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REVIEW

Therapeutic effects of CPAP on cognitive impairments associated with OSA

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Abstract

Obstructive sleep apnea (OSA) is the most common type of sleep apnea and caused by upper airway obstructions. Clinically, patients with OSA characteristically experience intermittent nocturnal hypoxemia and impaired sleep quality. Cognitive impairments are commonly seen in patients with an OSA diagnosis. A literature search on OSA, cognitive impairments and CPAP was performed with various electronic databases including Medline, EMBASE and Google Scholar. The chosen evidence was limited to human subject studies only, and reports on either central sleep apnea or non-classified sleep apnea were excluded. Available evidence has been systemically reviewed to ascertain what types of cognitive impairments are related to OSA as well as the pathological connections. In addition, effectiveness of continuous positive airway pressure (CPAP) was analyzed as a standard therapy for improving cognitive performance in patients with OSA. The review contributed in: (1) delineating OSA as a risk factor of cognitive impairments; (2) enumerating cognitive impairments seen in patients with OSA; (3) substantiating the relation between OSA and cognitive impairments from the pathological perspective of AD biomarkers; and (4) revealing duration of CPAP is crucial for its therapeutic effects on improving cognitive performance in patients with OSA.

Keywords Alzheimer's disease (AD) · Continuous positive airway pressure (CPAP) · Mild cognitive impairment (MCI) · Obstructive sleep apnea (OSA)

Introduction

Obstructive sleep apnea (OSA) is the most common type of sleep apnea, and it prevalence has been shown to be close to 3% in a veteran population [1]. The prevalence of OSA is related to a variety of factors including age [2], gender [3] and body mass index (BMI) [2, 4]. Clinically, OSA is characterized by intermittent hypoxia, hypercapnia, hypoventilation, and sleep disruption due to blocked or reduced airflow in the upper airway. Chronic intermittent nocturnal hypoxemia was suggested to be the cause for cognitive deficits seen in patients with OSA, as the severity of hypoxemia correlates significantly with the observed cognitive deficits [5]. In another study, a modest association was found between nocturnal hypoxemia and global cognitive decline, over a follow-up of more than 3 years [6]. Further, the OSA group was shown to have a significantly lower Mini-Mental State Examination (MMSE) score at baseline, compared to the control group in a cohort study [7]. Non-surprisingly, the severity of OSA was found to be inversely related to the Montreal Cognitive Assessment (MoCA) score [8]. However, the risk of developing mild cognitive impairment (MCI) or dementia was only related to either an elevated oxygen desaturation index or a high percentage of sleep time in apnea/hypopnea [9]. Neither sleep fragmentation nor sleep duration was noted to be related to the risk of developing MCI or dementia [9]. Our goal was to carry out a systemic review for ascertaining what cognitive functions are impaired in patients with OSA and search for pathological evidence between OSA and the associated cognitive impairments. At the same time, we want to analyze if continuous positive airway pressure is effective for improving the impaired cognitive functions seen in patients with OSA.

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Methods

A systemic review was conducted by searching the electronic databases Medline, EMBASE, and Google Scholar with the following keywords: Alzheimer's disease (AD), dementia, continuous positive airway pressure (CPAP), mild cognitive impairment (MCI), and obstructive sleep apnea syndrome (OSA). A few filters were used for the literature search: (1) language in English; (2) human subject studies; (3) published on or after 01/01/1985; and (4) abstracts are available. The original search returned a total of 493 results. After removing duplicates and review articles, 146 full text articles were left for further analysis. After the abstracts were reviewed, 106 studies were excluded for different reasons by a panel of three reviewers as they were either irrelevant, on central sleep apnea, or non-classified sleep apnea. The current review has focused on the remaining 40 reports (Fig. 1).

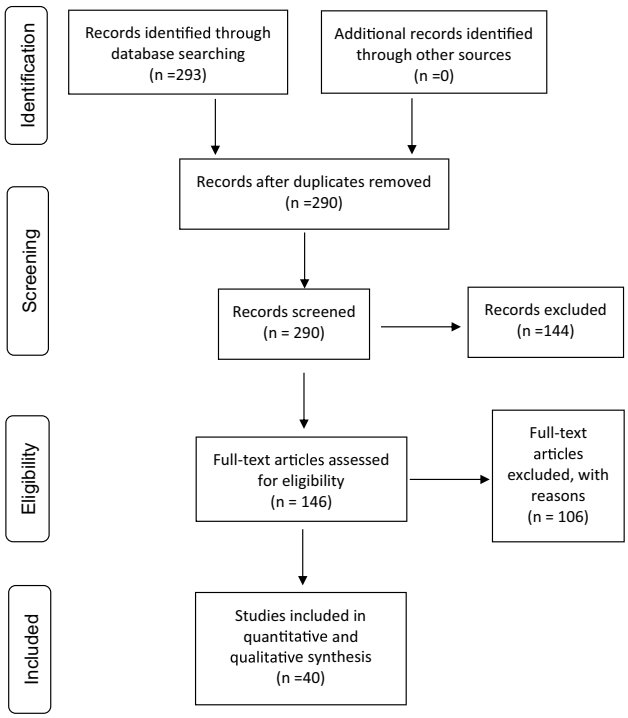

Fig. 1 A prisma flow diagram for literature search

Cognitive impairments associated with OSA

People with OSA have an increased risk of developing cognitive impairments compared to those without it [9]. Worse cognitive performance was seen in people with OSA than the controls in the following domains: attention [5, 10, 11], executive function [10, 12], intelligence [12], memory [12], and psychomotor speed [10, 12] (Table 1). In addition, alertness was noted to be impaired in patients with OSA [5]. As expected, attention and memory were impaired in those with severe OSA [13]. Patients with OSA also had a longer reaction time and poorer vigilance than the controls [14]. Moreover, impaired memory [15] and executive function [11, 15, 16] was shown to be associated with the severity of oxygen desaturation or severity of OSA. Nonetheless, no association was observed between OSA and measures of memory function, concentration and attention from a cross-sectional study with an elderly (79–97 years old) cohort [4]. Therefore, the effects of OSA on different cognitive functions need be further investigated, especially utilizing studies with longitudinal designs.

Respiratory disturbance during sleep was more often seen in elderly individuals with dementia, when compared to the controls [17]. OSA may aggravate cognitive impairments in people with dementia, and the cognitive dysfunction could be reversed in patients with AD through treatment toward sleep apnea [18]. Although AD and sleep apnea were reported to be two separate conditions [19], a significant positive correlation was also found between apnea index and severity of dementia for AD patients [20].

Table 1 Cognitive impairments seen in patients with OSA

Type of study	OSA (*n*)	Severity of OSA	Controls (*n*)	Cognitive changes in patients with OSA versus controls	References
Cohort study	31		10 (healthy)	Impaired attention and alertness	[5]
Cohort study	33	Newly diagnosed	17 (healthy)	Lower mean MMSE score	[7]
Cohort study	37	Moderate to severe	27 (healthy)	Worse attention, poorer executive function, and lower psychomotor speed	[10]
Cohort study	25	AHI $\geq 15\ h^{-1}$	15 (AHI $< 15\ h^{-1}$)	Worse memory, intelligence, and executive function	[12]
Cohort study	30	Severe	30	Impaired memory and attention	[13]
Cohort study	80	AHI $= 60 \pm 2\ h^{-1}$	80 (healthy)	Longer reaction time and poorer vigilance	[14]
Cohort study	16	Moderate to severe	14	Impaired memory and executive function	[15]
Cohort study	17		17 (healthy)	Impaired executive function	[16]

AHI apnea/hypopnea index, *MMSE* mini-mental status examination, *OSA* obstructive sleep apnea

Other factors for OSA-associated cognitive impairments

OSA is associated with cognitive deficits by interacting with the aging process [21]. For example, respiratory disturbance index of OSA was associated with the severity of cognitive dysfunction, and this association was seen only in patients who were younger than 80 years old [22]. Respiratory events negatively impacted memory function in older adults with an apolipoprotein epsilon 4 carrier status but not in those non-carriers [23]. Therefore, it is unclear on how genetic factors influence the relation between OSA and cognitive impairments. There are other factors that might interact with OSA to increase the risk of cognitive impairments. For example, OSA and short sleep duration were associated with all-cause dementia and AD; however, the associations were attenuated after the associated cardiovascular risk factors were adjusted [24]. Further, the extent of cerebrovascular impairment was shown to correlate with the severity of OSA [25]. The combined evidence suggests the overall cerebrovascular health is an important factor to consider when patients with OSA are evaluated for their cognitive performance.

OSA and AD pathological biomarkers

There are two classical AD pathological markers: amyloid plaques and neurofibrillary tangles. Amyloid plaques accumulate in the extracellular space, which is made up of different forms of β amyloid (Aβ) peptides including Aβ40 and Aβ42. By contrast, neurofibrillary tangles are intracellular accumulations of tau proteins. Patients with OSA had a lower Aβ42 from cerebrospinal fluid (CSF) and a higher Tau/Aβ42 ratio than the controls [12]. Significant correlations were found among CSF tau levels, sleep impairment, and CSF lactate levels in the OSA group [12]. Moreover, CSF Aβ42 levels were found to correlate with either memory impairment or nocturnal oxygen saturation parameters in patients with OSA [12]. Specifically, the OSA group had a higher Pittsburg compound B (Aβ plaque marker) deposition in the right posterior cingulate gyrus and right temporal cortex, when compared to the controls [26]. Similar to CSF Aβ42, CSF Aβ40 was decreased in patients with OSA compared to the controls [27]. Even in cognitively normal elderly people (55–90 years old), the severity of OSA was found to be associated with the annual rate of change of CSF Aβ42, as a measure of amyloid burden [28].

For serum biomarkers, OSA patients had significantly higher Aβ40, Aβ42 and total Aβ levels than the corresponding measures in the controls, and each biomarker positively correlated to the severity of OSA [29]. Compared to the controls, patients with OSA exhibited strikingly higher serum tau (P-181) levels, which positively correlated with serum levels of Aβ40, Aβ42 and total Aβ [29]. In conclusion, the existing evidence on AD pathological biomarkers supports OSA as a risk factor of cognitive impairments.

Cognitive performance improved with the CPAP treatment

Continuous positive airway pressure (CPAP) is the standard and effective treatment for patients with OSA [30]. The CPAP can significantly improve cognitive performance in patients with OSA [2]. For example, elderly patients with severe OSA who presented with cognitive impairments could benefit from CPAP treatment [31]. Improvements in executive functions, intelligence, and memory have been seen in patients with OSA receiving CPAP treatment [12]. In patients with severe OSA, CPAP therapy was beneficial on patients' occupational well-being and job productivity [32]. Interestingly, CPAP treatment may also delay cognitive deteriorations in patients with OSA [33]. However, there are some limitations with CPAP treatment. For example, CPAP is not indicated in patients with an apnea/hypopnea index (AHI) of ≥ 30 who have no subjective daytime sleepiness [34]. Some cognitive deficits including working memory, attention, executive function, and psychomotor speed were found to be resistant to CPAP treatment in patients with OSA [10]. For instance, immediate memory was the only cognitive function that had been improved with the CPAP therapy [13].

Duration of CPAP treatment is crucial

After patients with OSA received CPAP treatment for 12 months, executive function, memory and reactive time were significantly improved [2] (Table 2). Cognitive dysfunction in patients with OSA could be at least partially reversed using 6-month-long CPAP therapy [35]. For example, alertness and continuous attention were noted to be significantly improved after a 6-month course of CPAP treatment [5]. OSA patients were found to have most of their executive and learning disabilities normalized after using CPAP treatments for 4–6 months [16]. For those with OSA, even a 3-month course of CPAP treatment showed a significant improvement on MMSE scores [7], episodic and short-term memory, as well as executive function [31]. In patients with severe OSA, CPAP treatment for 3 months resulted in a significant improvement in cognitive functions related

Table 2 CPAP and its therapeutic effects on cognitive impairments

Type of study	OSA Severity	OSA + CPAP (*n*)	Controls (*n*)	CPAP duration	Therapeutic effects of CPAP on cognitive impairments	References
Cohort study		30	85	12 months	Improved executive function, memory, and reaction time	[2]
Cohort study		15	10 (healthy)	6 months	Improved attention	[5]
Cohort study	AHI ≥ 15 h^{-1}	10	15 (AHI < 15 h^{-1})	≥ 12 months	Improved performance at memory, intelligence, and executive function	[12]
Cohort study	Severe	30	30	4 months	Improved immediate memory	[13]
Cohort study	AHI = 60 ± 2 h^{-1}	80	80 (healthy)	12 months	Minor reaction time changes	[14]
Cohort study		10	17 (healthy)	4–6 months	Normalized executive function and learning disabilities but no effect on short-term memory impairments	[16]
Case study	Severe	20		12 months	Improved concentration and memory	[36]
RCT	AHI = 36.6 ± 5.1 h^{-1}	28	27 (36.4 ± 4.0 h^{-1})	1 month	Improved verbal episodic memory	[38]
RCT	AHI = 63.5 ± 7.8 h^{-1}	17	14 (AHI = 65.8 ± 8.2 h^{-1})	2 weeks	None	[39]
Cohort study	Severe	17	15 (healthy)	3 months and 12 months	Improved memory, attention, and executive function; reversed white matter changes with 12-month treatment	[40]

AHI apnea/hypopnea index, *CPAP* continuous positive airway pressure, *OSA* obstructive sleep apnea, *RCT* randomized controlled trial

to concentration and memory [36]. For AD patients with severe OSA (an AHI ≥ 30), CPAP treatment for 3 months was associated with a significantly slower cognitive decline than the control group (no CPAP treatment) during a follow-up of 3 years [37]. Although 1 month of CPAP treatment can lead to improved verbal episodic memory in patients with OSA [38], the therapeutic effects of CPAP could not be observed anymore when an even shorter duration (< 4 weeks) is used. For example, 2 weeks of CPAP or oxygen-supplementation treatment was insufficient to show beneficial cognitive effects [39]. A comparison of subjects randomized to 3 weeks of therapeutic versus placebo CPAP had no significant improvements in cognition for patients with AD and OSA [18]. Therefore, the duration of CPAP therapy is a crucial factor for improving the cognitive performance/functions in patients with OSA. It is also worthy to note that some domains of cognitive function might not be as sensitive to CPAP treatment as others [14].

By directly addressing the possible underlying causes for the pathological changes seen in patients with OSA including hypoxia, hypercapnia, and poor sleep quality, CPAP has proven to be effective in improving the associated impaired cognitive functions. CPAP treatment has been shown to increase the connectivity of the default mode network and attenuate cortical thinning [31]. More specifically, an increase in the connectivity was seen in the right middle frontal gyrus after 3 months of CPAP treatment [31]. Further, 12 months of CPAP treatment almost completely reversed white matter abnormalities [40]. More interestingly, significant improvements involving attention, executive function, and memory actually paralleled white matter changes for the therapeutic effects of CPAP [40].

In conclusion, patients with OSA are more likely to develop cognitive impairments. A minimal therapeutic duration of 4 weeks is needed if CPAP was used to treat patients with OSA for associated cognitive impairments or deficits. The underlying mechanism for cognitive impairments seen in patients with OSA need be investigated further for making more specific therapeutic treatments. It is also important for practitioners to properly educate their patients about CPAP

therapy and emphasize its potential benefits on preventive measures against cognitive deterioration processes. Lastly, patients that initially present with signs of cognitive deficits would likely benefit from a screening sleep test, possibly more from an instrumental study though it might not be available in a lot of countries.

Author contributions All the authors contributed to data analysis and interpretation, draft and critical revision of the manuscript for important intellectual content.

Compliance with ethical standards

Conflicts of interest None.

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