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Review Article

Sleep Disorders in Alzheimer's Disease

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Abstract

Alzheimer's disease is the leading cause of dementia worldwide. Patients typically exhibit cognitive impairment, memory loss, diminished social and occupational functioning, as well as language and motor disorders. Alzheimer's disease is characterized by the abnormal accumulation of amyloid-β (Aβ) and phosphorylated tau in the brain. These pathological changes not only disrupt neuronal function and lead to cognitive deficits, but also interfere with sleep regulation, resulting in sleep disorders. Such disturbances can diminish nighttime sleep quality and contribute to daytime functional impairments, further exacerbating cognitive decline. Therefore, exploring the interplay between cognitive impairment, Alzheimer's disease, and sleep disorders is crucial for enhancing the quality of life of Alzheimer's patients. This review summarizes current literature on the interconnections among Alzheimer's disease, cognitive impairment, and sleep disorders. Sleep disturbances are prevalent in Alzheimer's patients and can also occur in those with amnestic mild cognitive impairment, which often precedes Alzheimer's onset. Such sleep disorders may promote and accelerate the accumulation of amyloid-β and tau proteins [1-3]. Furthermore, Alzheimer's patients may be more vulnerable to sleep disturbances, creating a potential vicious cycle. Further investigation into these relationships may provide valuable insights for the treatment or prevention of Alzheimer's disease.

ABBREVIATIONS

AD: Alzheimer's Disease; MCI: Mild Cognitive Impairment; Aβ-Amyloid-β; REM: Rapid Eye Movement; NREM: Non-rapid Eye Movement; SWS: Slow-wave Sleep; EEG: Electroencephalography; SCD: Subjective Cognitive Decline; CSF: Cerebrospinal Fluid; aMCI : amnestic Mild Cognitive Impairment; PBN: Parabrachial Nucleus

INTRODUCTION

Alzheimer's Disease (AD) is currently recognized as the leading neurodegenerative disorder, primarily characterized by memory decline, cognitive impairment, and psychiatric abnormalities. Recent studies have suggested that sleep disturbances may also be symptoms of AD [4]. For instance, some research indicates that AD patients often experience significant disruptions in circadian rhythms and fragmented sleep, which correlate with damage to brain regions responsible for sleep regulation [5]. However, the role of sleep disorders in the pathogenesis of AD remains unclear. Some studies propose that sleep disturbances may exacerbate cognitive symptoms by interfering with memory consolidation processes reliant on sleep [6]. Sleep is crucial for physical recovery, energy replenishment, and mental health, playing a vital role in both memory consolidation and the clearance of waste from the brain. The link between sleep disturbances and AD is an active area of research. This review will examine the existing evidence connecting AD with sleep disorders.

Alzheimer's Disease and Cognitive Disorders

Alzheimer's disease is a common neurodegenerative disorder characterized by the gradual decline of cognitive function. Cognitive impairment is a core feature of AD referring to the decline in cognitive abilities such as memory, attention, and executive function due to various causes. This impairment not only affects the quality of life of patients but also places a heavy burden on families and society. Memory loss is one of the most common early symptoms of AD. Patients often experience short-term memory decline, such as repeatedly asking the same questions or forgetting recent events. As the disease progresses, long-term memory may also be affected, leading patients to forget significant life events or the names of loved ones [7]. Alzheimer's disease is the most prevalent form of dementia, with pathological characteristics that include amyloid-β plaques and neurofibrillary tangles. Older adults are the primary population affected by

AD and are also more susceptible to cognitive impairment. As age increases, cognitive abilities in older adults can range from normal cognition to Subjective Cognitive Decline (SCD), followed by Mild Cognitive Impairment (MCI), and eventually dementia. MCI is a transitional state between normal aging and dementia, which primarily manifests as Alzheimer's disease [8].

Alzheimer's Disease and Sleep Disorders

Sleep is beneficial for cognitive function and the central nervous system, enhancing learning and memory in humans. However, sleep quality tends to decline with age. Sleep disorders are common among the elderly, including healthy older adults. Recent studies have reported that patients with Huntington's disease, epilepsy, and Alzheimer's Disease are more likely to experience sleep disturbances. In AD patients, sleep disorders primarily manifest as insomnia, sleep fragmentation, sleep-related breathing disorders, and Restless Legs Syndrome (RLS) [9]. Animal studies have also shown that the accumulation of Aβ in rodent models of AD leads to increased sleep fragmentation [5-10]. Further clinical investigations have found that AD is selectively associated with the loss of < 1Hz oscillations in Non-Rapid Eye Movement (NREM) sleep [11]. Besides Aβ, tau protein-a key player in the pathogenesis of AD-has also been linked to the occurrence of sleep disturbances. Studies in rodents have demonstrated that tau in the brain is associated with disruptions in NREM oscillations [12]. In human studies, it has been found that the levels of tau in cerebrospinal fluid are correlated with reduced slow-wave sleep in AD patients [13]. Additionally, tau deposits have been observed in other brain regions that regulate sleep, such as the locus coeruleus and the basal forebrain, and similar phenomena have even been noted in normal aging individuals [14].

Electroencephalography (EEG) is an important tool for detecting and assessing sleep quality, and it can be used to monitor sleep changes in AD patients. Abnormal EEGs primarily occur during the NREM stage, which is characterized by Slow-Wave Sleep (SWS), sleep spindles, K-complexes, and slow wave activity. These features are altered in Mild Cognitive Impairment (MCI) and AD [15]. Sleep EEG has been proposed as an early predictor of AD, as these changes occur prior to the clinical onset of the disease, and different stages may exhibit distinct changes. For instance, in APPswe/PS1ΔE9 transgenic AD mice, compared to age-matched wild-type mice, a 4-month-old mouse (with no detectable Aβ or tau accumulation in the brain) showed a 9.1% reduction in waking time and a 73.1% increase in NREM sleep in a 12-hour dark environment, while in a 12-hour light environment, waking time increased by 22.5% and NREM sleep decreased by 18.2% [16]. Moreover, there are notable differences in EEG changes observed in 6-month-old AD mice (at which point Aβ accumulation and evident tau phosphorylation can be found in the cortex and hippocampus) [17]. Specifically, in a 12-hour dark environment, 6-month-old AD mice exhibited an 8.1% reduction in waking time and a 46.7% increase in NREM sleep; in a 12-hour light environment, waking time increased by 21.2% and NREM sleep decreased by 18.2%. It was also found that the power of theta and delta waves during NREM sleep was generally lower in AD mice compared to wild-type mice. In other studies, 8-10 month old AD mice and 12 month old Tg2576 mice displayed stage-dependent reductions in theta and delta power, with power spectra shifting to higher frequencies compared to wild-type mice, resulting in a significant decrease in delta power during NREM sleep [18]. The reduction in delta wave power during NREM sleep may serve as a sensitive and modifiable indicator for assessing sleep disruptions in AD. Further research on the relationship between AD and sleep disorders is crucial to elucidate the significance of these early EEG changes in the development of AD and the underlying molecular mechanisms.

Cognitive Disorders and Sleep Disorders

Cognitive impairment refers to a significant decline in cognitive functions such as thinking, memory, attention, and learning abilities, commonly observed in the elderly population, particularly in neurodegenerative diseases like AD Sleep duration and quality are crucial for cognitive impairment in older adults [19,20]. One study monitored sleep duration and quality in 78 participants aged over 60 using activity tracking, finding that participants with total sleep time of less than 5 hours exhibited significantly lower accuracy on the n-back test compared to those with total sleep time exceeding 7 hours. Additionally, participants with sleep efficiency < 85% showed a marked decrease in accuracy on the 0- and 1-back tests compared to those with sleep efficiency ≥ 85% [21].

Regarding the impact of cognitive impairment on sleep, numerous studies have provided valuable insights. Research indicates that individuals with cognitive impairment generally experience a decline in sleep quality, characterized by frequent awakenings at night and excessive daytime sleepiness [22]. Another study highlighted that the emotional state of cognitively impaired patients significantly affects their sleep quality, with symptoms of depression and anxiety exacerbating sleep problems [18-23]. Furthermore, pharmacological treatments can also influence sleep in cognitively impaired patients, as certain antidepressants have been shown to improve sleep quality in this population.

Potential Mechanisms for Sleep Disorders in Alzheimer's Disease

Currently, numerous studies have investigated the mechanisms underlying sleep disorders in AD. Research has identified the orexinergic system involvement in the regulation of the sleep-wake cycle, with orexin (also known as hypocretin) located in the lateral hypothalamus playing a central and critical role in this system. Analysis of the Cerebrospinal Fluid (CSF) of patients with aMCI (amnestic mild cognitive impairment) reveals abnormally elevated levels of orexin [24]. Dysregulation of the orexin system is also associated with sleep disorders and the pathology of AD. A comparative study involving 20 drug-naïve patients with MCI due to AD and 26 age- and sex-matched controls showed increased orexin levels in the CSF of AD-related

MCI patients [25]. Additionally, AD patients with comorbid psychiatric disorders exhibited more fragmented sleep, alongside higher CSF orexin levels [26].

Dysregulation of the glutamatergic and GABAergic systems is also believed to be closely linked to the progression of AD. Studies indicate that GABAergic neurons in the perifornical area and the Parabrachial Nucleus (PBN) can activate and maintain sleep. Meanwhile, glutamatergic neurons in the PBN are thought to play a significant role in wakefulness [27,28]. Slow-wave oscillations are a prominent feature during Non-Rapid Eye Movement (NREM) sleep and play an essential role in memory consolidation; however, these oscillations exhibit abnormalities in AD patients. This dysfunction can potentially be improved through GABA supplementation, suggesting that neurotransmitter replacement therapy may offer a means to address sleep disorders and restore sleep function impaired by AD [29].

Alzheimer's disease patients often experience disruptions in their sleep-wake cycles, which are typically regulated by circadian rhythm mechanisms [30]. Variations in circadian rhythm among AD patients are associated with sleep disorders, such as sleep fragmentation, increased sleep duration, and reduced daytime activity [31,32]. Specific changes in sleep primarily manifest as an imbalance between NREM and REM sleep [33]. Dysregulation of circadian rhythms can lead to sleep disorders and alter the brain regions that control circadian rhythms, resulting in pathological changes associated with AD. Additionally, circadian rhythm disruptions can enhance the cleavage of Amyloid Precursor Protein (APP), leading to the production of Aβ [34]. There exists a bidirectional relationship between sleep disorders and Aβ, where sleep disturbances promote the production and accumulation of Aβ [35-37], while Aβ accumulation may contribute to sleep disorders. Thus, Aβ, as one of the pathological markers of AD, is closely related to sleep disorders (Table 1).

Table 1: Key studies and findings that were referenced throughout this article.

Study	Sample Size	Key Finding(s)
Liguori, et al. 2016	n = 46	Increased levels of orexin are associated with REM sleep interruption and sleep fragmentation in patients with Mild Cognitive Impairment (MCI).
Liguori, et al. 2018	n = 42	AD patients who have Neuropsychiatric Symptoms (NPS) experience more fragmented sleep and exhibit higher levels of orexin.
Shin, et al. 2014	n = 117	AD patients often experience prolonged sleep duration, extended sleep latency, and low sleep efficiency, which are associated with cognitive impairment.
Lim, et al. 2013	n = 737	In older adults, sleep fragmentation is associated with an increased incidence of AD and a more rapid decline in cognitive function.
Chen, et al. 2018	n = 46	Chronic sleep disturbances may lead to dysregulation of Aβmetabolism in the brain, thereby increasing the risk of developing AD.
Manousakis, et al. 2018	n = 25	Circadian rhythm disturbances are evident in both MCI and AD. Intervening in circadian rhythms may serve as a potential therapeutic tool for cognitive decline.
Ju, et al. 2017	n = 17	Disruption of slow-wave sleep can lead to an increase in cerebrospinal fluid Aβlevels.
Casagrand, et al. 2017	n = 71	The frequency and severity of sleep disorders may be associated with the development of cognitive impairment.

DISCUSSION AND CONCLUSION

Sleep disorders are frequently observed in AD and severely affect the quality of life of those affected. Multiple studies indicate that these sleep disturbances can exacerbate the condition of patients with MCI, potentially leading to the progression to AD. Furthermore, sleep disorders may contribute to the accumulation of Aβ and tau, which result in memory and cognitive decline, further exacerbating AD symptoms. This review primarily explores the relationship among AD, cognitive impairment, and sleep disorders, while also examining the potential mechanisms underlying these sleep disturbances. Understanding these interconnections may provide valuable insights for the early prediction and treatment of AD.

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