Scientists detail alzheimer's progression, step by step

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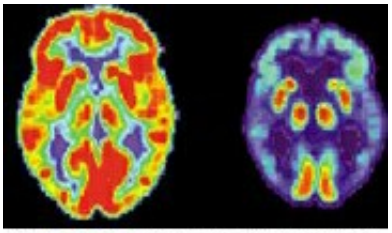

PET scans of normal brain (left) and an Alzheimer's brain. Photo: U.S. National Institute on Aging

As researchers learn more, therapy might someday address brain changes much sooner.

(HealthDay)—New research seeks to delineate just how Alzheimer's disease unfolds in the human brain.

Biological changes may happen earlier than scientists had previously thought, according to a new disease model. This suggests that early signs of risk could potentially become treatment targets long before symptoms of Alzheimer's begin to appear, the researchers said.

"We're getting a better idea of what is happening during the asymptomatic [symptomless] phases of the disease," said Dean Hartley, director of science initiatives at the Alzheimer's Association, who was not involved with the new research.

The scientists behind the new research identified distinct but overlapping phases in the course of Alzheimer's disease, each detectable by biological "markers" showing physical changes in the brain. They also have refined their model to distinguish between these "biomarkers" of Alzheimer's disease and those of normal aging.

In the first phase of Alzheimer's, brain markers signaling changes in beta-amyloid protein show up first, the model suggests. Beta-amyloid plaques are protein pieces from the fatty membrane surrounding nerve cells that clump together, contributing to nerve dysfunction.

In the second phase of the disease, signs of degeneration and death of brain cells occur.

Symptoms of dementia are seen in the third phase of Alzheimer's disease, according to the new model.

The refined model should help researchers design better research, guide the selection of study participants, suggest the ideal time to begin treatment and help measure the impact of treatment, said Dr. Clifford Jack Jr.

Jack is lead author of one of three related studies to be presented Tuesday at the Alzheimer's Association International Conference, in Boston. He said his research has been accepted for publication in the journal *Neurology*.

In addition to beta-amyloid proteins, "tau"—another protein—also plays a role in Alzheimer's, creating what are called "neurofibrillary tangles." Jack said the changes in the brain created by tau seem to occur first, but amyloid aggregation, or clumping, accelerates the changes in tau and causes it to spread.

The central message is that tau and beta-amyloid plaque interact with each other in a synergistic way, said Jack, a professor of radiology and a neuroradiologist at the Mayo Clinic College of Medicine, in Rochester, Minn.

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills. Symptoms typically appear after age 60, and about 5 million Americans may have the disease, according to the U.S. National Institute on Aging.

Jack and his team published a hypothetical model of the major Alzheimer's disease biomarkers in *Neurology* in 2010, describing how the biomarkers changed over time and were related to the beginning and progression of symptoms. For this study, the team reviewed studies that tested and evaluated that model, spurring them to further refine it.

How could the model spark new ideas for treating Alzheimer's disease? "What really makes sense probably is a combined therapeutic approach where you target a point or points in tau and in the amyloid pathways simultaneously," Jack explained.

Just as people often take statins—drugs that lower cholesterol—to reduce their risk of heart disease, it could someday be possible that those at risk for Alzheimer's could take medication to help prevent it, Jack said. He envisions a "cocktail" or combination of drugs that could target different points in the molecular pathways of the disease, administered at an early age, depending on a person's risk for Alzheimer's disease.

The Alzheimer's Association's Hartley said he's excited about the revised model. "It suggests that some of the treatments we're using may be too late in the progression of the disease."

Two related studies were also scheduled for presentation at the meeting.

Dr. Victor Villemagne at the University of Melbourne, in Australia, and colleagues followed about 200 people with and without signs of Alzheimer's disease over four years to estimate when beta-amyloid levels tend to become abnormal. The scientists concluded that Alzheimer's disease is a slow process, likely extending for more than 20 years.

The other study, led by Daniela Bertens at VU University Medical Center, in Amsterdam, Holland, provided more evidence that abnormal beta-amyloid is what triggers the development of Alzheimer's disease. The research included about 300 people with abnormal beta-amyloid, and followed them over four years, testing their cerebrospinal fluid for diagnostic signs of the disease.

Because these studies were presented at a medical meeting, the data and conclusions should be viewed as preliminary until published in a peer-reviewed journal.

More information: Learn more about Alzheimer's disease from the U.S. National Institute on Aging.