First detailed timeline established for brain's descent into Alzheimer's

July 11 2012

Scientists have assembled the most detailed chronology to date of the human brain's long, slow slide into full-blown Alzheimer's disease.

The timeline, developed through research led by scientists at Washington University School of Medicine in St. Louis, appears July 11 in The New England Journal of Medicine.

As part of an international research partnership known as the Dominantly Inherited Alzheimer's Network (DIAN), scientists at Washington University and elsewhere evaluated a variety of pre-symptomatic markers of Alzheimer's disease in 128 subjects from families genetically predisposed to develop the disorder. Individuals in the study have a 50 percent chance of inheriting one of three mutations that are certain to cause Alzheimer's, often at an unusually young age.

Using medical histories of the subjects' parents to estimate the age of the onset of symptoms for the study participants, the scientists assembled a timeline of changes in the brain leading to the memory loss and cognitive decline that characterizes Alzheimer's. The earliest of these changes, a drop in spinal fluid levels of the key ingredient of Alzheimer's brain plaques, can be detected 25 years before the anticipated age of onset.

"A series of changes begins in the brain decades before the symptoms of Alzheimer's disease are noticed by patients or families, and this cascade of events may provide a timeline for symptomatic onset," says first author Randall Bateman, MD, the Charles F. and Joanne Knight

Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis. "As we learn more about the origins of Alzheimer's to plan preventive treatments, this Alzheimer's timeline will be invaluable for successful drug trials."

As an example, Bateman says that the new data show that plaques become visible on brain scans 15 years before memory problems become apparent. Researchers in the DIAN plan to give treatments that remove or block plaque formation at this early stage of the disease's progression and monitor subjects to see not only if the plaques can be prevented or reduced, but also whether other Alzheimer's biomarkers measured in the study improve.

Primarily funded by the National Institutes of Health (NIH), the DIAN partnership is researching the rare, familial form of Alzheimer's disease that can cause symptoms to appear in affected people in their 30s and 40s--decades earlier than the more common form that typically occurs after age 65.

"These exciting findings are the first to confirm what we have long suspected, that disease onset begins years before the first sign of cognitive decline or memory loss," said Laurie Ryan, PhD, clinical trials program director at the National Institute on Aging, part of the NIH. "And while DIAN participants are at risk for the rare, genetic form of the disease, insights gained from the study will greatly inform our understanding of late-onset Alzheimer's disease."

Because individuals with these inherited forms of Alzheimer's are widely dispersed geographically, there are too few at any one center to conduct extensive research. That led DIAN principal investigator John C. Morris, MD, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology at Washington University, and his team to form the network four years ago.

"These new results could never have been gathered without the collaborative teamwork and dedication of our DIAN partners at institutions across the United States and in the United Kingdom and Australia," says Morris, who also is director of the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University.

Other results from the new study include:

- Elevated spinal fluid levels of tau, a structural protein in brain cells, appear 15 years before Alzheimer's symptoms.
- Shrinkage in key brain structures becomes discernible 15 years before symptoms.
- Decreases in the brain's use of the sugar glucose and slight impairments in a specific type of memory are detectable 10 years before symptoms.

Researchers also tested participants from DIAN families who do not have any of the mutations that cause inherited Alzheimer's.

"Family members without the Alzheimer's mutations have no detected change in the markers we tested," Bateman says. "It's striking how normal the Alzheimer's markers are in family members without a mutation."

Bateman is leading the development of Alzheimer's prevention and treatment trials in DIAN participants. He and his colleagues hope to launch trials later this year.

DIAN researchers now offer an expanded registry for families with inherited Alzheimer's mutations. They encourage anyone with a family history of multiple generations of Alzheimer's diagnosed before age 55 to visit http://www.DIANXR.org/, where they can register for follow-up

contact from researchers to determine whether their family is eligible for participation in DIAN studies.

More information: Bateman R, et. al. Clinical, cognitive, and biomarker changes in the Dominantly Inherited Alzheimer's Network. *The New England Journal of Medicine*, July 11, 2012.

Provided by Washington University School of Medicine