News Release

FOR RELEASE May 19, 2013, 2:00 p.m. EST

FOR MORE INFORMATION, CONTACT:
Nathaniel Dunford or Brian Kell
ndunford@thoracic.org or bkell@thoracic.org
ATS Office 212-315-8620 or 212-315-6442 (until May 15)
Cell phones 914-815-0503 or 516-305-9251
ATS Press Room: 215-418-2408 or 215-418-2409 (May 19-22)

Session A109: Poster Discussion Session - Poster Presentation
Sunday, May 19, 2013, 2:00 p.m. – 4:30 p.m.
Location: Grand Ballroom C-D (Level 5) Philadelphia Marriott Downtown

PRESS CONFERENCE: Sunday, May 19, 4:45 p.m., Room 110A (Level 100), Pennsylvania Convention Center

Study Finds that Sleep Apnea and Alzheimer's Are Linked

ATS 2013, PHILADELPHIA—A new study looking at sleep-disordered breathing (SDB) and markers for Alzheimer's disease (AD) risk in cerebrospinal fluid (CSF) and neuroimaging adds to the growing body of research linking the two.

But this latest study also poses an interesting question: Could AD in its "preclinical stages" also lead to SDB and explain the increased prevalence of SDB in the elderly?

The study will be presented at the ATS 2013 International Conference.

"It's really a chicken and egg story," said Ricardo S. Osorio, MD, a research assistant professor at NYU School of Medicine who led the study. "Our study did not determine the direction of the causality, and, in fact, didn't uncover a significant association between the two, until we broke out the data on lean and obese patients."

When the researchers did consider body mass, they found that lean patients (defined as having a body mass index <25) with SDB did possess several specific and non-specific biomarkers of AD risk (increased P-Tau and T-Tau in CSF, hippocampal atrophy using structural MRI, and glucose hypometabolism using FDG-PET in several AD-vulnerable regions). Among obese patients (BMI >25), glucose hypometabolism was also found in the medial temporal lobe, but was not significant in other AD-vulnerable regions.

"We know that about 10 to 20 percent of middle-aged adults in the United States have SDB [defined as an apnea-hypopnea index greater than 5] and that the number jumps dramatically in those over the age of 65," said Dr. Osorio, noting that studies put the percentage of people over the age of 65 with SDB between 30 and 60 percent. "We don't know why it becomes so prevalent, but one factor may be that some of these patients are in the earliest preclinical stages of AD."

According to Dr. Osorio, the biochemical harbingers of AD are present 15 to 20 years before any of its currently recognized symptoms become apparent.

The NYU study enrolled 68 cognitively normal elderly patients (mean age 71.4±5.6, range 64-87) who underwent two nights of home monitoring for SDB and were tested for at least one diagnostic indicator of AD. The researchers looked at P-Tau, T-Tau and Aβ42 in CSF, FDG-PET (to measure glucose metabolism), Pittsburgh compound B (PiB) PET to measure amyloid load, and/or structural MRI to measure hippocampal volume. Reduced glucose metabolism in AD-vulnerable regions, decreased hippocampal volume, changes in P-Tau, T-Tau and Aβ42, and increased binding of PiB-PET are recognized as markers of risk for AD and have been reported to be abnormal in healthy subjects before the disease onset.

Biomarkers for AD risk were found only among lean study participants with SDB. These patients showed a linear association between the severity of SDB and CSF levels of the biomarker P-Tau ($F = 5.83$, $t=2.41$, $\beta=0.47$; $p< 0.05$) and between SDB and glucose hypometabolism using FDG-PET, in the medial temporal lobe ($F=6.34$, $t=-2.52$, $\beta=-0.57$,$p<0.05$), the posterior cingulate cortex/precuneus ($F=11.62$, $t=-3.41$, $\beta=-0.69$, $p<0.01$) and a composite score of all AD-vulnerable regions ($F=4.48$, $t=-2.11$, $\beta=-0.51$, $p<0.05$). Lean SDB patients also showed smaller hippocampi when compared to lean controls ($F=4.2$, $p<0.05$), but no differences were found in measures of amyloid burden such as decreased Aβ42 in CSF or PiB positive scans.

Dr. Osorio and his colleagues are planning to test their hypothesis that very early stage preclinical AD brain injury that associates with these biomarkers can lead to SDB. They have proposed a two-year longitudinal study that would enroll 200 cognitively normal subjects, include AD biomarkers and treat those patients with moderate to severe SDB with continuous positive airway pressure, or CPAP, over time.

The purpose of the new study would be to determine the "direction" of causality between SDB and preclinical AD in elderly patients. After an initial assessment, the patients would be given CPAP to treat their sleep apnea. After six months, they would be evaluated again for biomarker evidence of AD.

"If the biomarkers change, it may indicate that SDB is causing AD," explained Dr. Osorio. "If they don't change, the probable conclusion is that these patients are going to develop AD with or without CPAP, and that AD may either be causing the apneas or may simply coexist with SDB as part of aging."

Either way, Dr. Osorio believes the relationship between SDB and AD deserves further study. "Sleep apnea skyrockets in the elderly, and this fact hasn't been given the attention it deserves by the sleep world or the Alzheimer's world," Dr. Osorio said. "Sleep particularly suffers from an outmoded perception that it is an inactive physiological process, when, in reality, it is a very active part of the day for the brain."

###

** Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Abstract 38456

Sleep-Disordered Breathing, Aging And Risk For Alzheimer's Disease In Cognitively Normal Subjects

Type: Scientific Abstract

Category: 16.04 - Sleep Disordered Breathing: Epidemiology, Genetics and Outcomes (SRN)

Authors: R.S. Osorio[1], J. Mantua[2], I. Ayappa[2], A.M. Mooney[2], Z. Taxin[2], J. Murray[1], M. Biagioni[1], C. Randall[1], Y. Li[1], M. Cummings[1], N. Spector[1], A. Rejon[1], H. Lau[1], L. Glodzik[1], D.M. Rapoport[2], M.J. De Leon[1]; [1]Center for Brain Health, New York University - New York, NY/US, [2]Division of Pulmonary, Critical Care, and Sleep Medicine, New York University Medical Center - New York, NY/US; Sleep and Aging Laboratory

Abstract Body

RATIONALE: Previous studies have shown that sleep-disordered breathing (SDB) may be a risk factor for developing Alzheimer´s disease (AD). Current evidence shows that a preclinical stage of AD may be recognized using cerebrospinal fluid (CSF) biomarkers, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET, Pittsburgh-Compound-B (PiB) PET, and structural MRI neuroimaging. The purpose of our study was to investigate whether known CSF and neuroimaging biomarkers for AD (decreased CSF Aβ42, increased CSF P-Tau or T-Tau, region specific brain glucose hypometabolism, increased brain amyloid load, or reduced hippocampal volume) were found in cognitively normal elderly subjects with SDB.

METHODS: Sixty-eight subjects (mean age 71.4±5.6, range 64-87) underwent comprehensive clinical exams, neuropsychological testing, two nights of home monitoring of SDB, and at least one of the following AD-research diagnostic procedures: CSF Aβ42, P-Tau and T-Tau; FDG-PET, PiB-PET; or structural MRI. SDB was classified based on the Apnea Hypopnea Index with hypopneas restricted to respiratory events associated with 4% desaturation (AHI4%), with normal breathing defined as AHI4%<5, mild SDB as AHI4% of 5-15, and moderate-severe as AHI4%>15.

Table 1. Mean values±standard deviation of sleep characteristics and BMI

SDB Group	Normal (n=18)	Mild (n=33)	Moderate-Severe (n=17)
BMI	23.8±3.8	25.8±3.8	29.4±6.8
ESS	4.7±3.5	6.2±3.8	5.4±3.1
AHI4%	2.6±1.3	8.3±2.9	36.9±16.9
RDI	12.3±5.5	22.4±9.3	50.4±16.3
Apnea Index	1.1±1.7	3.6±2.3	22.1±12.2

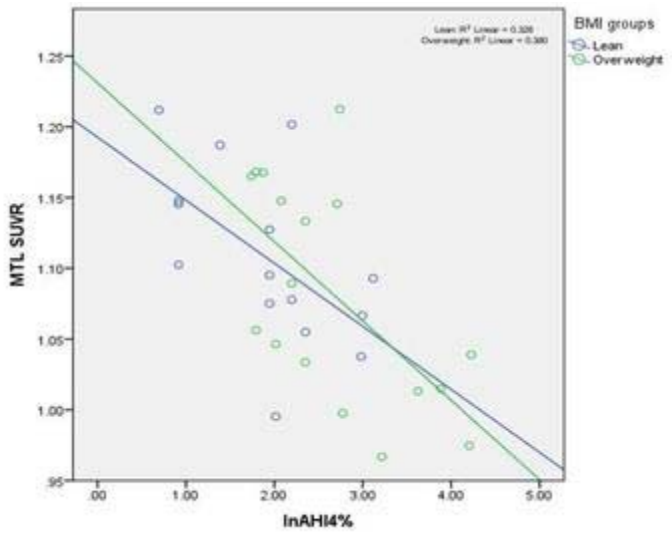
Mean Sp02	95.6±0.7	95.2±1.0	93.8±1.5

RESULTS: Of the 68 subjects, 18 (26.5%) had normal breathing, 33 (48.5%) mild SDB, and 17 (25%) moderate-severe SDB. There were no neuropsychological or clinical differences between the SDB groups except for higher BMI in the moderate-severe group ($p<0.05$). Lean SDB subjects (Body Mass Index [BMI] <25) showed glucose hypometabolism in the medial temporal lobe ($F= 18.00$; $p=0.00$; shown in Figure 1), lateral temporal lobe ($F=4.68$; $p=0.04$) and posterior cingulate cortex/precuneus ($F=9.18$; $p=0.00$), while overweight patients showed hypometabolism only in the medial temporal lobe ($F=9.21$; $p=0.00$). Results are shown in Table 2. Specific biomarkers features of AD such as increased CSF P-Tau ($F=5.83$; $p=0.02$) and glucose hypometabolism in AD-vulnerable regions (AD-mask: $F=4.48$; $p=.05$) were observed only in lean subjects.

Table 2. Regions of interest (ROI) and significance of ln(AHI4%) in predicting glucose metabolism.

	Region of Interest	**ß**	**P-Value**
Lean Subjects	Medial Temporal Lobe	-0.57	0.02
	Posterior Cingulate Cortex/ Precuneus	-0.69	0.00
	AD-Mask	-0.51	0.05
Overweight Subjects	Medial Temporal Lobe	-0.62	0.00

CONCLUSIONS: Our results show, in lean cognitively normal elderly, an association between SDB and several biomarker features of AD, offering partial support for an increased SDB risk for AD, and potential evidence that would explain the high prevalence (30-80%) of SDB in the elderly, where intermittent hypoxia is less dependent on obesity. However, our data do not address the direction of causality between SDB and AD and require longitudinal follow-up or intervention studies using continuous positive airway pressure (CPAP) for SDB.


Lean: R² Linear = 0.326
Overweight: R² Linear = 0.380
BMI groups
Lean
Overweight
MTL SUVR
1.25
1.20
1.15
1.10
1.05
1.00
.95
.00
1.00
2.00
3.00
4.00
5.00
lnAHI4%