Rapid changes in key Alzheimer's protein described in humans

August 28 2008

For the first time, researchers have described hour-by-hour changes in the amount of amyloid beta, a protein that is believed to play a key role in Alzheimer's disease, in the human brain. A collaborative team of scientists at Washington University School of Medicine in St. Louis and the University of Milan report their results this week in *Science*.

"Proving that we can directly measure amyloid beta in the human brain is an important step forward for both clinical and basic research, and that may be true not just in Alzheimer's disease but also in other serious neurological disorders," says co-first author David L. Brody, M.D., Ph.D., a Washington University neurologist who treats brain injury and general neurology patients at Barnes-Jewish Hospital.

The results of the study contradicted the expectations of researchers, who were hoping to learn why brain injury is linked to higher risk of Alzheimer's disease. They had hypothesized that such injuries, caused by motor vehicle accidents, assaults and falls, would lead to an increase in amyloid beta levels. Instead, they found recovery from brain injury, rather than the injury itself, seemed to increase amyloid. The better a patient's overall neurological status, the higher their amyloid beta levels rose.

"We can't at this point rule out a very early spike in amyloid right after a brain injury," notes Brody, assistant professor of neurology. "This study is just the beginning."

Amyloid beta levels were measured using a technique called microdialysis, which involves placing a small catheter into the brain tissue to sample the fluid in the spaces between cells. The Italian group, headed by Sandra Magnoni, M.D., and Nino Stocchetti, M.D., and located at the Ospedale Maggiore Policlinico, a major trauma center in Milan, brought substantial previous experience with microdialysis to the study.

In the study, 18 patients recovering from traumatic brain injuries or ruptured brain aneurysms had microdialysis catheters placed in their brain tissues to measure amyloid beta while they were in the intensive care unit. Patients' families in both St. Louis and Milan gave permission in advance, and the catheters were placed when the patients were having other monitoring procedures performed.

"The results have potentially important clinical implications because the measurement of amyloid beta in the human brain may turn out to be a good indicator of how well brain cells are communicating with each other, even in very sick patients," says senior author David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology at Washington University. "If the results are validated in further studies, this may assist physicians in making important patient management decisions in patients with acute neurological disorders."

In a study published in 2005, Holtzman and others showed that brain cell communication was directly linked to the levels of amyloid beta in a mouse model of Alzheimer's disease. When there was increased communication between brain cells, amyloid beta increased. When there was reduced communication, amyloid beta decreased. However, it was not known whether the same relationship between brain cell communication and amyloid beta levels would hold in humans.

"The new data fit well with the previous results in mice, because improved neurological status is likely to go along with increased communication between brain cells," says Brody. He and his colleagues plan to continue with similar studies that also will include direct measurement of brain electrical activity and the assessment of different forms of amyloid beta.

The results provide scientists important clues about the general origins of Alzheimer's. Further investigation is needed to answer the specialized question of why brain injury increases risk of Alzheimer's. This experiment was a test of a model that suggests brain injury accelerates harmful processes that cause Alzheimer's. Although scientists didn't find what they expected, this model still cannot be ruled out, according to Brody.

"We haven't measured how brain injury affects amyloid beta inside cells, nor have we determined whether brain injury affects the ability of amyloid beta to form small aggregates that may be especially harmful," he explains.

A second explanation for the link between brain injury and Alzheimer's suggests that injury may reduce the brain's ability to compensate for Alzheimer's-related damage, making the symptoms of the disease evident much earlier than they would otherwise appear. Evidence exists for both models, and both could be valid in different settings, according to Brody.

Brody emphasizes the researchers' gratitude to the families of patients who agreed to participate in the study. While the study did not directly benefit the patients, it provided scientists with an important opportunity to learn about amyloid beta and the connections between Alzheimer's and brain injury.

"Our ultimate goal is to develop interventions that we can apply after a traumatic brain injury to improve outcomes and reduce the long-term risk of Alzheimer's," he says.

Source: Washington University