

Searching for AD's Early Signs

The Alzheimer's Disease Neuroimaging Initiative (ADNI).

BY TOM VALEO

Much remains unknown about Alzheimer's disease (AD), but one thing seems certain: The trouble begins years and probably decades before the first memory problems appear. By that time, the damage to brain cells may be too advanced to halt.

Alzheimer's disease appears to begin with the accumulation of amyloid-beta, a protein of unknown function produced in vast quantities by the healthy human brain. Amyloid-beta emerges from nerve cells in the brain (neurons) and gets cut into smaller fragments by enzymes.

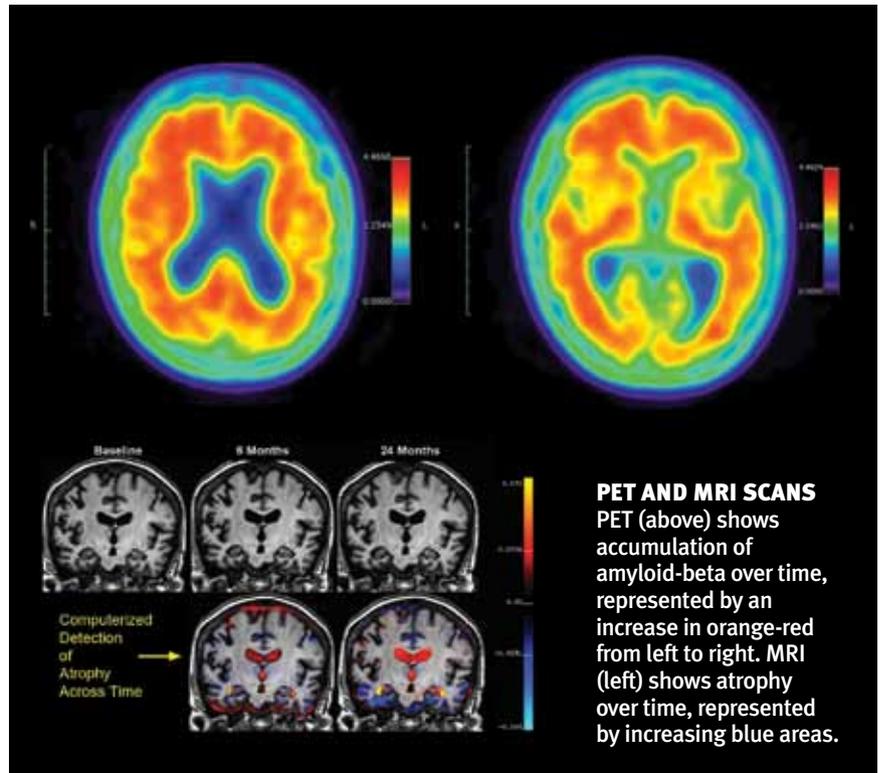
As a person ages, neurons appear to lose some ability to dispose of these protein fragments efficiently. At first, scientists believe, the fragments float in the cerebrospinal fluid that bathes the brain, disrupting signals that pass from neuron to neuron. Over time, these fragments start to form sticky, insoluble clumps (plaques) that trigger inflammation, further damaging the signals that pass between neurons and producing a cascade of changes that eventually destroys those neurons.

The effect of amyloid-beta varies widely among people. Some carry large quantities in their brain without displaying memory problems, while others with small amounts suffer severe dementia.

IDENTIFYING BIOMARKERS

Still, recent studies suggest that the presence of amyloid-beta floating in the cerebrospinal fluid, which is revealed by a spinal tap (lumbar puncture), provides one reliable indicator (biomarker) of emerging AD. A lumbar puncture that reveals a *decline* in the amount of amyloid-beta floating in the cerebrospinal fluid suggests that the protein fragments have started to form clumps in the brain. The accumulation of amyloid-beta in the brain can be detected with a positron-emission tomography (PET) scan as well.

A lumbar puncture may also reveal



PET AND MRI SCANS
PET (above) shows accumulation of amyloid-beta over time, represented by an increase in orange-red from left to right. MRI (left) shows atrophy over time, represented by increasing blue areas.

tau protein, which helps stabilize important parts of neurons. The presence of tau protein seems to suggest that neurons are breaking down, which causes the release of tau fragments into the cerebrospinal fluid.

Unfortunately, treatments that reduce levels of amyloid-beta in the brain have failed so far to relieve the memory problems that AD produces. Two treatments recently tested—bapineuzumab and solanezumab—produced no benefit even though both reduced levels of amyloid-beta in the brain. Many researchers believe starting treatment years or even decades before amyloid-beta starts to damage neurons might make a difference, but identifying people at risk would require finding biomarkers of the disease at earlier stages.

Tests for such biomarkers are being developed by the Alzheimer's Disease Neuroimaging Initiative (ADNI), a \$140 million project begun in 2004, funded primarily

by the National Institutes of Health and the National Institute on Aging.

There's just one problem with this encouraging news: Not enough people are volunteering for the study.

NOT ENOUGH VOLUNTEERS

"Our target is 100 more volunteers who have dementia due to AD," says Michael W. Weiner, M.D., ADNI's principal investigator and a driving force behind the project. "Currently, we have reached only 45 percent of our goal. Our progress is being slowed because we can't get enough subjects."

Ideally, such a study would follow vast numbers of healthy volunteers to detect the earliest signs of AD, but the expense and the time needed make such an approach unfeasible. Instead, ADNI includes volunteers who have been diagnosed by a physician as displaying signs

of mild cognitive impairment (MCI)—subtle memory problems that often progress to full-blown AD.

However, even though ADNI has 60 research sites in the United States and Canada, most potential volunteers do not live conveniently close to one.

“Probably more than 98 percent of people with AD are not being treated at an ADNI research site,” says Dr. Weiner, Fellow of the American Academy of Neurology (AAN), professor at the University of California, San Francisco, and director of the Center for Imaging of Neurodegenerative Disease at the nearby VA Medical Center. “Part of the reason may be that most physicians seeing patients with AD are not informing them about the ADNI research project. So we’d like to get the word out to the neurology community—doctors, patients, caregivers, and patient advocacy organizations—that this project is underway and we need volunteers.”

DISPELLING FEARS

Volunteers for ADNI must agree to requirements that some people find intimidating. After signing a consent form, for example, volunteers must fill out an extensive questionnaire containing questions about their family history and current health. Then, if accepted, volunteers receive periodic MRI and PET scans, cognitive tests, and two lumbar punctures to collect cerebrospinal fluid.

Although the procedures are safe and produce little discomfort, they arouse fear in some people. An MRI scan, for example, involves lying in a narrow tube—an experience that may cause intense claustrophobia for some. Such people are advised not to volunteer. Also, many people fear that a lumbar puncture will cause an intense headache and could lead to spinal cord damage.

Drawing spinal fluid is no worse than getting blood drawn, according to Dr

Weiner. “They give you a little Novocaine to numb the site, and all you feel is a needle prick,” he says. “The lumbar puncture is done well below the spinal cord so there’s no chance of damage. And only about 2 percent of the participants ever get a headache.”

The headaches don’t last long and generally respond well to typical treatments, such as ibuprofen and acetaminophen.

WHO CAN VOLUNTEER

People cannot volunteer if they have any other neurologic disease besides AD, or if they have a pacemaker, artificial heart valve, aneurysm clip, ear implant, or any type of metal fragments in their body. (The intense magnetic field created during an MRI scan can cause certain metals to heat up or move.)

People with depression, bipolar disorder, schizophrenia, or a history of alcoholism are usually excluded as volunteers, along with most current or former drug abusers.

In addition, all volunteers must be accompanied by a partner or “informant” who spends at least 10 hours a week with them and who can verify answers to ADNI questions about the volunteer’s thinking and behavior.

People accepted as ADNI volunteers are followed closely by experts in AD and kept abreast of new information in the field for as long as ADNI is operating—ideally for as long as they live. After volunteering, they receive an MRI at 3, 6, and 12 months, along with exams. After that, they are seen every 12 months and receive periodic phone calls from researchers.

Although volunteers don’t receive any

“ADNI received \$2 million to find healthy people at risk for developing AD, but not enough people are volunteering.”

new medications, they are contributing to groundbreaking research that will speed the development of treatments for AD, according to one of the principal investigators, Ron Petersen, M.D., Ph.D., director of the Alzheimer’s Disease Research Center at Mayo Clinic in Rochester, MN, and member of the AAN.

While the identity of each volunteer is carefully guarded, the information gathered on them is made available to researchers all over the world who are looking for answers to the mysteries of AD.

HELPING FIND TREATMENTS

“I think one of the real contributions of ADNI pertains to the way it makes data public as soon as is reasonable,” Dr. Petersen says. “The images and biomarker data are put on the ADNI website essentially in real time. People all over the world have been able to mine the data for answers to questions they want to ask. Many pharmaceutical companies have downloaded all the data, and this has been a boon to the field.”

Research results from ADNI have already been used in more than 300 articles in medical journals and will undoubtedly make an enormous contribution to understanding AD by revealing biomarkers of early disease, which will allow treatment to begin before symptoms appear, according to Dr. Petersen.

“We need to start treatment earlier,” he says. “Up to now, drugs for AD have been tested on mild to moderate dementia—and been found ineffective. Why? It may be we’re trying to intervene too late in the disease process. We need to move treatment back at least to the stage where people have even fewer symptoms, such as the stage of MCI. That’s the focus of ADNI.”