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EC NEUROLOGY
Mini Review

Sleep Disorders and Cognitive Decline

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Received: August 10, 2017; **Published:** September 22, 2017

Abstract

Sleep and sleep related disorders are involved in dementia pathogenesis. In particular, sleep quality, more than the sleep amount, plays a fundamental role in cognitive impairment.

Mounting evidence implicates disturbed sleep or lack of sleep as one of the risk factors for Alzheimer's disease (AD), but the extent of the risk is still uncertain. As sleep problems are of a growing concern in the population, these findings are of interest for potential prevention of AD.

Sleep related breathing disorders and insomnia are the main causes of neurodegenerative disorders and vice-versa older age and neurodegenerative disorder may induce alterations of circadian rhythm. A lot of studies demonstrated that sleep disorders treatment improves cognitive performances.

Keywords: *Alzheimer Disease; Obstructive Sleep Apnea; Sleep Disorders; Circadian Rhythm Alterations*

Abbreviations

AD: Alzheimer's Disease; CPAP: Continuous Positive Airway Pressure; MCI: Mild Cognitive Impairment; OSA: Obstructive Sleep Apnea; PAP: Positive Airway Pressure; REM: Rapid Eye Movement; SCN: Suprachiasmatic Nucleus; Aβ: Amyloid Beta; BLT: Bright Light Therapy

Introduction

Sleep is a complex phenomenon that is rooted in neurologic function. The central sleep and circadian regulation centers are located deep within the brain and include the anterior hypothalamus, the reticular activating system, the suprachiasmatic nucleus (SCN), and the pineal gland. It is generally understood that sleep is governed by an interaction of circadian and homeostatic processes. The homeostatic process of sleep, referred as the "sleep drive", is the fact that sleep tendency increases as getting further away from the last sleep period and decreases the longer that sleep time is accumulated. The circadian timing system underlies the temporal organization of most neurobehavioral and physiologic processes, including body temperature, melatonin production and the 24-hour sleep-wake cycle [1]. The SCN is a group of neurons located at the base of the hypothalamus, just above the optic chiasm, where the optic nerves meet and cross. The SCN is highly sensitive to light. Light entering the retina travels along the optic nerves to the SCN, which triggers the pineal gland to stop producing the melatonin. Melatonin is a neurohormone that is essential in sleep, in thermoregulation and in controlling the blood pressure; its production is highest during the night, when light stimuli are minimal or absent. The reticular activating system located within the midbrain has less to do with the actual sleeping process and more to do with maintaining a state of arousal and awareness of one's environment. Disruptions anywhere along this pathway can cause disruptions in the circadian rhythm and, ultimately, sleep disturbances [2].

Sleep is an active process where in certain brain structures are activated at certain stages of the sleep cycle and deactivated at others [3]. Normal sleep consists of four phases of non–rapid eye movement (non-REM) sleep and one phase of REM sleep, each of which has

distinct electroencephalogram characteristics. The brain cycles through these phases approximately every 90 minutes, with four or five cycles per night. Stage 1 is the transition between wakefulness and sleep; individuals in stage 1 sleep are easily awakened and may not even know they had been asleep. Stage 2 involves a loss of conscious awareness and the appearance of the characteristic "sleep spindles" and "K complexes" in the electroencephalogram, as well as a decrease in heart and respiratory rates and body temperature. In stages 3 and 4, also known as deep sleep, brain waves slowly and arousal is more difficult. If arousal occurs the individual is groggy and disoriented. REM sleep is the final stage and the stage during which dreaming occurs. During REM sleep, a person's eyes move rapidly, the heart and respiratory rates increase and muscle twitching often occurs. As part of the normal aging process, stages 3 and 4 and REM sleep decrease significantly, which may account for some of the frequent nighttime awakenings, difficulty returning to sleep, and daytime fatigue commonly reported by older adults.

Sleep disturbances are common in older adults with dementia [4]. Their etiology is complex involving multiple factors such as neurodegenerative changes in the brain, patient's environment, medical or psychiatric morbidity and medications used to treat chronic illnesses and dementia-related behavioral symptoms. There is also increasing evidence that sleep disturbances play an important role in mild cognitive impairment (MCI) [5]. An accurate diagnosis of the neurologic disorder and comprehensive review of current medications are important for understanding possible causes of patient sleep changes and for developing a plan of care, to improve nighttime sleep and daytime wakefulness and reduce caregiver burden.

Cross-sectional studies suggest that approximately 25% to 35% of individuals with AD have problems sleeping [6]. Sleep disturbances in AD are believed to be a result of a progressive deterioration and decrease in the number of neurons in the SCN, which cause fluctuations in neurohormones that are critical in the homeostatic maintenance of the circadian rhythm [7]. Common symptoms include nighttime sleep fragmentation, increased sleep latency, decreased slow-wave sleep and increased daytime napping.

Research made to determine if impaired sleep patterns appear years before AD diagnosis suggested that sleep disruptions are evident years before diagnosis of AD [8] and associations linking habitual sleep duration to significant decline of global cognitive function and subsequent risk for developing cognitive impairment including dementia are found in healthy older women [9].

Sleep Disorder and AD Prevention

Sleep disorders are among the most common clinical problems and possess a significant concern for the geriatric population. More importantly, about 40% of older adults have sleep-related complaints.

Recently, increasing evidence has indicated that disturbed sleep may not only serve as the consequence of brain atrophy, but also contribute to the pathogenesis of dementia and, therefore, significantly increase dementia risk. Since the current therapeutic interventions lack efficacies to prevent, delay or reverse the pathological progress of dementia, a better understanding of underlying mechanisms by which sleep disorders interact with the pathogenesis of dementia will provide possible targets for the prevention and treatment of dementia [10].

As the older segment of our population grows, cognitive decline and dementia will increase in prevalence with Alzheimer's disease (AD) as the cause in most cases. The identification of modifiable risk factors for dementia will be only means of reducing dementia prevalence or delaying its onset. Furthermore, it is likely that eventual treatments for AD, when available, will depend on the ability to identify individuals at greatest risk for developing AD. Sleep disturbances are common in later life - roughly half of older adults experience regular insomnia [11] and about as many have some degree of sleep-disordered breathing (SDB) [12] - and accumulating evidence suggests they may contribute to cognitive decline, at least in part, by promoting the development of AD pathology [13]. Because they are treatable, sleep disturbances are an important potential target for ongoing study in AD prevention. Moreover, understanding the mechanisms underlying an effect of sleep on subsequent cognitive decline and AD would allow for better identification of opportunities and optimal timing for treatment of sleep disorders, and ultimately perhaps, AD prevention [14].

OSAS and AD

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway [15]. The prevalence of this disorder is strictly dependent on its gravity. At ≥ 15 events/h apnea-hypopnea index (AHI), it ranges from 6 to 17% in the general population, with higher rates in men and increasing with age. The hypoxia induced by OSA severely affects the structure and function of blood vessels, culminating in morbidity and mortality. Its negative impact influences also cognitive functioning.

Recent papers showed the relationship between OSA and some neurological disorders, such as neurodegenerative diseases, stroke, epilepsy, and headache. OSA may accelerate the onset of mild cognitive impairment and Alzheimer's disease (AD) and might also represent an independent risk factor for Parkinson's disease (PD). OSA is also frequent in multisystem atrophy.

In the early stages of AD, continuous positive airway pressure (CPAP) treatment for OSAs might slow down the progression of the disease, thus highlighting the potential importance of OSA screening and a timely intervention in these patients. Moreover, CPAP is effective in reducing daytime sleepiness in PD.

OSA may induce seizures by means of sleep disruption and deprivation, as well as cerebral hypoxemia with consequent oxidative stress. It has been demonstrated that CPAP treatment is efficacious in controlling epileptic seizures.

OSA can represent a risk factor for stroke and death, mainly related to the endothelial dysfunction, with the formation of atherosclerosis caused by hypoxia through oxidative stress [16]. Persons with cognitive impairment have higher sleepiness scores and a more disrupted sleep, that may be related to the sleep-disordered breathing and intermittent hypoxia [17].

In mouse models of AD, chronic sleep deprivation augmented amyloid plaque formation, while increasing sleep with an orexin receptor antagonist reduced amyloid plaques. Moreover, *in vivo* studies demonstrated that the cerebral interstitial space increases by more than 60% during sleep, resulting in efficient convective clearance of beta-amyloid (Aβ) and other toxic compounds involved in the AD pathogenesis [18].

A good sleep consolidation seems to attenuate the effect of APOE genotype on incident of AD and development of neurofibrillary tangle pathology. Interventions to obtain a better sleep consolidation should be relevant to reduce the risk of AD in APOE ε4+ individuals [19].

An association between sleep-disordered breathing (SDB) and cerebrospinal fluid AD biomarkers has been showing cognitively normal older individuals and, consequently, therapies for SDB such as continuous positive airway pressure (CPAP) ventilations could delay the onset of MCI or dementia [20].

Circadian Rhythm Alteration and AD

Sleep disorder and Circadian Rhythm alterations are also frequent in every Alzheimer disease (AD) stage. Sleep and Amyloid beta (Aβ) deposition (an important molecule involved in AD pathogenesis) are strong related, as suggested by recent studies *in vivo* [21].

Amyloid beta accumulation negatively affects sleep-wake behaviors brain regions, poor sleep may increase risk of Amyloid Beta aggregation. For instance, obstructive sleep apnea may increase Amyloid beta deposition through effects on hypoxic stress and inflammation or by increasing Amyloid beta levels via increased wakefulness. Cognitive and physical activity levels have a bidirectional relationship with both sleep-wake patterns and AD and thereby may intensify the feedback loop between poor sleep and AD.

Fragmented sleep promotes Amyloid deposition, OSA favors fragmented sleep and hypoxic /inflammatory stress: OSA with APOE e4 increases susceptibility to AD.

On one side fragmented sleep also favors decreasing cognitive and physical activity, on the other side promotes neuronal activity, excessive Amyloid beta release with Amyloid deposition and injury to sleep/wake brain regions (Figure 1).

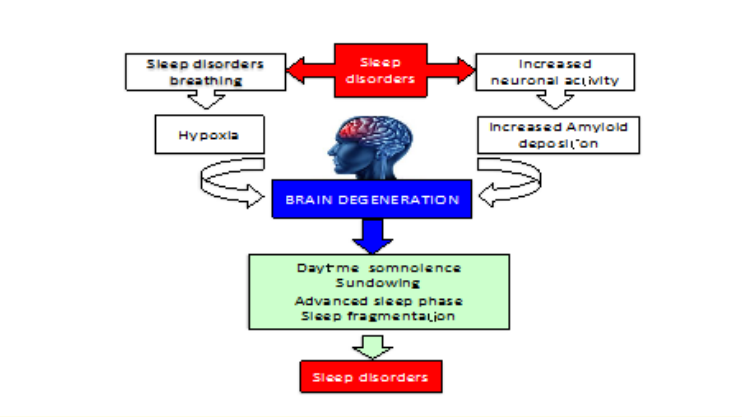

Figure 1: *Brain degeneration facilitation by sleep disorders.*

Pharmacological Treatment of Sleep Disorders in AD

There are three important causes to treat sleep disorders in AD people.

Sleep disturbances lead to worsening of memory and cognitive performances [22]; sleep behavioral disturbances such as wandering, day/night confusion, getting up repeatedly during the night, hallucinations are the mean cause of persons institutionalization [23]; there is increasing evidence of the relationship between sleep disturbances and AD [24].

Behavioral measures, bright light therapy (BLT), melatonin, and other drugs are preferred in these people, but more studies are needed because the evidence of efficacy is not enough in spite of the multiple treatments used [25].

Future directions for treatment are the establishment of BLT protocols and the development of drugs with new mechanisms of action, especially

1. Hypocretin receptor antagonists,
2. Melatonin receptor agonists,
3. Molecules that modulate the circadian clock.

The orexin receptor antagonists include the single orexin receptor antagonists and the dual orexin receptor antagonists (DORAs). Suvorexant is the first orexin receptor antagonist (DORA) that has been shown to be effective in treating insomnia. It appears to be suitable as a chronic therapy for insomnia given the minimal risk of physical dependence [26-27].

Ramelteon is a melatonin receptor agonist with high affinity for the melatonin receptors MT1 and MT2 used to treat insomnia [28]. It is well tolerated and appears to lack significant adverse effects, leading to reductions in sleep onset latency and increases in total sleep time. Agomelatine is a melatonin MT1 and MT2 receptor agonist and a weak 5-HT2C antagonist [29] that has been approved for the treatment of depression [30].

Actually several researchers are focusing on the identification of molecules and receptors that can alter the expression of clock genes [31]. Although such research is in a preliminary phase, these molecules could be the target to develop drugs that modulate the circadian clock.

Sleep Disorders Treatment for Preventing Alzheimer Disease Progression

An Italian multicenter study underlines the possibility that the sustained, long-term use of continuous positive airway pressure (CPAP) therapy can improve sleep and delay cognitive decline in persons with Mild Cognitive Impairment (MCI) or Alzheimer's disease dementia (AD) suffering from Obstructive Sleep Apnea(OSA) [32].

Starting from these considerations, the Italian SINDEM Sleep study group planned a multicenter longitudinal intervention study on the relevance of detecting and treating OSA in this population. The study assesses the change of cognitive decline in MCI and AD/OSA persons using CPAP (case group) compared to MCI and AD/OSA persons who do not choose ventilation or result unable to use CPAP and/or do not have a reliable caregiver (control group). In addition, the study investigates the effect of CPAP on quantity, quality and circadian rhythms of sleep.

A further study showed that the use of CPAP slows the deterioration of cognition, sleep and mood in persons with Alzheimer's disease and obstructive sleep apnea [33].

At the baseline, OSA people had a significant impairment, compared to controls, in tests of sustained attention, visuospatial learning, executive function, motor performance, and constructional abilities. After 15-days under CPAP treatment attentive, visuospatial learning, and motor performances returned to normal levels. At 4-months CPAP treatment did not result in any further improvement in cognitive tests. Performance on tests evaluating executive functions and constructional abilities was not affected by short-and long-term treatment with CPAP [34].

Conclusions

Sleep disorders are frequent and tend to occur almost invariably in association in individuals with cognitive decline: they have to be always carefully investigated using an in-depth sleep history, a physical examination and questionnaires and scales, whenever possible validated with acceptable and definite values of sensitivity and specificity, directly filled by the subjects with the support of the caregiver. Hypersomnolence should be always addressed in people with MCI, dementia, and in particular in nursing home residents. Regarding treatments, non-pharmacologic strategies are recommended as the most appropriate starting treatment. In recent years, increasing evidence for the role of melatonin and hypocretins in the cause and mechanism of these disturbances has been found. There is a bidirectional relationship between these disorders and AD pathophysiology, a fact that raises the possibility of modifying the course of AD itself by treating the sleep disorders. Pharmacological therapy can be recommended for short-term treatments. Any pharmacological therapy should be regular whenever possible, insomnia should be categorized in starting and maintaining insomnia, considering other sleep disturbances in comorbidity: in maintaining insomnia, in particular, the presence of SDB and/or parasomnias should be carefully investigated. To reduce or eliminate medications that may contribute to sleep apnea is recommended. Regarding excessive daily sleepiness (EDS) and circadian sleep rhythm disorder (CSRD), authors recommend multimodal approaches as combining bright light exposure during the day, decreasing light exposure at night, physical and social activity, regular schedules of wake and bedtime and melatonin administration. For the treatment of all kinds of SDB (OSA, Central sleep apnea, Cheyne Stokes breathing, etc.), persons should be referred to a sleep specialist and/or sleep center to define diagnosis and treatments. Even in people with cognitive decline, CPAP is recommended as the first-line of treatment independently of the age and cognitive impairment [35-36].

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Volume 8 Issue 2 September 2017