Learning to Care for Those in Harm's Way

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Genetic mutation linked to childhood ALS

Bethesda, Md. – Scientists have identified a novel form of Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig's Disease, that affects children, according to an international collaborative study, "Childhood Amyotrophic Lateral Sclerosis Caused by Excess Sphingolipid Synthesis," published May 30, 2021, in Nature Medicine. This is the first example of a mutation that perturbs a specific metabolic pathway as causative for ALS.

According to senior authors, Dr. Teresa Dunn, chair of the Uniformed Services University's (USU) Department of Biochemistry and Molecular Biology, and Dr. Carsten Bönnemann, senior investigator at the National Institute of Health's National Institute of Neurological Disorders and Stroke (NIH/NINDS), for the first time, it is demonstrated that ALS can be caused by changes in how the body regulates the levels of a specific class of lipids, the sphingolipids. The researchers also decided to test whether they could turn off the mutant SPLTC1 gene by creating small, interfering strands of RNA. This appeared to show promise for potentially treating this type of rare ALS.

ALS is a rare neurological disorder that progressively destroys muscle-controlling nerves in the brain and spinal cord leading to paralysis. About 12,000-15,000 people in the U.S. have ALS, and there are about 5,000 new cases each year. For unknown reasons, military veterans are nearly twice as likely to develop the disease, according to Dunn.

Understanding that the mutant SPTLC1 was leading to excessive sphingolipid levels, the researchers reasoned that if they could turn off the mutant SPTLC1 gene using a small, interfering RNA (siRNA), they could restore normal sphingolipid levels. Indeed, this approach shows promise for potentially treating this type of rare ALS.

The study began with a young woman from Italy whose case was so perplexing that Pope Francis himself imparted a blessing on her at the Vatican, before she embarked on her journey to the NIH Clinical Center, where she was examined by Bonnemann. Eventually, 11 other patients with similar clinical presentation were identified and studied. What is so unusual about their cases is that in contrast to most ALS patients who are diagnosed around 50-60 years of age and whose symptoms progress rapidly, these patients have an early onset and slowly progressing disease. Nonetheless, Dr. Payam Mohassel, NIH Clinical Research Fellow and lead author of the study, found that these patients have upper and lower motor neuron problems that are the hallmark of ALS.

Working together from across the globe, the team of researchers examined the patients' exomes, the sequences of DNA that hold the instructions for making proteins. They found each patient had slight

changes in the “spelling” of SPLTC1, a subunit (part) of the enzyme, SPT. SPT is the enzyme that initiates the production of sphingolipids, a class of lipids that are highly abundant in the nervous system and that play essential roles in how cells function. Four of the early-onset patients inherited changes in the SPTLC1 gene from a parent, while the other six had de novo (not inherited from either parent) mutations, which usually arise as cells are rapidly dividing after conception.

Mutations in SPTLC1 have previously been associated with another neurological disease, hereditary sensory and autonomic neuropathy, Type I (HSAN1). However, the HSAN1 mutations in SPTLC1 affect the enzyme much differently than the ALS mutations. The HSAN1 mutations make the SPT enzyme sloppy and allow it to generate atypical sphingolipids that are damaging to neurons. The researchers first thought the ALS-causing mutations were causing similar problems, but the patients’ blood tests showed something else. It was not formation of atypical sphingolipids as expected, rather, the patients had abnormally high levels of normal sphingolipids, suggesting an enhanced activity of the SPT enzyme. Like many enzymes, SPT is feedback inhibited by its products – as sphingolipids begin to accumulate, SPT activity is slowed down by the ORMDL proteins that bind to and inhibit SPT preventing excessive accumulation of these essential, but potentially toxic lipids. Ultimately, the researchers determined that the ALS-causing mutations interfere with the ability of the ORMDL proteins to inhibit SPT. In other words, in this form of ALS, the ORMDL brake that normally restrains SPT is not working.

The study was a collaborative effort between USU, the National Institute of Neurological Disorders and Stroke (NINDS/NIH), the National Institute of Child Health and Human Development (NICHHD/NIH), the University of Zurich in Switzerland, Universidade Federal do Rio Grande do Sul and Universidade de São Paulo, in Brazil, along with the University of Bari “Aldo Moro” in Italy, and the University of Duisburg-Essen in Germany.

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