

Section Editors

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Alzheimer disease

Before the diagnosis

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WHAT DID THESE RESEARCHERS STUDY? These researchers were interested in the idea of “cognitive reserve”—the brain’s ability to resist harm from disease.¹ They studied the specific example of Alzheimer disease (AD), and the idea that people with more cognitive reserve might be able to continue to function fairly well even as the disease advances. To do this, they studied people before they developed AD, at a stage called “preclinical AD.” In preclinical AD, people have the early brain changes of AD, but do not show any definite problems with thinking and memory.

To do their study, they used a tool called a PET scan, which looks at how the brain uses glucose (sugar). One of the earliest changes in AD is lower than normal use of brain glucose, and in general, the lower the brain glucose, the more advanced the AD. If people with more cognitive reserve had lower brain glucose, it would support their idea—even though the disease was more advanced (lower brain glucose), the person continued to function relatively well. It would also suggest that we need to understand cognitive reserve better, because we might be able to harness it to slow the onset of AD.

WHY DID THESE RESEARCHERS STUDY THIS IN THE PATIENTS? The level of glucose in the brain may indicate whether people have or may later be diagnosed with AD. Researchers measured the glucose in the brain by several tests including taking pictures of the brain (FDG-PET). The authors did this to see whether people with normal thinking and memory had brain changes (glucose levels) due to AD.¹ Identifying preclinical AD is important because researchers are beginning drug trials to prevent individuals from developing AD.

WHAT IS COGNITIVE RESERVE? Brain damage due to preclinical AD, symptomatic AD, and other medical conditions often causes memory and thinking problems. The term “cognitive reserve” reflects the idea that some people are able to maintain normal memory and thinking despite brain damage caused by these conditions.^{2,3} The more cognitive reserve that one has, the better able that person is to maintain normal thinking and memory. People with more cognitive reserve may use alternative brain pathways or have different ways of thinking and problem solving

that allow them to cope better with brain damage. There is no one way to measure cognitive reserve. Those who have greater cognitive reserve may also have more or better quality of education, greater natural abilities, better reading skills, and may take part in more physical, social, and intellectual activities.^{2,4}

In this study, the researchers used the patient’s education level to measure his or her cognitive reserve. Fifty-two people were included in the study. They used a brain scan to measure brain glucose. The brain needs glucose (sugar) to work properly. One of the earliest changes in AD is lower than normal use of brain glucose. The researchers divided people into 2 groups: those who had preclinical AD and those who did not. They identified people with preclinical AD by measuring levels of a substance in the spinal fluid. Spinal fluid levels of this substance, called amyloid beta₄₂ (Aβ₄₂), are usually low when the brain changes of AD are developing.

WHAT DID THE RESEARCHERS FIND? First, the researchers focused on the preclinical AD group. When they compared those with more education to those with less education, they saw differences. Those with more education actually had lower brain glucose levels in several regions.

HOW DID THE RESEARCHERS INTERPRET THESE FINDINGS? They believe that cognitive reserve allowed these people to function relatively normally *despite* low glucose level (that is, *despite* more brain damage).

WHY IS THIS STUDY IMPORTANT? This study helps us to better understand how differences in cognitive reserve may determine whether, or when, people show AD symptoms. Other studies that tested people who already had symptoms of AD showed similar findings: those with more education had lower brain glucose than people with less education, even though the severity of their symptoms was the same. Those with more education seemed to function at the same level despite more advanced disease. The current study adds to what we know from research by others. It shows that cognitive reserve seems to help people maintain good thinking and memory even *before* they show any AD symptoms.

WHAT ARE THE NEXT STEPS? It will be important to test these scientific findings in different groups of people to make sure that the results apply to everyone and not just the group these researchers tested. There may be something special about these people in this study. For example, they live close to a large university and have higher education on average than most other people in the United

States. These same results might not be found in others. It would also be interesting to see whether the same results would be found if other measures of cognitive reserve, not just years of education, were used. Ultimately, a better understanding of preclinical AD and cognitive reserve might lead to new ways of protecting against the development of AD.

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About preclinical Alzheimer disease

WHAT IS PRECLINICAL ALZHEIMER DISEASE? In the same way that some cancers can grow for a long time before the person shows symptoms, scientists think that people can have Alzheimer disease (AD) for a long time even though they do not show any AD symptoms. People with “preclinical AD” have normal memory and thinking, but the AD process has already started in their brains. Right now, scientists think that AD starts with abnormal changes in brain proteins and the appearance of AD lesions in the brain. Later, brain cells begin to die. It is thought that problems in thinking and memory occur at this stage, once brain cell death has started.

HOW IS PRECLINICAL AD MEASURED? Preclinical AD is measured using biomarkers. A biomarker reflects what is going on in the body. AD researchers are especially interested right now in biomarkers that are obtained from the cerebrospinal fluid (CSF) and from brain scans.

The CSF circulates through the spine and bathes and cushions the brain inside the skull. Because CSF surrounds the brain, it contains proteins that are important to brain function. Doctors can take a small amount of CSF from a person’s lower spine and test it to measure the levels of certain proteins. Researchers think that abnormal levels of proteins called amyloid beta₄₂ (Aβ₄₂) and tau, together with normal thinking and memory, usually indicate that a person has preclinical AD.

A brain scan can be used to see whether an individual has “plaques” made of Aβ that indicate that AD has started to develop. But, instead of being dissolved in the CSF, the Aβ protein in plaques is in a different form than the Aβ protein found in the CSF. Aβ in plaques is solid. Each plaque is made up of a collection of small fibers made up of the Aβ protein. Before the brain scanning takes place, a chemical is injected into the bloodstream through the arm. The chemical travels through the bloodstream to the brain, and temporarily binds to the Aβ plaques. This chemical allows the plaques to be seen on a brain scan. Preclinical AD is diagnosed when a person with normal thinking and memory has many plaques on his or her brain scan.

DO A LOT OF PEOPLE HAVE PRECLINICAL AD? About 20% to 40% of people older than 50 years have preclinical AD.⁵

WILL EVERYONE WITH PRECLINICAL AD GO ON TO DEVELOP FULL-BLOWN AD? On average, having preclinical AD increases the chances that someone will later develop AD symptoms.^{6,7} However, some people with preclinical AD will not develop any symptoms of AD over their lifetime.⁵ What we do not know is whether those people would have developed AD if they had lived longer. Scientists think that abnormal AD biomarkers may occur 20 or more years before a person shows any symptoms. To see whether this idea is true, researchers are planning to track people with preclinical AD for many years to find out how many develop AD in the future.

CAN MY DOCTOR TEST ME FOR PRECLINICAL AD? Not right now. Scientists do not know enough about preclinical AD to predict whether a particular person will eventually show symptoms of AD. We also think that there are individual characteristics, such as cognitive reserve and genetics, that may affect whether and when someone shows AD symptoms during their lifetime. Much more research needs to be done before doctors will routinely test people with normal thinking and memory for preclinical AD.

WHY IS STUDYING PRECLINICAL AD IMPORTANT? So far, no medications have been shown to be very good treatments for AD. This may be because the drugs are being given too late. Once people start showing the symptoms of AD, the brain has already suffered substantial damage. Many researchers believe that drugs to prevent, or to slow down, the AD process will be most effective if these drugs are given in the preclinical stage. Clinical drug trials will begin later this year to see whether removing the plaques of AD in those who have preclinical changes will be effective. We hope that those efforts are successful in order to stop people from getting this devastating disease.

FOR MORE INFORMATION

AAN Patients and Caregivers site
<http://patients.aan.com/golhome>

Alzheimer Research Forum
<http://www.alzforum.org/new/detail.asp?id=3379>

Alzheimer’s prevention clinical trials in people with preclinical AD
<http://www.dementiatoday.com/exciting-current-and-upcoming-alzheimers-therapy-trials/>

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