Brain damage found in cognitively normal people with Alzheimer's marker

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Researchers at Washington University School of Medicine in St. Louis have linked a potential indicator of Alzheimer's disease to brain damage in humans with no signs of mental impairment.

Although their cognitive and neurological assessments were normal, study participants with lower levels of a substance known as amyloid beta 42 (A-beta 42) in their cerebrospinal fluid (CSF) had reduced whole brain volumes, suggesting that Alzheimer's changes might already be damaging their brains. Scientists previously showed that low CSF levels of A-beta 42 mark the presence of amyloid deposition in the brain, a key diagnostic marker of the amyloid plaques that characterize Alzheimer's disease.

Evidence is mounting that Alzheimer's harms the brain for many years before physicians and family members can detect symptoms, and this has led many to conclude that successful Alzheimer's treatments may only be possible if scientists find ways to identify pre-symptomatic sufferers.

The results are an encouraging sign that this search for new indicators, known as antecedent biomarkers, may be succeeding, according to senior author David M. Holtzman, M.D., the Andrew and Gretchen Jones Professor and chair of the Department of Neurology at the School of Medicine and neurologist-in-chief at Barnes-Jewish Hospital.

"We still need to confirm with long-term follow-up studies that subjects with this biomarker and brain damage go on to develop the cognitive changes characteristic of Alzheimer's," says Holtzman. "For now, the evidence we've uncovered further proves that identification and treatment prior to the start of the symptoms of Alzheimer's disease are likely going to be essential to preventing irreversible brain injury."

The results were published in the February issue of *Annals of Neurology*.

A-beta 42 is a protein fragment that clumps together in the brain to form the plaques that have long been the diagnostic hallmark of the disease. In an earlier study, the same Washington University researchers showed that when A-beta 42 decreases in CSF, it begins to build up in the brain.

"The new results show that something associated with amyloid deposition in the brain ? either the amyloid itself or some toxic product of it ? is causing brain damage in people who are still cognitively normal," says Holtzman.

For the study, led by Anne Fagan, Ph.D., research associate professor of neurology, scientists analyzed CSF samples and brain scans of two groups of subjects at the university's Alzheimer's Disease Research Center. The first group of 29 volunteers had very mild cognitive impairment; the remaining 69 volunteers were cognitively normal. Their ages ranged from 60 to 91.

Researchers analyzed CSF samples and took magnetic resonance imaging (MRI) scans of subjects' brains. They used a computer program to analyze the MRI scans and determine whole brain volume, a measurement of the amount of space taken up by a patient's gray and white matter minus the CSF fluid circulating in the skull.

Participants with normal levels of A-beta 42 in their CSF had whole brain volumes within expected ranges. But in both the cognitively impaired subjects and in cognitively normal volunteers with decreased CSF A-beta 42, the size of the brain was smaller.

In addition to A-beta 42, researchers analyzed CSF levels of a family of proteins called tau proteins. These proteins are a component of structures called neurofibrillary tangles that increase as Alzheimer's disease progresses. Scientists believe

increased levels of tangles in the brain lead to increased CSF tau levels.

Researchers found CSF tau levels did not increase until subjects became mentally impaired.

"We've thought for some time that in Alzheimer's disease, amyloid builds up first followed by an increase in tangle accumulation," Holtzman says. "This is some of the first evidence in living people that this idea may be right: large scale changes in amyloid seem to precede large scale changes in tau, which are then linked to the onset of clinical dementia symptoms."

Researchers will follow cognitively normal subjects with reduced CSF amyloid levels and brain volumes to see if they eventually become demented, potentially confirming A-beta 42 as an antecedent biomarker for Alzheimer's disease. They continue to look for additional Alzheimer's biomarkers in CSF samples and brain scans.

Source: Washington University School of Medicine (news : web)