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Sleep problems may be early sign of Alzheimer's

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Sleep disruptions may be among the earliest indicators of Alzheimer's disease, scientists at Washington University School of Medicine in St. Louis report Sept. 5 in *Science Translational Medicine*.

Working in a mouse model, the researchers found that when the first signs of Alzheimer's plaques appear in the brain, the normal sleep-wake cycle is significantly disrupted.

"If sleep abnormalities begin this early in the course of human Alzheimer's disease, those changes could provide us with an easily detectable sign of pathology," says senior author David M. Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of Washington University's Department of Neurology. "As we start to treat Alzheimer's patients before the onset of dementia, the presence or absence of sleep problems may be a rapid indicator of whether the new treatments are succeeding."

Holtzman's laboratory was among the first to link sleep problems and Alzheimer's through studies of sleep in mice genetically altered to develop Alzheimer's plaques as they age. In a study published in 2009, he showed that brain levels of a primary ingredient of the plaques naturally rise when healthy young mice are awake and drop after they go to sleep. Depriving the mice of sleep disrupted this cycle and accelerated the development of brain plaques.

A similar rising and falling of the plaque component, a protein called

amyloid beta, was later detected in the cerebrospinal fluid of healthy humans studied by co-author Randall Bateman, MD, the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University.

The new research, led by Jee Hoon Roh, MD, PhD, a neurologist and postdoctoral fellow in Holtzman's laboratory, shows that when the first indicators of brain plaques appear, the natural fluctuations in amyloid beta levels stop in both mice and humans.

"We suspect that the plaques are pulling in amyloid beta, removing it from the processes that would normally clear it from the brain," Holtzman says.

Mice are nocturnal animals and normally sleep for 40 minutes during every hour of daylight, but when Alzheimer's plaques began forming in their brains, their average sleep times dropped to 30 minutes per hour.

To confirm that amyloid beta was directly linked to the changes in sleep, researchers gave a vaccine against amyloid beta to a new group of mice with the same genetic modifications. As these mice grew older, they did not develop brain plaques. Their sleeping patterns remained normal and amyloid beta levels in the brain continued to rise and fall regularly.

Scientists now are evaluating whether sleep problems occur in patients who have markers of Alzheimer's disease, such as plaques in the brain, but have not yet developed memory or other cognitive problems.

"If these sleep problems exist, we don't yet know exactly what form they take—reduced sleep overall or trouble staying asleep or something else entirely," Holtzman says. "But we're working to find out."

More information: Roh JH, Huang Y, Bero AW, Kastne T, Stewart

FR, Bateman RJ, Holtzman DM. Disruption of the sleep-wake cycle and diurnal fluctuation of amyloid-β in mice with Alzheimer's disease pathology. *Science Translational Medicine*, Sept. 5, 2012.