Glutamate identified as predictor of disease progression in multiple sclerosis

April 30 2009

(PhysOrg.com) -- UCSF researchers have identified a correlation between higher levels of glutamate, which occurs naturally in the brain as a byproduct of metabolism, and greater disease burden in multiple sclerosis patients. The study is the first to measure glutamate toxicity in the brain over time and suggests an improved method for tracking the disease and predicting its course.

The research team employed a novel technique, developed by Radhika Srinivasan, PhD, study author and assistant researcher in the UCSF Department of Radiology and Biomedical Imaging, to measure glutamate levels in clinical trial patients. The technique was based on a sophisticated form of imaging known as proton MR spectroscopy, which uses simple radio-frequency pulses targeting specific brain chemicals.

Study findings were presented today (April 29, 2009) during the American Academy of Neurology annual scientific meeting in Seattle.

Glutamate, a neurotransmitter, in normal levels performs fundamental processes like memory and sensory perception. In excess, it triggers a cascade of negative reactions in the brain leading to many of the complications associated with neurologic diseases such as MS, Parkinson's disease, stroke, ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease) and Alzheimer's disease by destroying nerve cells and causing seizures, injury after stroke, and the perception of pain, among other problems.

Already a target for therapeutic drug development, the identification of the glutamate pathway for MS suggests a new way for clinicians to monitor treatment of these drugs.

"This is the first time that we have had the ability to measure glutamate toxicity in the brain in real time, which gives us a marker for monitoring disease progression as well as our treatment of the disease," said Daniel Pelletier, MD, study author, associate professor of neurology and a member of the Multiple Sclerosis Research Group at the University of California, San Francisco.

"For instance, we already have anti-glutamate drugs, so now we can assess, with imaging, the impact of the therapy and the progression of the disease," he said.

Elevated levels of glutamate in the brain are understood clinically as a cause of cell injury and death. Injury to neuro-axons, which are the long fibers that extend from the cell body of a neuron cell toward other nerve cells, is partly responsible for disability progression in MS. In a previous study using proton MR spectroscopic imaging, the research team reported that MS brains have significant elevation of glutamate concentrations. For this study, researchers looked for levels of glutamate and levels of NAA (n-acteylaspartate), a marker of axonal integrity in mature brains, to see if a relationship existed.

The team scanned 265 MS patients annually and followed them for an average of 1.8 years. Accounting for disease duration and age of onset, researchers found that significant annual loss of NAA, which is a measure of neurodegeneration, was associated with concentration of glutamate. This finding indicated that the higher the level of glutamate, the greater the expected neuro-axonal loss over time.

According to the authors, the study is the largest clinical analysis to date

of metabolism byproducts in the brain, and the results strongly support the link between the excess of glutamate and decline of neuro-axonal integrity in MS.

The finding, Pelletier says, goes beyond MS. "Now that we have those markers, we can quantify levels of glutamate for other neurologic diseases, which could be another way to track disease progression and therapeutic intervention."

Source: University of California - San Francisco