Study examines relationship between two proteins associated with Alzheimer's disease

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A study that examined the relationship between two cerebrospinal fluid proteins associated with Alzheimer disease in clinically and cognitively normal older patients suggests that amyloid-β (Aβ)-associated clinical decline was linked to the presence of elevated phospho-tau (p-tau), according to a report published Online First by *Archives of Neurology*, a JAMA Network publication.

Identifying clinically normal older individuals destined to develop Alzheimer disease (AD) is increasingly important as therapeutic interventions to prevent dementia are developed, the authors write in their study background.

Rahul S. Desikan, M.D., Ph.D., of the University of California-San Diego School of Medicine, and colleagues evaluated 107 healthy individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI). They examined the relationship of cerebrospinal fluid (CSF) levels of phospho-tau 181 (p-tau 181p) and CSF Aβ 1-42 with clinical decline using, among other measures, the global Clinical Dementia Rating (CDR) scale and the Alzheimer Disease Assessment Scale-cognitive subscale.

The results indicate a "significant relationship" between decreased CSF Aβ 1-42 and change in those assessment measures in participants with elevated CSF p-tau 181p .

"These findings provide important insights into the preclinical stage of

AD," the authors comment. "Consistent with prior studies, our results indicate that in clinically normal older individuals, Aβ deposition by itself is not associated with clinical decline; the presence of p-tau represents a critical link between Aβ deposition and accelerated clinical decline. Furthermore, our findings point to p-tau as an important marker of AD-associated degeneration."

The authors note that while their findings indicate that CSF Aβ 1-42 in combination with CSF p-tau 181p "may better predict clinical decline" than CSF Aβ 1-42 in combination with CSF t-tau, prior studies have shown that CSF p-tau and t-tau when combined with CSF Aβ 1-42 are "equally predictive of decline."

Researchers note that early intervention trials should consider both the CSF p-tau 181p and CSF Aβ 1-42 status of participants and the authors suggest their findings highlight the need to develop therapies that specifically target tau.

"It is feasible that although Aβ initiates the degenerative cascade, elevated levels of tau may represent a second phase of the AD pathologic process where neurodegenerative changes occur largely independent of Aβ," the authors conclude.

In an editorial, David M. Holtzman, M.D., of Washington University, St. Louis, writes: "If both academic groups and the pharmaceutical industry are going to move toward prevention trials to delay the onset of cognitive impairment and dementia, biomarkers will need to be used to select people who are clinically normal but at high risk for near-term cognitive decline. Without such an approach, trial size will be enormous and cost prohibitive, and individuals may be subjected to treatments that have the potential for toxicity with no clear benefit."

"Results from this new study, as well as previous studies with similar

findings, strongly suggest that in otherwise health individuals aged 55 to 85 years, use of these CSF biomarkers may allow for selection of approximately 20 percent of such a population that meet the criteria for the presence of amyloid deposition and neurodegeneration to select for a secondary prevention trial that could be completed with a clinical and cognitive readout during a 3-year period," Holtzman continues.

"The ultimate goal in treating any disease is to delay or prevent its occurrence. With the looming epidemic of AD, we are now at the point where we can and need to design rational trials to delay or prevent dementia," he concludes.

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