Clinical decline in Alzheimer's requires plaque and proteins

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According to a new study, the neuron-killing pathology of Alzheimer's disease (AD), which begins before clinical symptoms appear, requires the presence of both amyloid-beta (a-beta) plaque deposits and elevated levels of an altered protein called p-tau.

Without both, progressive clinical decline associated with AD in cognitively healthy older individuals is "not significantly different from zero," reports a team of scientists at the University of California, San Diego School of Medicine in the April 23 online issue of the Archives of Neurology.

"I think this is the biggest contribution of our work," said Rahul S. Desikan, MD, PhD, research fellow and resident radiologist in the UC San Diego Department of Radiology and first author of the study. "A number of planned clinical trials – and the majority of Alzheimer's studies – focus predominantly on a-beta. Our results highlight the importance of also looking at p-tau, particularly in trials investigating therapies to remove a-beta. Older, non-demented individuals who have elevated a-beta levels, but normal p-tau levels, may not progress to Alzheimer's, while older individuals with elevated levels of both will likely develop the disease."

The findings also underscore the importance of p-tau as a target for new approaches to treating patients with conditions ranging from mild cognitive impairment (MCI) to full-blown AD. An estimated 5.4 million Americans have AD. It's believed that 10 to 20 percent of Americans

age 65 and older have MCI, a risk factor for AD. Some current therapies appear to delay clinical AD onset, but the disease remains irreversible and incurable.

"It may be that a-beta initiates the Alzheimer's cascade," said Desikan. "But once started, the neurodegenerative mechanism may become independent of a-beta, with p-tau and other proteins playing a bigger role in the downstream degenerative cascade. If that's the case, prevention with anti-a-beta compounds may prove efficacious against AD for older, non-demented individuals who have not yet developed tau pathology. But novel, tau-targeting therapies may help the millions of individuals who already suffer from mild cognitive impairment or Alzheimer's disease."

The new study involved evaluations of healthy, non-demented elderly individuals participating in the ongoing, multi-site Alzheimer's Disease Neuroimaging Initiative, or ADNI. Launched in 2003, ADNI is a longitudinal effort to measure the progression of mild cognitive impairment and early-stage AD.

The researchers studied samples of cerebrospinal fluid (CSF) taken from ADNI participants.

"In these older individuals, the presence of a-beta alone was not associated with clinical decline," said Anders M. Dale, PhD, professor of radiology, neurosciences, and psychiatry at UC San Diego and senior author of the study. "However, when p-tau was present in combination with a-beta, we saw significant clinical decline over three years."

A-beta proteins have several normal responsibilities, including activating enzymes and protecting cells from oxidative stress. It is not known why a-beta proteins form plaque deposits in the brain. Similarly, the origins of p-tau are not well understood. One hypothesis, according to Desikan, is

that a-beta plaque deposits trigger hyperphosphorylation of nearby tau proteins, which normally help stabilize the structure of brain cells. Hyperphosphorylation occurs when phosphate groups attach to a protein in excess numbers, altering their normal functions. Hyperphosphorylated tau – or p-tau – can then exacerbate the toxic effects of a-beta plaque upon neurons.

The discovery of p-tau's heightened role in AD neurodegeneration suggests it could be a specific biomarker for the disease before clinical symptoms appear. While high levels of another tau protein – t-tau – in cerebrospinal fluid have been linked to neurologic disorders, such as frontotemporal dementia and traumatic brain injury, high levels of p-tau correlates specifically to increased neurofibrillary tangles in brain cells, which are seen predominantly with AD.

"These results are in line with another ADNI study of healthy controls and MCI participants that found progressive atrophy in the entorhinal cortex – one of the areas of the brain first affected in AD –only in amyloid positive individuals who also showed evidence of elevated p-tau levels," said Linda McEvoy, PhD, assistant professor of radiology and study co-author.

"One of the exciting dimensions of this paper was the combined use of cerebrospinal fluid markers and clinical assessments to better elucidate the neurodegenerative process underlying Alzheimer's disease in individuals who do not yet show clinical signs of dementia," added co-author James Brewer, MD, PhD, an associate professor of radiology and neurosciences at UC San Diego School of Medicine. "We do not have an animal model that works very well for studying this disease, so the ability to examine the dynamics of neurodegeneration in living humans is critical."

Nonetheless, the scientists say more research is needed. They note that

CSF biomarkers provide only an indirect assessment of amyloid and neurofibrillary pathology and may not fully reflect the underlying biological processes of AD.

"This study highlights the complex interaction of multiple pathologies that likely contribute to the clinical symptomatology of Alzheimer's disease," said co-author Reisa Sperling, MD, a neurologist at Massachusetts General Hospital and Brigham and Women's Hospital. "It suggests we may be able to intervene in the preclinical stages of AD before there is significant neurodegeneration and perhaps prevent the onset of symptoms."

Provided by University of California - San Diego