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Finding Alzheimer's disease before symptoms start

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Johns Hopkins researchers say that by measuring levels of certain proteins in cerebrospinal fluid (CSF), they can predict when people will develop the cognitive impairment associated with Alzheimer's disease years before the first symptoms of memory loss appear.

Identifying such biomarkers could provide a long-sought tool to guide earlier use of potential drug treatments to prevent or halt the progression of Alzheimer's while people are still cognitively normal.

To date, medications designed to stop the brain damage have failed in clinical trials, possibly, many researchers say, because they are given to those who already have symptoms and too much damage to overcome.

"When we see patients with high blood pressure and high cholesterol, we don't say we will wait to treat you until you get congestive heart failure. Early treatments keep heart disease patients from getting worse, and it's possible the same may be true for those with pre-symptomatic Alzheimer's," says Marilyn Albert, Ph.D., a professor of neurology at the Johns Hopkins University School of Medicine. She is primary investigator of the study whose results are published in the Oct. 16 issue of the journal *Neurology*. "But it has been hard to see Alzheimer's disease coming, even though we believe it begins developing in the brain a decade or more before the onset of symptoms," she adds.

For the new study, the Hopkins team used CSF collected for the Biomarkers for Older Controls at Risk for Dementia (BIOCARD)

project between 1995 and 2005, from 265 middle-aged healthy volunteers. Some three-quarters of the group had a close family member with Alzheimer's disease, a factor putting them at higher than normal risk of developing the disorder. Annually during those years and again beginning in 2009, researchers gave the subjects a battery of neuropsychological tests and a physical exam.

They found that particular baseline ratios of two proteins—phosphorylated tau and beta amyloid found in CSF—were a harbinger of mild cognitive impairment (often a precursor to Alzheimer's) more than five years before symptom onset. They also found that the rate of change over time in the ratio was also predictive. The more tau and the less beta amyloid found in the spinal fluid, the more likely the development of symptoms. And, Albert says, the more rapidly the ratio of tau to beta amyloid goes up, the more likely the eventual development of symptoms.

Researchers have known that these proteins were in the spinal fluid of patients with advanced disease. "But we wondered if we could measure something in the cerebral spinal fluid when people are cognitively normal to give us some idea of when they will develop difficulty," Albert says. "The answer is yes."

Alzheimer's disease disrupts critical metabolic processes that keep neurons healthy. These disruptions cause neurons to stop working, lose connections with other nerve cells, and finally die. The brains of people with Alzheimer's have an abundance of two abnormal structures—amyloid plaques and "tangles" made of tau.

The plaques are sticky accumulations of beta-amyloid that build up outside of the neurons, while the tangles form inside the neurons. When there are too many tangles inside the cells, the cells start to die. In a normal brain, tau helps the skeleton of the nerve cell maintain itself.

When too many phosphate groups attach themselves to tau, too much of the protein develops and tangles form.

Albert says researchers believe that the relative amount of beta-amyloid in the spinal fluid decreases as Alzheimer's progresses because it is getting trapped in the plaques and therefore isn't entering the fluid.

Though the BIOCARD study has been going on for nearly two decades, this is some of the first predictive data to come out of it, Albert says, owing to the length of time it takes for even high-risk middle-aged people to progress to dementia. Only 53 of the original patients have progressed to mild cognitive impairment or dementia, giving a sample size just large enough to draw some preliminary conclusions. These first symptoms include memory disruptions such as repeating oneself, forgetting appointments, and forgetting what others have said.

Albert cautions that the biomarker ratio at this point is not accurate enough to precisely predict whether a particular individual is progressing to dementia, and further analysis of information about the group over time is needed.

However, she says, if the findings prove valid, they not only could guide the use of early treatments with drugs that become available, but also may also help test new drugs by seeing if they alter the rate at which the proteins change over time.

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