Neuroscience and Biobehavioral Reviews 47 (2014) 656–669

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Can sleep apnea cause Alzheimer's disease?

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form 17 August 2014
Accepted 22 October 2014
Available online 30 October 2014

Keywords:
Sleep apnea
Alzheimer's disease
Sleep fragmentation
Hypoxia
Oxidative stress
Autophagy

ABSTRACT

Both obstructive sleep apnea (OSA) and Alzheimer's disease (AD) are increasing health concerns. The objective of this study is to review systematically the effects of OSA on the development of AD. The search was conducted in PubMed and Cochrane CENTRAL, and followed by a manual search of references of published studies. Cross-sectional, cohorts, and randomized clinical trials were reviewed. Besides clinical studies, we also discuss neuroimaging data, experimental animal evidence, and molecular mechanisms. Although a causal relationship between OSA and AD is not yet established, OSA induces neurodegenerative changes as a result of two major contributing processes: sleep fragmentation and intermittent hypoxia. As such, inflammation and cellular stress are sufficient to impair cell–cell interactions, synaptic function, and neural circuitry, leading to a decline of cognitive behavior. Sustained OSA could promote cognitive dysfunction, overlapping with that in AD and other neurodegenerative diseases. Early treatment by positive airway pressure and other current standards of care should have a positive impact to alleviate structural and functional deterioration. With better understanding of the cellular and neurophysiological mechanisms by which OSA contributes to AD, we may identify novel molecular targets for intervention.

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http://dx.doi.org/10.1016/j.neubiorev.2014.10.019
0149-7634/

1. Introduction

A growing body of the literature has identified a critical link between sleep and health. With modern life styles, more people are sleeping less than their biological needs (Bixler, 2009; Krueger and Friedman, 2009; Knutson et al., 2010). Inadequate sleep, reduced physical activity, and increased caloric intake all contribute to the development of obesity and obstructive sleep apnea (OSA). Severe OSA further induces sleep fragmentation, intermittent hypoxia, and oxidative stress during reoxygenation. In this context, we discuss how sleep disorders interfere with daily functions and impair cognitive reserve. This is pertinent to the evaluation and treatment of mild cognitive impairment (MCI) and dementia (vascular, Alzheimer's, and other forms of neurodegeneration).

OSA is a prevalent medical problem with a high socioeconomic burden (Committee on Sleep Medicine and Research Board on Health Sciences Policy, 2006). It affects a high percent of the elderly population as discussed below, though a 1996 UK study estimated a minimal prevalence of 5.7% in men and 1.2% in women at 35–69 years of age (Davies and Stradling, 1996). Polysomnography (PSG) remains the gold standard for diagnosis. To establish a diagnosis of OSA based on criteria from the American Academy of Sleep Medicine, patients typically have an apnea-hypopnea index (AHI) $\geq$5 events/h on PSG in association with symptoms of impaired daytime function, or $\geq$15 events/h when asymptomatic. Besides AHI, the extent and duration of intermittent hypoxia and the severity of impairment of sleep architecture also predict daytime dysfunction and medical complications. Sleep disordered breathing (SDB) is a more generalized term, including habitual snorers not yet fitting into the diagnostic criteria of OSA. The rate of undiagnosed cases is high, estimated to involve 82% of men and 93% of women (Daulatzai, 2013). Does OSA cause a subset of Alzheimer's disease (AD) and other forms of neurodegeneration? If so, does treatment of OSA prevent AD progression? Here, we address the link between OSA and AD by performing systematic reviews of clinical studies. We also discuss relevant neuroimaging findings as well as experimental results from animal and cellular research. Some of the key issues are: differentiation of cognitive functional domains primarily affected in OSA patients and AD patients; structural correlates; and potential reversibility by treating OSA.

2. Systematic review of clinical studies

2.1. Data sources and searches

Following guidelines specified in the Cochrane Handbook (Higgins and Green, 2011) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al., 2009), we searched PubMed and Cochrane CENTRAL. The following medical subject headings (MeSH) and key words were used: "Sleep apnea" (or "sleep apnoea") and "Alzheimer's disease". The duration of the search starts from the beginning of each database till the beginning of 2014, the time of submission of this review.

2.2. Data extraction and analysis

Duplicated entries in different databases were scrutinized. This was followed by a manual search of references of published studies. Inclusive criteria encompassed studies describing general data (study design), patients (number of included patients, mean age, gender), type of diagnostic criteria and/or intervention strategy used, and timing of determination, with full text English language publication available for evaluation. Besides original research listed in the tables, some pertinent reviews with new information were also covered in the text, as they were particularly helpful in identifying original studies not covered in the original search. Studies of most non-AD causes of neurodegeneration were excluded, with the exception of discussion of some Parkinson's disease and vascular (multi-infarct) dementia studies, as they show substantial overlap with AD.

The validity of statistical association between OSA and AD was assessed by evaluation of alternative explanations from chance, bias, and confounding influences. Potential causal effects were determined by positive criteria of the strength of association, totality of evidence, biological credibility, and dose-response or threshold effect. The generalizability is discussed in regard to the features of the study population. Risk of bias was assessed for allocation, blinding, incomplete outcome, selective reporting, comparable treatment groups, and other sources that might increase the risk of bias, such as carry-over effects in crossover designs or conflicts of interest.

2.3. Results

The electronic search to January 2014 resulted in a total of 50 results on PubMed, and no pertinent new ones on Cochrane CENTRAL. There were 19 full text articles meeting eligibility criteria and these were obtained. Additional records were identified by cross-checking the reference lists and updated search at the time of revision of this review manuscript in July 2014. We reviewed studies about three major issues: (1) the prevalence and distribution of sleep disorders in the elderly; (2) in people with OSA, whether there is an increased incidence of AD or other types of dementia, and whether there is a potential association between OSA and AD; and (3) whether treatment improves cognitive dysfunction in OSA patients.

2.4. A priori 1: Increased incidence of sleep disordered breathing with age

Self-report questionnaire and sleep diagnostic findings can be quite different, even in the same population. The initial estimate of 2905 Japanese-American men (71–93 year old) in the Honolulu-Asia Aging Study showed a 2% incidence of apnea and 8% of daytime sleepiness (Foley et al., 1999). Portable sleep studies showed that the incidence of SDB reached 70% in people older than 80 and the incidence of severe OSA (AHI $\geq$30 events/h) was 19% (Foley et al., 2003).

There are also differences among different populations across time and space. Among the 5201 participants from the Cardiovascular Health Study (65 years and older), 33% men and 19% woman reported loud snoring. Observed apnea was seen in 13% of men and 4% of women (Enright et al., 1996). This estimate is higher than the questionnaires in the Honolulu-Asia Aging study mentioned above (Foley et al., 1999). The sensitivity and specificity of self-reported snoring have been assessed in patients 60 years or older in a sleep clinic; men showed 65% sensitivity and 72% specificity, whereas women had 61% sensitivity and 81% specificity (Bliwise et al., 1991). PSG remains the gold standard for diagnosis.

In a full spectrum that encompasses SDB, sleep problems are common in the elderly. In demented patients, the incidence of sleep disturbance reached 71%, whereas the non-demented controls showed a lower rate of 55.7% (Rongve et al., 2010). In asymptomatic elderly, the presence of moderate to severe OSA was seen in 53 subjects among the 151 Norwegians sampled, whereas white matter changes were present in 199 patients. Even after adjustment for hypertension, there was a significant association between OSA and white matter change (Kim et al., 2013).