

Role of Obstructive Sleep Apnea in Cognitive Impairment

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ABSTRACT

Obstructive sleep apnea (OSA) is a prevalent sleep related breathing disorder characterized by repetitive collapse of the upper airways leading to intermittent hypoxia and sleep disruption. Clinically relevant neurocognitive, metabolic and cardiovascular disease often occurs in OSA. Systemic hypertension, coronary artery disease, type 2 diabetes mellitus, cerebral vascular infarctions and atrial fibrillation are among the most often cited conditions with causal connections to OSA. Emerging science suggest that untreated and undertreated OSA increases the risk of developing cognitive impairment, including vascular dementia and neurodegenerative disorders, like Alzheimer's disease. As with OSA, cardiovascular disease and type 2 diabetes mellitus, the incidence of dementia increases with age. Given our rapidly aging population, dementia prevalence will significantly increase. The aim of this treatise is to review current literature linking OSA to dementia and explore putative mechanisms by which OSA might facilitate the development and progression of dementia.

Keywords: Cognitive, Comorbidities, Dementia, Obstructive sleep apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common, chronic disorder of sleep and breathing characterized by partial or complete occlusion of the upper airway during sleep leading to insufficient airflow, hypoxemia and sleep fragmentation.¹ Consequently, daytime sleepiness, morning headaches, irritability, diminished concentration and fatigue are common in OSA.² The prevalence of OSA is increasing, now affecting 20%-30% of males and 10%-15% of females in the USA.³ Curiously, OSA is more common in selected populations (i.e. Hispanic, African American, Asian), in cases evaluated for bariatric surgery (70%-80%),⁴ and in cerebrovascular disease (60%-70%).^{5,6} Mokhlesi et al.⁷ queried the Truven Health MarketScan Research Database between 2003-2012 and identified 1,704,905 OSA patient insurance claims and compared these to 1,704,417 matched controls to determine the burden of OSA associated comorbidities. The investigators found all comorbid conditions were of significantly greater prevalence in the OSA group. Type 2 diabetes mellitus (T2DM) and ischemic heart disease were more prevalent in men, as opposed to hypertension and depression in women with OSA. Others describe increase risk of neurocognitive impairment and death in OSA.⁸ In spite of increasing prevalence and increasing well-defined health risks, estimates are that less than 5% of US adults with OSA are treated.^{9,10}

There is evidence to support the notion that OSA plays a causal or facilitating role in conditions often associated with impaired cognition, including Alzheimer's disease (AD) and vascular dementia (VaD) (Table 1).^{11,12} Mild cognitive impairment (MCI), neuropsychiatric disorders and stroke have also been associated with OSA.¹³ The mechanism by which OSA alters cognition are poorly defined and may be dependent on individual phenotype and disease specific factors. As an example, evidence supports OSA activation of the sympathetic, renin-angiotensin-aldosterone system as a putative mediator of OSA induced brain hypoperfusion and subsequent VaD.¹⁴ Additionally, OSA was demonstrated responsible for AD cerebral spinal fluid (CSF) biomarker changes in β -amyloid₄₂ in the elderly, an indication that OSA may alter β -amyloid₄₂ metabolism promoting amyloid plaques.¹⁵ Elucidating mechanisms by which

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Table 1: Conditions Associated with Cognitive Impairment and OSA

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|-------------------------------------------------------------------------------------------------|
| Atherosclerotic cardiovascular disease (intracranial bleeding, cerebrovascular ischemia) (28) |
| Arrhythmia (hypoperfusion, thromboembolic cerebral ischemia) (31) |
| Endocrine disorders (Hypothyroidism, T2DM, Dyslipidemia) (38) |
| Psychiatric disorders (MDD, anxiety)(42) |
| Neurodegenerative disorders: AD, LBD, Parkinson's disease, and frontotemporal degeneration (73) |

T2DM, Type 2 Diabetes Mellitus; MDD, Major depressive disorder; AD, Alzheimer's disease; LBD, Lewy- body dementia

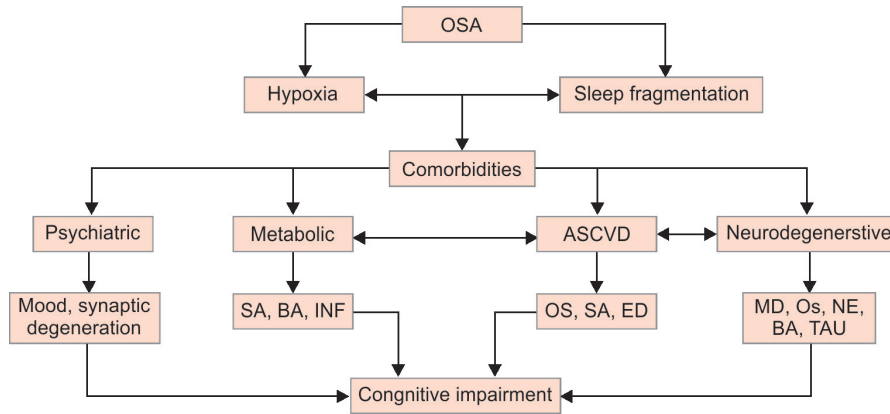
OSA creates cognitive impairment might allow disease specific therapeutic targets with promise of improved neural endpoints.

OSA Comorbidities and Altered Cognition: Potential Mechanisms

Hypoxemia, sleep fragmentation and daytime sleepiness are major contributors to cognitive impairment in OSA, affecting executive

Flowchart 1: Proposed mechanisms by which OSA impairs cognition

OSA, obstructive sleep apnea; ASCVD, atherosclerotic cardiovascular disease; SA, sympathomimetic activation; INF, inflammation; BA, beta amyloid accumulation; OS, oxidative stress; ED, endothelial dysfunction; MD, myelin decrease; NE, neural excitability, reduced; TAU, Tau hyperphosphorylation



functions, attention, memory and vigilance.¹⁶ In general, hypoxemia and sleep fragmentation, affect memory, attention and executive functions, mainly by causing neuronal injury in the prefrontal cortex and hippocampus.¹⁷ However, OSA comorbidities likely affect cognitive throughput by alternative diverse mechanisms. Some comorbidities, such as atrial fibrillation related cerebral infarction, impair cognition through reasonably well elucidated pathways, namely embolic stroke. Conversely, the mechanism by which other OSA comorbidities (endocrinopathies, hypertension, psychiatric disorders, lipid disarrangement, etc.) impair cognitive function is speculative and a subject of robust scientific interest. Flowchart 1 illustrates the proposed mechanisms by which selected OSA comorbidities adversely affect neuronal health and impair cognition. In the lines that follow, we succinctly review conditions comorbid with OSA known to impair cognition and describe the proposed mechanisms of action.

Cardiovascular disease and Stroke: Cardiovascular disease is the leading cause of death in the United States and worldwide. Subjects afflicted with atherosclerotic cardiovascular disease have a higher incidence of OSA¹ and cognitive dysfunction.¹⁸ Furthermore, cardiovascular disease and OSA, share other common comorbid conditions, such as obesity and endocrinopathies, conditions that are independently associated with decreased cognition.¹¹

Prospective studies have established that sleep apnea increases mortality, incident stroke and cardiovascular disease.¹⁹⁻²³ Long term follow up of both the Sleep Heart Health Study and the Wisconsin Sleep Cohort show nearly 3-4 fold higher associations between baseline OSA and incident stroke.^{24,25} Multiple studies describe a stroke risk in OSA of similar magnitude to vascular risk factors, such as hypertension and obesity.²⁴⁻²⁶

OSA may mediate vascular cerebral injury via intermittent deoxygenation-reoxygenation induced oxidative stress, mitochondrial dysfunction, endothelial dysfunction and metabolic deregulation.²⁷ Similarly, arousals may induce vascular disease risk through cerebral hypoperfusion, altered cerebral autoregulation, impaired endothelial function and increased inflammation.²⁸⁻³⁰

Atrial fibrillation, a cardiac rhythm disturbance that predisposes to thromboembolic cerebral ischemia, occurs in 32-49% of subjects afflicted with OSA.³¹ Indeed, patients with atrial fibrillation have a 4-5 fold increase in incident stroke without systemic anticoagulation.³² Experimentally induced obstructive apnea can cause acute atrial

fibrillation in a healthy canine heart.³³ Additionally, there is evidence that positive airway pressure (PAP) treatment of OSA protect against recurrence of atrial fibrillation following successful cardioversion in subjects afflicted with both conditions.³⁴

Endocrine disorders, Diabetes mellitus type 2 (T2DM): OSA and T2DM share several risk factors such as obesity and age. However, there is experimental evidence that the relationship between OSA and T2DM is bidirectional and independent of obesity.³⁵ Experimentally induced short-term sleep loss and intermittent hypoxemia in normal subjects promote insulin resistance with associated elevated systemic insulin levels and higher blood glucose.³⁶ Withdrawal of experimental sleep loss or treatment of non-obese OSA insulin resistant subjects with continuous positive airway pressure (CPAP) results in resolution of insulin resistance.³⁷

Excess insulin is a major contributor to neurocognitive decline in T2DM. Insulin degrading enzyme functions to reduce excess extracellular insulin and clear β -amyloid. Excessive insulin levels compete with the binding site of the insulin degrading enzyme, increasing the amount of β -amyloid, thereby, theoretically, facilitating Alzheimer's disease.³⁸

Independent of compounding variables, insulin resistant subjects have endothelial dysfunction as evidenced by resistance to insulin's effect on endothelium-mediated vasodilatation.³⁹ Endothelial dysfunction may promote neuronal injury by vascular dysregulation and ischemia.

Psychiatric disorders, Major depressive disorder (MDD): Several studies have demonstrated a relationship between OSA and depression.⁴⁰ Sleep complaints, weight gain, poor concentration, fatigue and anhedonia are features common to major depressive disorders (MDD) and OSA. It has been established that OSA patients are more prone to MDD than the general population.⁴¹ Effective CPAP treatment of OSA in MDD reduced anxiety and depression and improved neurocognitive function.⁴² The exact mechanism by which treating OSA improves cognitive function in patients with MDD remains speculative. Improving sleep architecture and oxygenation with subsequent improvement in alertness and quality of life after CPAP treatment of OSA might play a mechanistic role in cognitive benefits achieved after CPAP treatment.³⁴

Neurodegenerative disorders: Dementia is a growing problem as populations' age worldwide. The cost of treating dementia in the US alone was estimated to be between \$157 and \$215 billion



dollars in 2010.⁴³ The rise in dementia with its associated morbidities creates hardship on caregivers,⁴⁴ threatens the economic health of families and adds significantly to the cost of the healthcare system.⁴⁵ Unfortunately, treatment studies targeting β -amyloid have not consistently ameliorated dementia risk.⁴⁶ Emerging animal and human data indicate that frequent sleep disruptions and curtailed sleep increase synaptic activity and decrease glymphatic clearance leading to β -amyloid and tau deposition. Hence proper sleep may protect against neurodegeneration and AD,^{45,47,48} especially in individuals with genetic risks for dementia.⁴⁹⁻⁵²

Several studies have found cross-sectional associations between sleep disturbances and worse neurocognitive function,^{53,54} while others have not.⁵⁵⁻⁵⁷ Evidence from few prospective studies in older non-Hispanic white adults supports longitudinal associations between OSA and Alzheimer's disease related disorders (ADRD)^{21,58,59} Notably, hypoxemia, but not sleep fragmentation, mediated these associations.^{15,59} The underlying mechanisms linking OSA to cognitive decline in ADRD are unclear and may be multifactorial. One established framework suggests that hypoxemia accelerates cognitive aging; or OSA exerts damage through cerebrovascular disease.

Of interest, brain hypoperfusion, as seen in OSA, has been associated to pathological processes involved in AD.⁶⁰⁻⁶⁶ Moreover, chronic hypoxemia promotes the progression of cerebral small vessel disease, resulting in lacunar infarcts, white matter lesions, white matter fiber tract abnormalities, and gray-matter loss. Most notably, oxygen desaturation has been associated with an increased risk in developing MCI, perhaps as a prodromal phase to AD. Therefore, OSA patients may experience earlier onset of MCI and AD.^{54,67-70}

Anatomically, certain regions of the brain, such as the prefrontal and frontal lobes and hippocampus,¹⁷ are notably vulnerable to hypoxic-ischemic injury. Given the many deleterious effects associated with hypoperfusion in OSA, further studies looking at the relationships between hypoperfusion, early brain matter loss, and cognitive decline are needed to help clarify any contributions OSA may have to the onset and progression of AD.⁷¹

In a recent study, *Baril et al.*⁷² demonstrated alterations in selected cerebrospinal fluid and blood biomarkers common to both OSA and AD (Table 2). Biomarkers linked to β -amyloid, tau proteins, cytokines, acute-phase proteins, homocysteine, oxidative stress markers, and clusterin, seem to be able to identify adults with OSA at risk for dementias.⁷² Although a single biomarker of dementia risk in OSA has not been identified, biomarker combinations offer promise in selecting OSA cases at greatest risk for neurodegeneration. Further, serum or CSF biomarker responses to CPAP treatment of OSA might serve as surrogates of disease progression. Undeniably, methods that reliably predict neurodegeneration or progression of cognitive dysfunction will facilitate earlier clinical intervention and personalized treatment approaches, thereby, potentially reducing dementia burden.

CONCLUSION

OSA is a treatable chronic sleep disorder wherein recurrent episodes of complete or partial upper airway obstruction during sleep promote hypoxemia, hypercapnia, sleep fragmentation, oxidative stress, and inflammation. Adverse effects of untreated OSA include psychiatric, metabolic, cardiovascular and neurocognitive risk. Recently, science has established OSA as an independent risk factor for dementia. Given that the sleep fragmentation

Table 2: Shared blood fluid biomarkers of dementia and obstructive sleep apnea

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|-------------------------------------------------|----------------------------|
| Tau proteins | Increased ^{74,75} |
| Cytokines (IL-6, IL-1 β , TNF- α) | Increased ^{76,77} |
| Acute-phase proteins (hsCRP, ACT) | Increased ^{76,78} |
| Homocysteine | Increased ^{76,79} |
| Superoxide dismutase | Decreased ^{80,81} |
| MDA/8-OHdg | Increased ^{80,81} |
| Clusterin | Increased ^{82,83} |

IL-6, Interleukin-6; IL-1 β , Interleukin -1 β ; TNF- α , Tumor necrosis factor α ; hsCRP, high sensitivity c-reactive protein; ACT, α 1-antichymotripsin , MDA/8-OHdg, malondialdehyde; 8-OHdg, 8-hydroxy-2'-deoxyguanosine

and hypoxemia of OSA is readily reversed with CPAP therapy, identification and treatment of OSA in some cognitively impaired subjects should improve neural health outcomes. This manuscript highlights proposed mechanisms by which OSA negatively affects cognition and propagates neuronal injury culminating in dementia. Understanding the potential mechanisms that increase risk of cognitive impairment and dementia in OSA should facilitate the identification of clinical and/or biochemical phenotypes with highest propensity for dementia and, thereby, target these cases for early preventative strategies to reduce risk of dementia.

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