Obstructive Sleep Apnea Associated with Dementia Risk

BY JAMIE TALAN

A ‘BEST PAPER’ PICK: Neurology Today editorial advisory board member David Gill, MD, a cognitive behavioral neurologist at Unit Rehabilitation & Neurology in Rochester, NY, selected this as one of the “best papers” on dementia from the AAN annual meeting.

**ARTICLE IN BRIEF**

In an analysis of data from two epidemiological studies, investigators reported that more than half of study participants who had obstructive sleep apnea (OSA) had developed dementia and OSA was independently associated with the dementia diagnosis.

Researchers at Washington University School of Medicine in St. Louis mined data on sleep apnea from two large epidemiological studies to see whether disordered breathing at night put community-residing elderly people at risk for dementia. They found that it did.

Yo-EI Ju, MD, an assistant professor of neurology and a sleep disorders expert, wanted to determine whether obstructive sleep apnea (OSA) increases risk of dementia in both men and women. A 2011 study in the Journal of the American Medical Association by Kristine Yaffe, MD, and colleagues at the University of California, San Francisco (UCSF) found that OSA was a risk factor for dementia in women. “Since OSA is more common in men, we wanted to perform a similar study in a group that included both men and women, to assess for any gender differences,” Dr. Ju said.

**STUDY DESIGN**

Dr. Ju reviewed medical information from 208 older people who had been followed for over a decade in two longitudinal studies supported by the NIH National Heart, Lung, and Blood Institute: the Sleep Heart Health Study — a multicenter study to determine cardiovascular and other consequences of sleep-disordered breathing — and the Cardiovascular Health Study, an observational study of risk factors for cardiovascular disease in adults 65 years or older. The presence of OSA was detected by unattended polysomnography from 1995-1997, and defined as apnea and hypopnea index (with 4 percent SpO2 desaturations) ≥5/hour. An expert panel assessed the cognitive status of the participants one to three years later. The St. Louis team selected only those participants with normal cognitive status at this time. They were able to look at annual assessments to see who developed dementia and when they developed it. Then, they looked at the time to dementia between those with and without OSA, using Cox regression.

The results were adjusted for gender, age, and apolipoprotein E4 (APOE4) allele status. In a presentation of preliminary findings at the AAN annual meeting, Dr. Ju reported that OSA was diagnosed in 110 (53 percent) of the study participants. By 2006, 106 people had developed dementia and OSA was independently associated with the dementia diagnosis (Hazard Ratio (HR)=1.65, 95% CI=1.10-2.48, p=0.017) after adjustment for female gender, age (HR=1.09, p=0.002), and APOE4 allele (HR=1.56, p=0.042).

The investigators are now analyzing the most recent data up to 2012. Their goal is to determine why sleep apnea puts people at greater risk of dementia. There are several possibilities that could explain how OSA can contribute to dementia. Apnea causes frequent awakenings from sleep, sometimes hundreds of times a night, Dr. Ju said. “It could be the lack of deep sleep or the repeated drops in oxygen levels in OSA, or some other mechanism, that is driving this relationship between OSA and dementia.”

**EXPERTS WEIGH IN**

In the 2011 JAMA study by Dr. Yaffe, UCSF professor of psychiatry, neurology, and epidemiology and biostatistics, and associate chair of clinical and translational research in the department of psychiatry, and her colleagues found that while the two conditions have been linked, no one was sure whether OSA began before the cognitive decline. They had information on both conditions from a subset of the Study of Osteoporotic Fractures, an NIH-funded multicenter, observational study of 10,000 older women recruited in the 1980s and 1990s; in 2002, the researchers expanded the study to include cognitive measures.

They reported that the 105 women (35.2 percent) with sleep-disordered breathing were almost twice as likely to develop mild cognitive impairment or dementia than those without OSA. Sleep fragmentation or sleep duration were not associated with the risk of MCI or dementia. That sleep fragmentation was not linked to the risk suggested that...
Obstructive Sleep Apnea, Dementia
Continued from page 6

it was the hypoxia that was the mechanism behind the increased risk.

“I am delighted that another group has seen an association between sleep apnea and dementia,” said Dr. Yaffe. While the UCSF group studied women, she said, “there was no reason to think the risk would be any different for men.” She said that it would be helpful to factor in other comorbidities, such as obesity, diabetes, and cardiovascular disease. She added that education also plays a role in the risk for dementia and should be part of the equation in any analysis.

Clifford B. Saper, MD, PhD, the James Jackson Putnam professor of neurology and neuroscience at Harvard Medical School and chairman of the neurology department at Beth Israel Deaconess Medical Center, said that there is “a lot of evidence that OSA and sleep fragmentation cause cognitive impairment.” Dr. Saper and his colleagues did a study of 700 participants in the Rush Memory and Aging Project. At the time of the initial enrollment, they were healthy elderly people who had wrist actigraphy and detailed cognitive testing. The Harvard scientists found that sleep fragmentation was associated with impairment on several cognitive measures.

“Others have found treating OSA improves some aspects of cognitive function in healthy people, and even more so in Alzheimer patients,” citing 2012 papers in the *Sleep Medicine Review* and the *Journal of Clinical Sleep Medicine*. In fact, in our own Cognitive Neurology Unit, the most common treatable cause of dementia is OSA,” Dr. Saper said.

That said, Dr. Saper noted that epidemiological data are often hard to

Continued on page 9
interpret. “Because the data are analyzed after the fact, it is hard to know whether the patients had increased risk of dementia due to OSA, or just were more likely to be diagnosed with dementia because their OSA made the symptoms of their underlying dementia worse,” he said.

Donald L. Bliwise, PhD, a professor of neurology at Emory University School of Medicine, said that it is interesting that the new study reported during the AAN meeting found a risk of OSA to incident dementia that was independent of APOE genotype. “But the abstract does not present data on whether there may have been effect modification by genotype (as would be obtained through a stratification approach).”

Additionally, he said, “other population-based studies demonstrated an association between apolipoprotein E4 and OSA. So I would expect that this study would have found a similar association, regardless of dementia. In this situation, one usually thinks of genotypes as reflecting diathesis, [a non-biological or genetic predisposition], whereas OSA would be more likely to reflect specific pathophysiologic (and potentially treatable) vulnerability. But it may well be that if OSA is a physiologic biomarker of aging, it is also associated with APOE4, and then what they are observing is simply the very same vulnerability in a different organ system.” •

**Obstructive Sleep Apnea, Dementia**

*Continued from page 8*

TUNE IN: What is the relationship between obstructive sleep apnea and risk for dementia?


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- The Sleep Heart Health Study: [www.jhuccct.com/shhs](http://www.jhuccct.com/shhs)
- The Cardiovascular Health Study: [www.chs-nhlbi.org](http://www.chs-nhlbi.org)
- Study of Osteoporotic Fractures: [http://sof.ucsf.edu/interface](http://sof.ucsf.edu/interface)