Time until dementia symptoms appear can be estimated via brain scan

17 September 2021, by Tamara Bhandari

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Researchers at Washington University School of Medicine in St. Louis have developed an approach to estimating when a person who is likely to develop Alzheimer's disease, but has no cognitive symptoms, will start showing signs of Alzheimer's dementia.

The algorithm, available online in the journal *Neurology*, uses data from a kind of brain scan known as amyloid positron emission tomography (PET) to gage brain levels of the key Alzheimer's protein amyloid beta.

In those who eventually develop Alzheimer's dementia, amyloid silently builds up in the brain for up to two decades before the first signs of confusion and forgetfulness appear. Amyloid PET scans already are used widely in Alzheimer's research, and this algorithm represents a new way of analyzing such scans to approximate when symptoms will arise. Using a person's age and data from a single amyloid PET scan, the algorithm yields an estimate of how far a person has progressed toward dementia—and how much time is left before cognitive impairment sets in.

"I perform amyloid PET scans for research studies, and when I tell cognitively normal individuals about positive results, the first question is always, 'How long do I have until I get dementia?'," said senior author Suzanne Schindler, MD, Ph.D., an assistant professor of neurology. "Until now, the answer I'd have to give was something like, 'You have an increased risk of developing dementia in the next five years.' But what does that mean? Individuals want to know when they are likely to develop symptoms, not just whether they are at higher risk."

Schindler and colleagues analyzed amyloid PET scans from 236 people participating in Alzheimer's research studies through Washington University's Charles F. and Joanne Knight Alzheimer Disease Research Center. The participants were an average of 67 years old at the beginning of the study. All participants underwent at least two brain scans an average of 4½ years apart. The researchers applied a widely used metric known as the standard uptake value ratio (SUVR) to the scans to estimate the amount of amyloid in each participant's brain at each time point.

The researchers also accessed over 1,300 clinical assessments on 180 of the participants. The assessments typically were performed every one to three years. Most participants were cognitively normal at the start of data collection, so the repeated assessments allowed the researchers to pinpoint when each participant's cognitive skills began to slip.

Schindler spent years trying to figure out how to use the data in amyloid PET scans to estimate the age at which symptoms would appear. The breakthrough came when she realized that amyloid accumulation has a tipping point and that each individual hits that tipping point at a different age. After this tipping point, amyloid accumulation

follows a reliable trajectory.

"You may hit the tipping point when you're 50; it may happen when you're 80; it may never happen," Schindler said. "But once you pass the tipping point, you're going to accumulate high levels of amyloid that are likely to cause dementia. If we know how much amyloid someone has right now, we can calculate how long ago they hit the tipping point and estimate how much longer it will be until they are likely to develop symptoms."

People in the study who reached the tipping point at younger ages took longer to develop cognitive symptoms than those who reached it later in life. Participants who hit the tipping point at age 50 typically took nearly 20 years to develop symptoms; those who hit it at age 80 took less than 10 years.

"When we look at the brains of relatively young people who have died with Alzheimer's, they typically look pretty healthy, other than Alzheimer's," Schindler said. "But older people more frequently have damage to the brain from other causes, so their cognitive reserves are lower, and it takes less amyloid to cause impairment."

The power of this new technique is that it requires just one brain scan, plus the person's age. With that data, the model can estimate the time to symptom onset, plus or minus several years. In this study, the correlation between the expected age of symptom onset and the true age at diagnosis was better than 0.9 on a scale of 0 (no correlation) to 1 (perfect correlation).

After age, the genetic variant APOE4 is the strongest risk factor for Alzheimer's dementia. People who carry one copy of the variant are two to three times more likely to develop Alzheimer's dementia than the general population, and people who carry two copies are 10 times more likely. In this study, people with the high-risk variant hit the tipping point younger, but once that point was passed, they followed the same trajectory as everyone else.

"APOE4 seems to have a seeding effect," Schindler said. "At very low levels, below the tipping point, you see amyloid rising in people with APOE4 while it's not changing in people without APOE4. That means APOE4 carriers are going to hit the tipping point sooner. People with two copies of APOE4 hit the tipping point about 10 years earlier than people with no copies. But after that point, we see no difference between the APOE4 carriers and noncarriers."

At an out-of-pocket cost of about $6,000, amyloid PET brain scans are too expensive for routine clinical use. However, this algorithm could help accelerate the pace of drug development by streamlining clinical trials.

"Most participants in clinical trials designed to prevent or slow Alzheimer's symptoms do not develop symptoms during the trials," Schindler said. "That's a lot of time and effort—for the participants as well as the researchers—that doesn't yield useful data. If we could do trials only on people who are likely to develop symptoms in the next few years, that would make the process of finding therapies much more efficient."

More information: Suzanne Schindler et al, Predicting Symptom Onset in Sporadic Alzheimer Disease With Amyloid PET, *Neurology* (2021). DOI: 10.1212/WNL.0000000000012775

Provided by Washington University School of Medicine