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Finding in arginine paradox study translates into treatment for teen

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In the spring of 2010, Baylor College of Medicine's Dr. Brendan Lee received a desperate email from the mother of one of his patients. The teen – who had been Lee's patient for most of his life – was in hypertensive crisis and none of the usual treatments could bring his blood pressure down to normal. His heart was enlarged and not pumping well – a problem called cardiomyopathy that was the result of more than a decade of difficult-to-control high blood pressure.

Finding the solution to the disorder plaguing now 17-year-old Jonathan Oliphint was a long quest that Lee, a professor of molecular and human genetics at BCM, undertook when he first saw him as a young child in the metabolic clinic at Texas Children's Hospital. The problem led Lee back to the laboratory for years of painstaking experiments.

Two years ago, he was finally able to bring the results back to the youngster's bedside for a successful treatment. He and his colleagues Drs. Sandesh Sreenath Nagamani and Ayelet Erez, both assistant professors of molecular and human genetics at BCM, describe the treatment online in the *American Journal of* Human Genetics. The study will publish in the May 4 print issue of the journal.

"Having an immediate impact on the life of a child is the most rewarding feeling," said Lee. "The theme we have pursued in the study of these rare genetic diseases is that they can lead to insights into more common disease mechanisms, and this has borne true. We cannot, however, forget the direct and immediate impact our work can have on the patients with

the rare diseases. This is a beautiful example of that. Jonathan was one of the original patients who led us to think about this problem in the late 1990s."

The problem was that Jonathan's genetic disorder – argininosuccinic aciduria – meant that he lacked a functional gene to make an enzyme called argininosuccinate lyase. Without that enzyme, he could not make arginine, a critical amino acid. Arginine plays an important role in the urea cycle, which enables the body to avoid the toxic buildup of the materials that can make ammonia. A buildup of ammonia in the body damages the body's organs and brain.

Giving Jonathan arginine prevented the damaging buildup of ammonia, but by age 3, he was experiencing two other symptoms – high blood pressure and neurodevelopmental delay. Lee and members of his laboratory sought to find out why these problems continued in Jonathan and others like him. In November 2011, they published their results in the journal *Nature Medicine*.

"Arginine is the single amino acid in the body that makes nitric oxide, a chemical critical to many bodily processes," said Lee, also a Howard Hughes Medical Institute investigator. The problems Jonathan suffered were what one would expect from a deficiency in nitric oxide. What Lee and his colleagues discovered was that because Jonathan lacked the enzyme argininosuccinate lyase, he not only could not make arginine, he also could not use exogenously delivered arginine (the arginine he received to treat his disease) to make nitric oxide. The enzyme plays a dual function. The first is to make arginine and the second is to hold together a complex of proteins that transfers arginine to the part of the cell where it can make nitric oxide.

Lee talked to his team and decided that they knew how to treat the problem based on their work in the laboratory and with mice. He asked

Jamie Oliphint, Jonathan's mother, to have him admitted to Texas Children's Hospital. There Nagamani helped wean him off his ineffective blood pressure medicine and started him on an organic nitrate – the kind of drug that people with heart disease take to relieve the chest pains of angina.

"Over a period of four days, his blood pressure and pulse became normal," said Lee. "In the two years since, his heart has become stable. We switched to a formulation containing inorganic nitrite later because it was more effective."

Rather than trying to make up for the enzyme deficiency that left Jonathan unable to make nitric oxide, Lee and his team bypassed that entirely. In effect, the medicine they gave Jonathan the nitric oxide he needed to maintain a stable blood pressure.

Jonathan's mother also said that after the treatment, Jonathan showed some improvement in testing and he seemed more aware of the world around him.

"Last year, when he was still in middle school, he passed the regular reading TAKS test," she said. He also seems more aware of the attitudes of his fellow students, she said.

Lee and his colleagues also describe a study in mice that further confirmed the problem facing the youngster. Lee and his colleagues did gene therapy in the liver of mice with Jonathan's disease. The gene therapy corrected the problem that resulted in the buildup of ammonia but not the high blood pressure and other problems.

Jamie Oliphint said that she and Lee had discussed the problem several years ago and Lee said it was just a theory then. He could not do it until he had more information.

He wants more information before the treatment is used more widely, and he is planning a clinical trial of the treatment in children with Jonathan's disorder.

More information: http://www.cell.com/AJHG/

Provided by Baylor College of Medicine