The casual relationship between AD and sleep disorders

Xinyi Wang 1,*,†, Donglai Wu 2,†

1 Tianjin Yaohua High School, Tianjin, 300000, China
2 Wuhan Britain China School, Wuhan, Hubei 430030, China
* Corresponding Author Email: dblake6@une.edu
† These authors contributed equally.

Abstract. As people get older, organs inside our bodies are not as strong as before. Besides the illness from their body, many of the elders are worrying about another torture, Alzheimer’s disease (AD). For the old people who are suffering from AD, their brains cannot work as usual as before and most times, they cannot sleep as usual. Sleep disorder, which is a cause of Alzheimer's disease, is common among those patients who suffer from AD. This article analyzes the origins, whether other factors first triggered the loop, as well as the interaction between sleep disorders and AD forms a closed loop in which they interact and contribute to each other and list the pharmacological and non-pharmacological treatments for AD and sleep disorders, respectively.

Keywords: Alzheimer’s disease (AD), Sleep disorder, AD treatment.

1. Introduction

AD is a brain neurodegenerative infection that affects most persons with dementia around the world. Patients with the Alzheimer's disease have symptoms such as the ability to think and remember, no emotional or cognitive awareness, and are frequently followed by consequences such as neuritis and sleep disorders. Alzheimer's disease primarily affects middle-aged and older people. Patients' and their family’s quality of life at a later age is severely harmed by their inability to care for themselves. There is no doubt that AD is putting pressure on society, and that the severity of AD's effects will rapidly increase if no positive action is taken to intervene [1]. With the economic growth of some countries and the resulting increase in aging, there is no doubt that AD is putting pressure on society and that the severity of AD's effects will rapidly increase if no positive action is taken to intervene.

The main pathological features of Alzheimer's disease, which directly lead to irreversible cognitive impairment in AD patients, are beta-amyloid deposits, abnormal phosphorylation of tau proteins, dramatic reduction in neuronal numbers, and fibrous tangles in the renal meridians, according to many studies. Drugs that improve the cognitive and organic mechanisms of Alzheimer's patients have been discovered, but scientists have yet to discover the true intricate causes or risk factors that trigger AD beyond genetic and environmental factors, age, and other factors, nor have they discovered a method or specific drug that can reverse AD. Insomnia, excessive daytime sleepiness, sleep apnea, and sundowning syndrome are examples of sleep disorders produced by a lot of sleep rhythm disturbances that can have a substantial impact on the central nervous system. It directly affects the quality of sleep and activates behaviors that happen amid rest and is sometimes associated with numerous psychiatric and psychological disorders, providing health risks. Sleep difficulties are common among adolescents, middle-aged, and more seasoned grown-ups due to the increased stress today. In addition, rest unsettling influences are common among people with AD and are more likely to produce changes in sleep quality and structure in the elderly population, which is undoubtedly no less torturous for people with AD [2]. At the same time, studies have shown a high association between sleep and neurodegenerative disorders including AD, Parkinson's disease and epilepsy [3]. As the existing research is scattered and disorganized, a clear structure is needed to provide a clear overview for future scholars.

Previous studies have included theories that sleep disorders increase the risk of developing AD, and that people with AD do have symptoms of sleep disorders, which suggest some interaction between the two diseases. Knowing the internal relationship between AD and sleep disorders
can offer assistance us superior get it the pathology of AD and sleep disorders, better understand the nerves, learn more about them and develop the number of more effective treatments for them. There have been many scientific theories about the co-morbidities between the two, and in the 1970s and 1980s, attention was drawn to the sleep of people with dementia, and their sleep structure and other physiological characteristics were studied using polysomnography as a control variable. 1980 saw the beginning of the understanding of REM sleep behavior disorders. However, it is still unclear what causes the disorders or whether the two contribute to each other. At first, it was thought that both AD and sleep disorders were co-existing geriatric conditions due to aging, but in recent years many studies have also shown that the two may be mutually reinforcing. As a result, many animal models have been developed to replace humans with studies to explain the effect of sleep disorders on cognitive impairment in people.

This article concluded the interactions between sleep disorders and AD form a closed loop in which they interact and reinforce each other. Although research into the relationship between AD sleep disorders is still in its early stages of advancement, the field has accumulated a considerable body of scholarship suggesting that the relationship has complex multidimensional implications, but not many studies have provided a very clear overview of the causes of both. However, a comprehensive audit of the important writing would be especially supportive in synthesizing the most research insights and uncovering the most inquire about patterns within the field. Therefore, this literature is serious to reply the taking after inquiring about questions: what causes sleep disturbance, and how do these factors contribute to AD? What causes AD and how do these factors contribute to sleep disorders? In this article, a point-by-point approach was used to summarize the possible causes of AD and sleep disorders, whether other factors trigger the cycle in the first place, and discuss treatment options for AD in different sections.

2. Sleep Disorder Leads To AD

It is proved that there are relationships between sleep disorder and Alzheimer’s disease and normally this is divided into two procedures. Firstly, sleep disorders are formed for some reason then the products of sleep disorders will finally result in AD in elders. Alzheimer is credited with the primary portrayal of the foremost characteristic neurotic brain change—neurofibrillary tangles (NFT).

2.1. Reasons leading to sleep disorder

In clinic research, many reasons are claimed that will lead to sleep disorders. Normally, sleep is divided into two stages, the REM stage and the NREM stage. The NREM stage can be advanced and partitioned into N1, N2, and N3 three stages [2]. N1 stage is the move arrange from alertness to rest; N2 is the light rest organize; N3 is the profound rest arrange, which is the shortest part of the sleep but also the most important part. Most kinds of sleep disorders would destruct this balance by increasing the possibility of wakefulness or shortening the time of the N3 stage, lowering the quality of sleep. Rest clutters can be classified into six categories, concurring to the Universal Classification of Rest Clutters, third version (ICSD-3), which include insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders (CRSWDs), parasomnias, and sleep-related development disorders [4]. In the “Circadian Beat Disarranges Workshop”, the symptom is irregular sleeping time, which affects 3 million Americans [5], and is mostly caused by irregular sleeping time. Insomnia is also a very common sleep disease, which is caused by many kinds of factors such as depression, anxiety, obesity, and cancer, the symptom is having difficulties falling asleep and waking up earlier [6]. According to research, type 2 diabetes is also proved related to sleep disorder, as many type 2 diabetes patients are observed suffering from different forms of sleep disorder, which hugely affects their living standard [4].
2.2. How to sleep disorder leads to AD

There are two key factors that lead to Alzheimer’s disease, one is Aβ, and another is tau protein. Amyloid beta is the metabolites of the cells in the brain during wakefulness. During sleep, the convective flow of interstitial fluid helps to remove the amyloid beta from the extracellular space. Firstly, Alzheimer’s disease is caused by the damage to central nervous system and dysfunction of the nerve system. Amyloid beta is very common in the central nervous system; however, the pathological accumulation is considered the main reason for damaging neurons, which leads to Alzheimer’s disease [3]. According to the amyloid cascade speculation, there is a fundamental defect in the handling of the amyloid forerunner protein (APP) that leads to an abundance of the 4 kD A part. This part shapes a -creased sheet structure spontaneously. The 4kD part is destructive to neurons and neural connections in two shapes: as an early solvent monomeric, dimeric, or oligomeric shape, or as an totaled statement known as the decrepit or hypochondriac plaque. Alzheimer’s disease is thought to be caused by Aβ damaging effects[7]. Tau protein is found within the somatodendritic compartment of neurons, oligodendrocytes, and non-neural tissues but it is most prevalent in the axons of central anxious framework neurons. As a heat-stable protein, tau (tubulin-associated unit) was recouped from porcine brain extricates. Early in 1983, it was discovered that there are numerous phosphorylation sites on the tau protein and some of them will result in the negative assembly of microtubules. Tau is predominantly an intracellular protein that regulates microtubule stability by lowering microtubule binding. Phosphorylated tau (p-tau) inhibits microtubule binding. P-tau stimulates the formation of tau tangles, which then become neurofibrillary tangles (NFTs). The hyperphosphorylation of tau protein will lead to neurodegenerative disease, including the Alzheimer’s disease.[6]

3. AD patients suffer from sleep disorders

Numerous studies have shown that the proportion of AD patients suffering from sleep disorders ranges from 20% to 80% [8,9]. There are many typical sleep disorders including sleep-wake cycle disorder, restless legs syndrome, and sunset syndrome [10], which severely reduce the quality of life of Advertisement patients and cause severe financial and emotional stress to their families. APP/PS1+SCN2B/- transgenic mouse models have been successfully constructed to provide tools for studying the development of SCN in AD [11]. They found that the SCN2B gene promotes AD by increasing pathogenic APP-APPβ-CTF and AICD and reducing the breakdown of metabolizable sAPPα fragments, using a stable mouse model after crossbreeding and by studying neurons in their cerebral cortex and hippocampus [12]. Many models have been developed to help study the mechanisms by which AD is generated.

3.1. Causes leading to AD

Although there is a closed loop between AD and sleep disorders, there are still different factors that lead to the beginning of the closed loop, which is what caused the AD in the first place. This paragraph discusses the factors that may contribute to AD and how they play a part within the pathology of rest clutters.

3.1.1 Oxidative stress

Oxidative stress is closely linked to the pathogenesis of AD. ROS damages mitochondria, not only causing premature apoptosis, but also rendering antioxidant enzymes inactive, and leading to oxidation of large molecules such as DNA, as a result, synapses and neurons are damaged. In this way, they are involved in the pathogenesis of AD [13]. In contrast, oxidative stress causes UCHL1 (ubiquitin carboxy-terminal hydrolase) to be oxidized and reduced, and the hydrolase inactive, resulting in APP and BACEI not being well degraded and increased Aβ involvement in AD pathogenesis [14].
3.1.2 Neuroinflammation

Neuroinflammation is included within the pathogenesis of Alzheimer's disease and Aβ with tau proteins and NLRP3 inflammatory vesicles in microglia. When microglia are activated early on, they can help clear toxic Aβ from within the lymphoid class, but microglia are inhibited by chronic stimulation and phagocytic activity is reduced, thus promoting the deposition of more Aβ, accumulating toxic material, and accelerating AD development [15].

NLRP3 vesicles, activated by Aβ protofibrils (insoluble), can secrete potentially neurotoxic cytokines via the NLRP3-caspase-1 pathway. This in turn has a key role in re-AD [16]. It was also shown that Aβ deposition and neurofibrillary disorganization in AD transgenic mice were improved by the knockdown of NLRP3 inflammatory vesicles [17].

3.1.3 Changes in SCN

Some researchers have demonstrated the presence of Suprachiasmatic Nucleus (SCN) neurophysiological clutter within the Advertisement mouse demonstrate by studying the SCN in Tg-SwDI mice and the changes in the resistance sites. They found that middle-aged AD mice had reduced SCN neuron A-type potassium current and diminished AP recurrence aimed the day and expanded neuronal movement at night relative to wild mice of that age [18].

3.2. How AD leads to sleep disorder

Many accounts in the academic community describe the reasons for changes in the body that modify the sleep profile of people with AD other than those in 1.1. This section will look at oxidative stress, inflammation, hypothalamic supraoptic nucleus and basal forebrain cholinergic neurons, and hippocampal alterations as reasons and prospects for sleep disorders in Alzheimer's disease.

3.2.1 Oxidative stress

Researchers have studied the effects of acupuncture on sleep disturbances and the inhibition of prefrontal oxidative stress damage in mice and have shown that it can prolong sleep in rats, suggesting that the mechanism may be related to oxidative stress [19]. It is believed that due to stress, the brain produces free radicals during daytime operations, which are scavenged during sleep [20]. It has been shown that patients with diverse degrees of obstructive rest apnea-hypopnea disorder (OSAHS) have different levels of oxidative stress damage, which may be because patients' Hcy is altered by oxidative stress [21].

3.2.2 Inflammatory chemicals from the periphery

Inflammatory chemicals from the periphery can get across the blood-brain barrier or trigger vagal afferent neurons. Neural complexes containing the neurotensin (NTS) are used in vagal stimulation. The NTS sends signals to areas of the brain that affect sleep, causing sleep to change. Furthermore, sleep modules such as the hypothalamus are altered by NTS stimulation due to the generation of pro-inflammatory chemicals [22].

3.2.3 SCN atrophy

The SCN acquired in the brains of more seasoned patients with Alzheimer's illness was shown to have extensive atrophy [23]. The circadian signaling of SCN is altered and it is unable to work with the hypothalamus in its task of regulating sleep, and neurofibrillary tangles and Aβ deposition occur, which can cause or deepen sleep disturbances in people with AD [24].

3.2.4 Degeneration of BFCNs (basal forebrain cholinergic neurons)

Degeneration of BFCNs (basal forebrain cholinergic neurons) and reduction in cortical and hippocampal Ach affect memory function and REM abnormalities in patients with AD, leading to sleep-wake cycle disturbances [25]. Cholinergic-related structures in AD patients play an vital part in rest, such as the superior septal nucleus and the pons, whose degenerative degeneration can lead to sleep disturbances [25]. Abnormal excitability of dopamine controlled BFCNs in elderly AD patients leads to arousal disturbances. The prefrontal cortex is associated with
dopamine neuronal firing, and dopamine renal spermatozoa and receptors cover a wide range of relevant important subcortical targets, therefore, prefrontal cortex atrophy, leads to reduced cognitive regulation [26]. Melatonin receptors (MT1 and MT2) regulate circadian rhythms, and patients with AD have low melatonin levels and a significantly reduced number of neurons [15]. Changes in chronotropic factors represented by light exposure and reduced light perception in AD patients due to reduced visual nerve acuity, resulting in sleep disturbances [27]. It has been shown that sleep regulation is more functional in wild-type rats than in transgenic rats, and therefore the degree of rest unsettling influence in Advertisement patients may be genetically related [28].

4. Treatment of sleeping disorders and AD

The treatment of the two diseases is commonly pharmaceutical. In this part, several treatments are introduced, and the explanation of the effects are explained.

4.1. Treatments of AD

Alzheimer's disease is characterized by cognitive impairments, cerebral shrinkage, and neuropathological abnormalities such as neuronal loss, the buildup of misfolded and aggregated amyloid peptides (Aβ), and tau proteins[29]. The multifaceted character of polygenic Alzheimer's disease (AD) poses considerable therapeutic development hurdles [30]. Precision pharmacology (PP) is a new conceptual paradigm that tries to investigate and predict the entire effect of a molecular mechanism of action, known as the pharmacodynamic (PD). The application of PP in AD is expected to result in a unique and new scientific taxonomy, as well as a well-known functioning lexicon and terminology. Nilvadipine is a dihydropyridine (DHP) calcium channel blocker that is used to treat hypertension in various countries. Other than coordinate calcium channel blocking and maintaining intracellular calcium homeostasis, nilvadipine is said to offer a variety of neuroprotective actions. In transgenic mouse models of Alzheimer's disease, it reduces Amyloid beta 40 and 42 amino acid peptides (Aβ 40 and Aβ rance) through the blood-brain barrier in vivo. Many other DHPs, on the other hand, lack these characteristics, and some may even boost Aβ 40 and Aβ 42 synthesis in vitro.

4.2. Treatments of sleeping disorders.

4.2.1 Pharmacological treatment

The use of a mixture of medications containing midazolam maleate tablets has been shown to improve mental status improve self-care and assist in enhancing the inflammatory response to the organism [31]. Intensive pharmacological regimens (quetiapine + midazolam and quetiapine + midazolam + trazodone) have been demonstrated to improve sleep quality and cognitive function while minimizing side effects [23]. Similarly, studies have demonstrated that midazolam in combination with quetiapine improves sleep difficulties in Alzheimer's patients [32].

Besides the pharmacological treatments of sleep disorder, the latest researches also show new approaches to curing sleep disorder, which is claimed as non-pharmacological treatment.

4.2.2 non-pharmacological treatment

Positive meditation has been found in numerous studies to benefit individuals with mellow to direct Alzheimer's infection. Some researchers examined serum inflammatory mediators in individuals treated orally with memantine pills to those treated with positive meditation treatment and found that their sleep difficulties were effectively addressed [12]. Two other studies also suggest this idea [33].

5. Conclusion

There's a causal relationship between rest clutters and Advertisement, leading to a vicious circle, this article has discussed the leading factors of sleep disorder and also the Alzheimer's disease.
Additionally, the bidirectional relationship between them is further explained β-amyloid peptides (Aβ) and hyperphosphorylated tau proteins are claimed as the most important factors in this closed loop, which are the products of sleep order and the leading factors of Alzheimer’s disease. After this, the article discussed pharmacological and non-pharmacological treatments for AD, as well as combination therapies. Despite this initial understanding of the causes of the disease, large prospective cohort studies are needed to assess the impact of sleep interventions on AD, as only by increasing research in these areas can more effective treatment options be identified. Hopefully, this article can help the future further research in the area of sleep disorder and Alzheimer’s disease.

References


