Biomarkers of cell death in Alzheimer's reverse course after symptom onset

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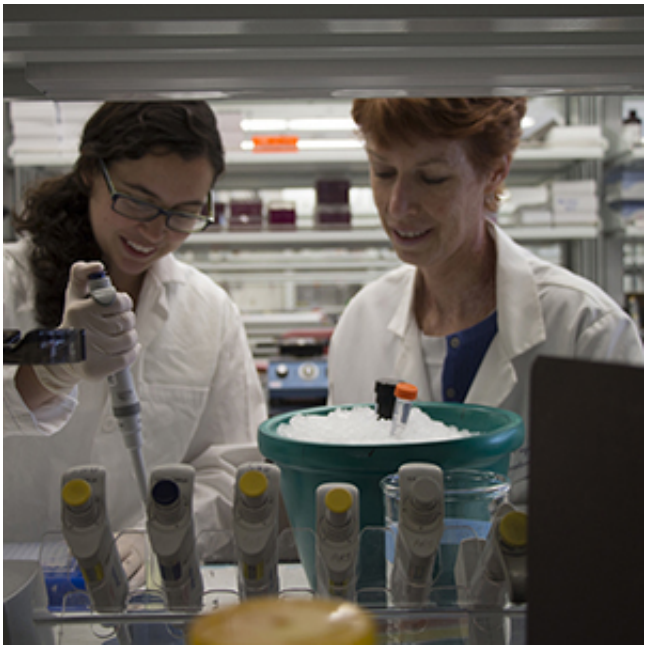

Anne Fagan, right, led a group of researchers who discovered that some markers for early Alzheimer's disease change significantly after patients develop dementia. Fagan is pictured with graduate student Courtney Sutphen. Credit: Michael C. Purdy

Three promising biomarkers being studied to detect Alzheimer's disease in its early stages appear to undergo a surprising shift as patients develop symptoms of dementia, researchers at Washington University School of Medicine in St. Louis report.

Scientists use the biomarkers to assess brain changes linked to the disease in research volunteers. The levels of markers of neuronal injury increase in the spinal fluid for a decade or more before the onset of dementia, but in a new twist, the research shows for the first time that they later reverse course, decreasing as symptoms of memory loss and mental decline appear.

The results appear online March 5 in *Science Translational Medicine*.

"We're not sure why this reversal occurs, but understanding it may be very important for clinical trials of drugs to treat or prevent Alzheimer's," said senior author Anne Fagan, PhD, research professor of neurology. "Changes in the levels of these biomarkers likely will be among the criteria we use to assess the success or failure of Alzheimer's drugs, so we need to know how these biomarkers normally behave in the absence of treatment."

Motivated by the realization that Alzheimer's damages the brain for a decade or more before it causes dementia, researchers have identified several biomarkers of the disease in patients before they develop symptoms. They hope to use the biomarkers to diagnose patients and start treatment long before the onset of problems with memory and other brain functions that characterize dementia.

Fagan and her colleagues studied data from the Dominantly Inherited Alzheimer's Network (DIAN), a multinational research project led by Washington University. All DIAN participants come from families affected by genetic mutations that cause rare inherited forms of Alzheimer's. Carriers of their family's mutation can develop symptoms of mental decline as early as their 30s.

DIAN participants regularly are evaluated using a variety of tests, including analyses of Alzheimer's biomarkers in their spinal fluid. For

the new study, Fagan and her coauthors looked at three injury-related biomarkers in spinal fluid samples collected at multiple evaluations of 26 DIAN participants. All the participants had an Alzheimer's-causing mutation.

Two of the biomarkers, tau and p-tau, are structural proteins that form the neurofibrillary tangles seen in the brains of Alzheimer's patients; the third is a neuronal calcium sensor called VILIP-1. Levels of the three biomarkers increase after neurons are injured and are linked to decline of cognitive function. Evidence suggests that as Alzheimer's assaults the brain, dying cells release the biomarkers, freeing them to be washed into the spinal fluid.

As expected, levels of the biomarkers increased over time in participants who had not yet developed dementia. But the researchers were surprised to find that in most participants who had dementia, levels of the three biomarkers decreased over time. The drop in levels was relatively small but consistent and statistically significant.

"This was very interesting, particularly given that previous studies have shown that other indicators of Alzheimer's disease, such as brain shrinkage, continue after the onset of dementia," Fagan said.

Fagan speculated that increasing levels of the biomarkers prior to dementia likely reflect an intense stage of cell death, while decreasing levels as dementia begins indicate a slowing of this process. However, it's also possible that such reductions result from a decrease in the number of remaining brain cells that have yet to be killed by Alzheimer's, she said.

To advance the research, the scientists are gathering data on new DIAN enrollees and continuing to follow participants in the current study.

"Our findings are limited both by the small number of participants we studied and by the fact that we only had a few years of longitudinal follow-up," Fagan said. "Additional data taken over longer periods of time will help us draw more definitive conclusions."

Additional research also is needed to learn whether levels of the biomarkers undergo a similar change in patients with the more common sporadic forms of the disease, which are typically diagnosed later in life.

More information: Fagan AM, Xiong C, Jasielec MS, Bateman RJ, Goate AM, Benzinger TLS, Ghetti B, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Salloway S, Schofield PR, Sperling RA, Marcus D, Cairns NJ, Buckles VD, Ladenson JH, Morris JC, Holtzman DM. The Dominantly Inherited Alzheimer Network. Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. *Science Translational Medicine*, online March 5, 2014.

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