, Thorsten

Hornemann, Ph.D., of the University Hospital Zurich, Switzerland, who found that these toxic lipids were elevated in HSAN-1 patients.

It was with this knowledge that the Mass General team flooded the mutant mice with L-serine — and they never develop neuropathy. When they were fed alanine, within no time the animals had ulcers and severe neuropathy.

“Everything depends on the availability of the right amino acid,” said Dr. Florian Eichler, the Mass General neurologist who led the research.

With this finding, the team returned to the family reunion — and this time they arrived with jars of white powder, L-serine.

Down the muddy roads, Eichler kept saying to himself: “We are finally going to solve this disease.”

That was in 2010. Blood was drawn before and after a lunch of pancakes and burgers. Larry Deater was handed his jar, and the other 13 containers were passed around. Each family had enough L-serine for a three-month trial. They would compare a high dose (400 milligrams per kilogram) to a low dose of 200 milligrams per kilogram.

Blood was drawn and tested each week for 10 weeks. The high dose was able to reduce deoxysphinganine levels to a normal range. They were eight times higher than normal. Some of the patients said that they felt sensations returning. When the study stopped, the levels of the toxic lipids soared once again.

The results were so impressive that they took the findings to the Food and Drug Administration and were able to get a grant to help fund a double-blind study. This time, word of the findings spread across the world and other families with this rare mutation also signed on for the new study.

By late 2012, the Boston scientists had recruited 18 patients. Half of them are from the Deater lineage. There are only 100 patients with this HSAN-1 reported worldwide.

The challenge was this: How do you recruit for a double-blind study when patients can simply order L-serine powder online and start taking it? The deal

they struck: Join the study and be randomized to the amino acid or a placebo powder for one year, and then the second year everyone will get the amino acid.

The patients who enrolled were compliant: They sent their bottles back every month, and they were able to measure L-serine in their weekly blood samples.

They measured neuropathy, and the scores got worse over the first year in those on a placebo dose. The scores did not get worse in patients receiving L-serine. The next year, all patients in the study had stabilized with L-serine in their system.

One patient in the study died. It was Larry Deater. He died of cancer at 59.

“Larry was an old general fighting his last battle,” Eichler said. “He rallied his whole family to be part of research.”

David Elston, Larry’s cousin, passed the disease on to two of his three daughters. They were all in the study. His condition is so bad that he can put his hand in fire and not even realize he is burning. He can no longer use his hands or feet. His daughters began having symptoms as teenagers. So did he.

Since the study stopped, they have continued to take L-serine and were happy when they were just notified about the study findings. There was a time when they could not get hold of L-serine and felt their symptoms worsening. They now buy it in bulk.

“I feel like I don’t have as much shooting pain,” he said.

The study results were published in 2019 in the journal Neurology.

“This is a beautiful example of how we can see changes in blood that parallel an individual’s symptoms,” Eichler said. “We were able to stabilize the disease.”

The treatment is cheap and readily available without a prescription. Ultimately, it should be given early enough in people with this mutation to stop the build-up of toxic lipids, he said.

“This is their Lorenzo’s Oil. How much longer can you withhold treatment from these patients? They will have to take it three times a day,” Eichler said. The neurologist is now talking to pharmaceutical companies to see if they can create a long-acting L-serine.

He said the findings may also have implications for other conditions that trigger neuropathy, including Type 2 diabetes and chemotherapy-induced neuropathy. There is evidence that these toxic lipids are higher in people with Type 2 diabetes.

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The Deater family lore dates back seven generations and involves two women, two babies and a curse.

An ancestral Thomas got two girls pregnant but denied paternity of one of the boys. He married one girl and his older brother married the other. The two boys — Charles and Alvin — were raised as cousins. As young men, they developed the same vexing ulcer symptoms, sensory neuropathy and bone infections. Charles died as a young man and never married. His mother is said to have cursed Thomas Deater’s family.

Family reunions are rife with amputations and wheelchairs and crutches.

Alvin also grew sick with the curse. So did his younger sister, Mae. Still, Alvin would marry and bring a dozen children into the world. Seven would go on to lose sensation in their feet and hands. Sometimes, the first signs arrived when someone stepped on a nail without even knowing it happened.

Seven of Alvin’s children suffered from the same vexing problems, and it was one of these children — Harvey Deater (Larry’s father) — who finally brought the family puzzle to doctors at Thomas Jefferson Hospital in Philadelphia. Harry was 27, and the scientists conducted an extensive work-up, which was

published in a medical journal in 1939. Ultimately, the ulcers led to infections, weakened muscles and amputation.

The genetic mutation would not have been realized had it not been for the Deater family. In 2001, geneticist Khemissa Bejaoui, Ph.D., working in Dr. Brown's laboratory at Mass General, helped identify the HSAN1 gene. At the same time, Australian researcher Garth Nicholson and his colleagues identified a similar genetic mutation that was causing the disease in a few Australian families. Several missense mutations were identified, classified as C133W (the most common), C133Y (in the Deater family) and V144D.