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Study of Lou Gehrig's disease shifts 'origin' focus to brain's motor neurons

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Lou Gehrig's disease, also known as amyotrophic lateral sclerosis, or ALS, might damage muscle-controlling nerve cells in the brain earlier in the disease process than previously known, according to research from the Cedars-Sinai Board of Governors Regenerative Medicine Institute. The findings, published in the Nov. 12 *Journal of Neuroscience*, could shift researchers' attention from the spinal cord to the brain's motor cortex as the disease's initial point of dysfunction.

"In this study, we show the exact progression of ALS in animals that have an inherited form of the disease, and we expose the brain's significant role in initiating the disease process thought previously to originate in the muscle or spinal cord," said Clive Svendsen, PhD, professor and director of the Board of Governors Regenerative Medicine Institute. "We did this by selectively removing the disease-causing mutation just from the brains of ALS animals, and found that this alone had a big impact on disease initiation and progression."

ALS causes weakness and gradual paralysis of muscles throughout the body, and although the timing and sequence of progression is unpredictable, it often begins in the arms or legs and eventually affects the breathing muscles in the chest. Patients generally live only three to five years after onset.

The disease is known to affect motor neurons - nerve cells that control muscles - in the brain, brainstem and spinal cord. It also inflicts damage in the nerve pathways extending from the spinal cord out to the muscles

of the body. Breakdown of communication at the neuromuscular junctions - the points where nerve fibers connect to muscle fibers - is what ultimately leads to muscle weakness and failure.

In previous research using laboratory mice with the disease, the earliest, most obvious anatomical damage has been seen in the neuromuscular junctions and in the spinal motor neurons, called the lower motor neurons. Most ALS research has focused on these areas. But recent studies in both humans and lab mice have suggested that motor neurons in the brain - the upper motor neurons - may be involved in disease progression, although the extent and significance of this involvement has remained unknown. This study was designed to better define the process by which ALS progresses and to explore the role of brain motor neurons in disease development and progression.

Most animal studies of the disease are conducted with laboratory mice that have been genetically engineered and bred to model ALS, but for this research, investigators used rats with ALS because they more accurately portray the disease's variable course in humans.

"We found that spinal motor neurons die before symptoms begin and before nerve damage occurs between the spinal cord and the muscles. In fact, motor neuron death starts in the spinal cord and radiates out to the muscle and the brain over time. Motor neurons in the brain are not lost until the final stages of the disease, but starting very early in the process they appear to exist in a dysfunctional form. When we suppressed the ALS mutation in the brains of animals, onset of the disease was delayed, the animals lived longer, spinal motor neurons survived longer, and the neuromuscular junctions stayed healthy longer," said Svendsen, the Kerry and Simone Vickar Family Foundation Distinguished Chair in Regenerative Medicine.

"These results suggest that an early dysfunction of motor neurons in the

brain may be a significant contributor to later disease development and progression, opening the possibility that experimental therapies targeting this 'upstream' dysfunction could have a beneficial impact on the disease's catastrophic 'downstream' effects," said Svendsen, the article's senior author.

Gretchen Thomsen, PhD, a scientist in Svendsen's laboratory and first author of the paper, said, "It is likely that dysfunction at a cellular level, without cell death, goes undetected for years prior to symptom onset and clinical diagnosis. It is imperative that we identify patients at high risk of developing ALS and devise and initiate treatments that can intervene before an irreversible cascade of motor neuron circuitry failure sets in."

More information: The *Journal of Neuroscience*: "Delayed disease onset and extended survival in the SOD1G93A rat model of ALS following suppression of mutant SOD1 in the motor cortex," publishing Nov. 12, 2104

Provided by Cedars-Sinai Medical Center