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FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2017

CAN TREATING SLEEP PROBLEMS LOWER DEMENTIA RISK?

- *Sleep disordered breathing may be a modifiable risk factor for Alzheimer's -*
- *Obstructive sleep apnea accelerates Alzheimer's disease biomarkers -*

LONDON, July 18, 2017 – Several new research analyses reported at the Alzheimer's Association International Conference 2017 (AAIC 2017) in London found significant associations between sleep disordered breathing (SDB) and the accumulation of biomarkers for Alzheimer's disease. These findings highlight the idea that SDB is a modifiable factor that may help lower the risk of dementia and possibly slow the progression of dementia where it already exists.

Sleep disordered breathing is characterized by repeated episodes of hypopnea (under breathing) and apnea (not breathing) during sleep. The predominant form of apnea, Obstructive Sleep Apnea, occurs when an individual's upper airway closes partially or fully, but efforts to breath continue. OSA occurs in an estimated 3 in 10 men and 1 in 5 women.

Research reported at AAIC 2017 found:

- SDB accelerated the accumulation of brain β -amyloid both in cognitively normal individuals and individuals with mild cognitive impairment (data from the Alzheimer's Disease Neuroimaging Initiative (ADNI)).
- Obstructive sleep apnea (OSA) was associated with increased brain β -amyloid deposition, decreased cerebrospinal fluid (CSF) levels of β -amyloid and increased tau protein levels.

"The Centers for Disease Control and Prevention says more than one third of American adults do not get enough sleep on a regular basis. Clearly this is not good for brain health or overall health," said Dean M. Hartley, PhD, Alzheimer's Association Director of Science Initiatives. "Sleep disordered breathing is treatable in many cases. Through early diagnosis and effective treatment of these sleep disorders, there is the potential to improve cognition and possibly reduce dementia risk. But first we need to know more about the connections between these medical conditions."

Sleep-Disordered Breathing and Obstructive Sleep Apnea Are Associated With Amyloid Deposition

Three analyses reported by investigative teams at Wheaton College in Wheaton, Illinois, at AAIC 2017 examined sleep patterns among participants in ADNI to characterize potential effects of SDB and OSA on brain changes associated with mild cognitive impairment and Alzheimer's disease.

Amanda Shim and colleagues examined brain β -amyloid-42 accumulation in a cohort of 516 cognitively normal subjects and found that those with SDB had higher levels in CSF at baseline and more rapid accumulation over time. They found no interactive effect between OSA and the Alzheimer's risk gene APOE-e4. This suggests that OSA may be independently associated with brain amyloid burden.

Megan Hogan and colleagues performed similar analyses to assess the effects of OSA in 798 subjects with mild cognitive impairment (MCI). As with the cognitively normal cohort, both baseline β -amyloid-42 levels and the rate of accumulation were higher in subjects with OSA. While MCI does not always lead to dementia, a person with MCI is at an increased risk of developing Alzheimer's or another dementia. These results suggest that SDB may be an independent risk factor for Alzheimer's and raises the possibility that interventions aimed at treating SDB may also reduce Alzheimer's risk.

A combined analysis of the cognitively normal and mild cognitive impairment populations, plus a third group with Alzheimer's disease (n=325), evaluated the effects of OSA on levels of several Alzheimer's disease biomarkers in cerebrospinal fluid (CSF) and brain β -amyloid burden measured by positron emission tomography. Analyses showed:

- Associations between OSA and CSF A β 42 levels in the MCI and Alzheimer's groups.
- Significant OSA associations were observed with [brain] A β 42 levels in CN and MCI participants.
- OSA subjects experienced faster increase in [brain] A β 42 over time in the CN and MCI groups.
- OSA participants experienced a faster decrease in CSF A β 42 and increases in TAU and PTAU volumes over time in both the CN and MCI groups.

According to research team leader, Omonigho Bubu, MD, MPH, these results "highlight the importance of checking for and accurately diagnosing sleep disordered breathing, especially in people at risk for dementia, and more importantly in people diagnosed with MCI, so that it can be addressed and treated."

"If OSA accelerates deposition of beta amyloid in the brain, then it becomes a possible target for therapeutic intervention. More research is needed to confirm these findings," Bubu said.

About the Alzheimer's Association International Conference

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

AAIC 2017 home page: www.alz.org/aaic/

AAIC 2017 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call +1 800.272.3900.

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- Amanda Shim, et al. Sleep Disordered Breathing, APOE4 and β -Amyloid Deposition in Cognitive Normal Elderly. (Funder(s): Wheaton College Faculty Development Grant)
- Megan Hogan, et al. Obstructive Sleep Is Associated with Longitudinal Increases in Amyloid Burden in Elderly Mild Cognitive Impairment Individuals. (Funder(s): Wheaton College Development Grant)
- Omonigho Bubu, MD, MPH, et al. Effect of Obstructive Sleep Apnea (OSA) on Rate of Change of AD Biomarkers in Cognitive Normal, MCI and AD Elderly: Findings from the Alzheimer's Disease Neuroimaging Initiative (ADNI) Cohort. (Funder(s): Wheaton College Faculty Development Grant)

Abstract 17967 / Proposal ID P3-415

Diagnosis and Prognosis: Neuropathology
Posters Tuesday, July 18, 2017: 9:30 AM

Sleep Disordered Breathing, APOE4 and β -Amyloid Deposition in Cognitive Normal Elderly

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Background: Sleep Disordered Breathing (SDB) is commonly reported in the elderly, and recent studies in humans and animals describe associations between SDB and Alzheimer disease (AD). ApoE4 allele is considered the most important risk factor for sporadic AD. We examined whether SDB is associated with changes in amyloid burden in a sample of cognitively normal elderly. The interactive effect of SDB*APOE4 on amyloid burden was also examined.

Methods: Data used were obtained from the ADNI database (adni.loni.usc.edu). Study participants included a total of 516 cognitively normal subjects and were a subset of the ADNI cohort. SDB was self-reported and participants were labeled SDB+, or SDB-. Brain A β -42 levels were determined at baseline and follow-up visits.

Multi-level mixed effects linear regression models were used to examine the relationship between SDB and A β -42 volumes. First, we fit a linear regression model for each participant separately at each time point, and second, we regressed unknown time-specific regression coefficients against time. Our models were adjusted for sex, and body mass index. There was no difference between OSA groups for APOE e4 status, age and history of cardiovascular disease. The interactive effect of SDB*APOE4 on amyloid burden was also examined.

Results: There was significant variation between subjects in mean A β -42 volumes at baseline (intercept) (mean SUVR; B = 0.006, p < .0001), as well as significant variation in the change in A β -42 volumes over time (slope) (mean SUVR; B = 0.006, p < .0001). The covariance between the baseline A β -42 level and A β -42 volume change over time indicated that SDB subjects experienced a faster increase in brain A β -42 volumes over time (p < .0001). The interactive effect of SDB*APOE4 on amyloid burden was not significant.

Conclusions: Among community-dwelling cognitively normal older adults, SDB is associated with greater β -amyloid burden changes over time regardless of APOE4 status. This suggests that clinical interventions aimed at SDB, such as treatment with CPAP or dental appliances, implemented during the early phase in which tissue damage precedes clinical symptoms and neuronal dysfunction, may mitigate the progression of cognitive impairment.

Abstract 18058 / Proposal ID P3-414

Diagnosis and Prognosis: Neuropathology
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Obstructive Sleep Apnea Is Associated with Longitudinal Increases in Amyloid Burden in Elderly Mild Cognitive Impairment Individuals

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Background: Cross sectional analysis has shown an association between OSA severity and A β burden using amyloid-PET, globally and regionally in the precuneus among MCI patients. However, whether OSA accelerates longitudinal increases in A β burden in MCI patients is presently unclear.

Methods: Study participants included a total of 798 subjects with a diagnosis of MCI and were a subset of the ADNI cohort (adni.loni.usc.edu). OSA was self-reported and participants were labeled either as OSA+, or OSA-. A β burden was determined by florbetapir SUVRs calculated by averaging across the 4 cortical regions and dividing this cortical summary ROI by a composite reference region. Mean and variance of the A β data at each time point by OSA status were determined. To test whether OSA is associated with the rate of change in A β data longitudinally, SAS PROC MIXED was used to fit the model with randomly varying intercepts and slopes allowing dependence on OSA status. The final model was adjusted for sex, body mass index and CPAP use status since there was no difference between OSA groups for APOE e4 status, age and history of cardiovascular disease.

Results: At baseline, there was significant variation between subjects in mean A β -42 volumes (intercept) (mean SUVR; B = 0.0008, Z-value = 11.02, $p < .0001$). A significant variation in the change (slope) in A β -42 volumes over time was also seen (mean SUVR; B = 0.0084, Z-value = 11.63, $p < .0001$). The covariance between the baseline A β -42 level and A β -42 volume change over time indicated that SDB subjects experienced a faster increase in brain A β -42 volumes over time ($p < .0001$). The rate of change in A β -42 deposition also varied significantly across OSA groups over the follow-up period.

Conclusions: Obstructive Sleep Apnea possibly facilitates longitudinal increases in amyloid burden in elderly Mild Cognitive Impairment individuals. Further research examining mechanisms underlying effects of OSA on the longitudinal increases in A β burden is needed.

Abstract 17593 / Proposal ID P3-192

Diagnosis and Prognosis: Neuropathology
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Effect of Obstructive Sleep Apnea (OSA) on Rate of Change of AD Biomarkers in Cognitive Normal, MCI and AD Elderly: Findings from the Alzheimer's Disease Neuro- Imaging Initiative (ADNI) Cohort

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Background: We examined the effect of OSA on longitudinal changes in brain amyloid deposition, and AD Cerebrospinal fluid (CSF) biomarkers.

Methods: Data from 1639 subjects (516 Cognitive Normal (CN), 798 Mild Cognitive Impairment (MCI) and 325 AD, mean ages = 74.4 ± 5.8 ; 73.4 ± 7.4 and 75.1 ± 7.8 respectively), in the ADNI database was used. OSA was self-reported and participants were labeled OSA positive, or OSA negative (mean ages = 72.3 ± 7.1 ; and 73.9 ± 7.3 respectively). AD biomarkers included CSF A β -42, TAU, PTAU and brain florbetapir-PET A β burden. Separate multi-level mixed effects linear regression models were used to examine the relationship between OSA and the rate of change of AD biomarkers over time (mean = 2.52 ± 0.51 years) in each group (CN, MCI and AD). The final models were adjusted for sex, BMI, and CPAP status. No significant difference existed between OSA groups for APOE e4 status, age and history of cardiovascular disease.

Results: Cross-sectional analyses showed associations between OSA and CSF A β -42 levels ONLY in the MCI, and AD groups ($P < 0.05$ for all). OSA was associated with TAU levels ONLY in MCI patients ($P = 0.02$). Furthermore, significant OSA associations were observed with A β -42 levels only in CN and MCI participants ($P = 0.02$ for all). Longitudinal analyses revealed significant variations in the change in A β -42 volumes over time and the covariance between baseline A β -42 and A β -42 change over time showed that OSA subjects experienced faster increase in A β -42 over time ($p < .0001$ for all) in both the CN and MCI groups. Significant variations were observed in CSF A β -42, TAU and PTAU levels over time and the covariance parameters between the baseline CSF A β -42, TAU and PTAU volume change over time indicated that OSA participants experienced a faster decrease in CSF A β -42 and increases in TAU and PTAU volumes over time ($p < .0001$ for all) in both the CN and MCI groups.

Conclusions: OSA possibly accelerates longitudinal changes in brain amyloid deposition, and CSF biomarkers burden, both in elderly cognitive normal and MCI individuals. Further research examining mechanisms underlying these observed effects are needed.