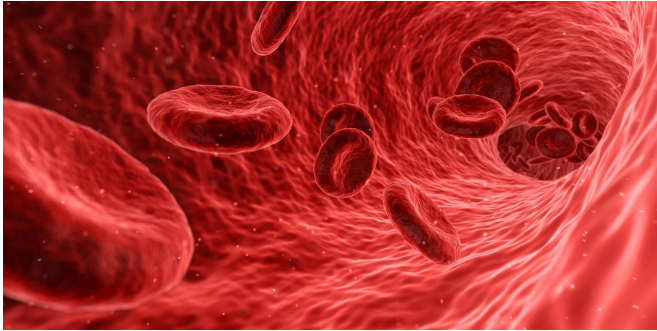


Blood test detects Alzheimer's damage before symptoms

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A simple blood test reliably detects signs of brain damage in people on the path to developing Alzheimer's disease—even before they show signs of confusion and memory loss, according to a new study from Washington University School of Medicine in St. Louis and the German Center for Neurodegenerative Diseases in Germany.

The findings, published Jan. 21 in *Nature Medicine*, may one day be applied to quickly and inexpensively identify brain damage in people with not just Alzheimer's disease but other neurodegenerative conditions such as multiple sclerosis, traumatic brain injury or stroke.

"This is something that would be easy to incorporate into a screening test in a neurology clinic," said Brian Gordon, Ph.D., an assistant professor of radiology at Washington University's Mallinckrodt Institute of Radiology and an author on the study. "We validated it in people with Alzheimer's disease because we know their brains undergo lots of neurodegeneration, but this marker isn't specific for Alzheimer's. High levels could be a sign of many different neurological diseases and injuries."

The test detects neurofilament light chain, a

structural protein that forms part of the internal skeleton of neurons. When brain neurons are damaged or dying, the protein leaks out into the cerebrospinal fluid that bathes the brain and spinal cord and from there, into the bloodstream.

Finding high levels of the protein in a person's cerebrospinal fluid has been shown to provide strong evidence that some of their brain cells have been damaged. But obtaining cerebrospinal fluid requires a spinal tap, which many people are reluctant to undergo. Senior author Mathias Jucker, Ph.D., a professor of cellular neurology at the German Center for Neurodegenerative Diseases in Tübingen, along with Gordon and colleagues from all over the world, studied whether levels of the protein in blood also reflect neurological damage.

They turned to a group of families with rare genetic variants that cause Alzheimer's at a young age—typically in a person's 50s, 40s or even 30s. The families form the study population of the Dominantly Inherited Alzheimer's Network (DIAN), an international consortium led by Washington University that is investigating the roots of Alzheimer's disease. A parent with such a mutation has a 50 percent chance of passing the genetic error to a child, and any child who inherits a variant is all but guaranteed to develop symptoms of dementia near the same age as his or her parent. This timeline gives researchers an opportunity to study what happens in the brain in the years before cognitive symptoms arise.

The researchers studied more than 400 people participating in the DIAN study, 247 who carry an early-onset genetic variant and 162 of their unaffected relatives. Each participant had previously visited a DIAN clinic to give blood, undergo brain scans and complete cognitive tests. Roughly half had been evaluated more than once, typically about two to three years apart.

In those with the faulty gene variant, protein levels

were higher at baseline and rose over time. In contrast, protein levels were low and largely steady in people with the healthy form of the gene. This difference was detectable 16 years before cognitive symptoms were expected to arise.

In addition, when the researchers took a look at participants' brain scans, they found that how quickly the protein levels rose tracked with the speed with which the precuneus—a part of the brain involved in memory—thinned and shrank.

"Sixteen years before symptoms arise is really quite early in the disease process, but we were able to see differences even then," said Washington University graduate student Stephanie Schultz, one of the paper's co-first authors. "This could be a good preclinical biomarker to identify those who will go on to develop clinical symptoms."

To find out whether protein blood levels could be used to predict cognitive decline, the researchers collected data on 39 people with disease-causing variants when they returned to the clinic an average of two years after their last visit. The participants underwent brain scans and two cognitive tests: the Mini-Mental State Exam and the Logical Memory test. The researchers found that people whose blood protein levels had previously risen rapidly were most likely to show signs of brain atrophy and diminished cognitive abilities when they revisited the clinic.

"It will be important to confirm our findings in late-onset Alzheimer's disease and to define the time period over which neurofilament changes have to be assessed for optimal clinical predictability," said Jucker, who leads the DIAN study in Germany.

All kinds of neurological damage can cause the neurofilament light protein to spill out of neurons and into blood. Protein levels are high in people with Lewy body dementia and Huntington's disease; they rise dramatically in people with multiple sclerosis during a flare-up and in football players immediately after a blow to the head.

A commercial kit—very similar to the one used by the authors—is available to test for protein levels in the blood, but it has not been approved by the FDA

to diagnose or predict an individual's risk of brain damage. Before such a test can be used for individual patients with Alzheimer's or any other neurodegenerative condition, researchers will need to determine how much protein in the blood is too much, and how quickly protein levels can rise before it becomes a cause for concern.

"I could see this being used in the clinic in a few years to identify signs of brain damage in individual patients," said Gordon, who is also an assistant professor of psychological & brain sciences. "We're not at the point we can tell people, 'In five years you'll have dementia.' We are all working towards that."

More information: Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease, *Nature Medicine* (2019). DOI: [10.1038/s41591-018-0304-3](https://doi.org/10.1038/s41591-018-0304-3) , <https://www.nature.com/articles/s41591-018-0304-3>

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