Comorbidities can increase plasma biomarker levels associated with Alzheimer's disease

May 26 2022

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A simple blood test to diagnose Alzheimer's disease, perhaps even years before symptoms appear, is an exciting possibility, but a new study shows that much more research is needed before these blood tests are routinely used in the clinical diagnostic setting.

The study appears online in the current issue of *Nature Medicine*.

Two hallmarks of Alzheimer's disease are tau tangles and beta-amyloid plaques. Tau is a protein found in neurons in the brain. In a healthy brain, tau helps transport nutrients in nerve cells. When an abnormal

form of tau builds up, tau tangles are formed. Beta-amyloid plaques are accumulations of brain protein fragments, which can impact cognition. The interaction of these proteins may speed up brain changes that can lead to Alzheimer's disease. Tau and beta-amyloid levels can be tested in cerebrospinal fluid, which is retrieved through a lumbar puncture, or through PET imaging of the brain.

"Blood-based biomarkers are the goal in screening for and diagnosing Alzheimer's disease because they are less costly and invasive, but we need to understand these biomarkers in community-based populations before we use them clinically," said Michelle Mielke, Ph.D., professor and chair of epidemiology and prevention at Wake Forest University School of Medicine and the study's principal investigator.

Two blood markers, phosphorylated tau 181 and 217 (p-tau181 and p-tau217), are promising new biomarkers specific to Alzheimer's disease and may provide a new avenue for screening or detecting Alzheimer's disease in the general population. However, comorbidities such as chronic kidney disease or history of stroke can also increase these levels and potentially give false positive results, according to Mielke.

"Before these blood-based biomarkers enter clinical use, it's critical that we establish reference ranges and understand the differences age, sex and any underlying health conditions might play," Mielke said.

In the study, researchers examined p-tau181 and p-tau217 in 1,329 participants aged 30 to 98 years through the Mayo Clinic Study of Aging to evaluate their diagnostic use as a predictor of elevated brain beta-amyloid and tau tangles using PET imaging.

Researchers found that while p-tau181 and p-tau217 increase with age, the increase is mainly among people who are amyloid positive, which provides additional evidence that these biomarkers are specific to

Alzheimer's disease and not other neurodegenerative diseases.

The study's findings also confirmed that plasma p-tau181 and p-tau217 are predictors of elevated brain amyloid and tau, as measured by PET imaging, but the results were not as good those previously reported in patients seen in specialized memory clinics. A reason for this is that the study showed that multiple comorbidities such as chronic kidney disease, history of myocardial infarction or clinical stroke were also associated with higher plasma p-tau levels. According to Mielke, this elevation is likely attributed to the underlying conditions and not Alzheimer's disease and should be considered in the development of cut points for clinical use.

"More research is needed in larger studies, especially in more diverse populations," Mielke said. "It's important for patients and providers to understand that, although these blood markers are very promising, it will take time to implement in the clinic. We need more data first."

More information: Michelle Mielke, Performance of plasma phosphorylated tau 181 and 217 in the community, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-01822-2.
www.nature.com/articles/s41591-022-01822-2

Provided by Wake Forest University Baptist Medical Center

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