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Sleep Pattern: Preventing Factors for Alzheimer Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Author ZK contributed to the framework, the literature searches, composition, and writing the review. Author KS contributed to the conception, composition, and revision of this manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Alzheimer's disease is investigated by scientists broadly. Although there is no definitive treatment, a better medical intervention can be assumed as a preventive medicine which postpones the onset of disease and delays its progression. Understanding that the sleep changes affect the brain which it will be stabilized later as a cardinal manifestation of disease leads us to review recent studies and theories. In this review, we show that the interruption of circadian rhythm along with disruption of immune and endocrine systems can cause neuronal physiology changes. These changes can enhance neuro inflammation pathology by the time through Aβ deposition forming plaques in the brain tissue. Besides higher level of Aβ in CSF, immune system dysfunction occurred by aging will change solubility of Aβ. Furthermore, the defect in insulin and subsequently decreases in insulin receptor impair glucose metabolism. The dysregulation of glucose metabolism expedites the degenerative pathway and contributes to other oxidative stresses in neurons. The cortex of brain gradually will be damaged extremely and the brain size will shrink intensely and atrophy. In

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summary, we found that improving of sleep quality can reduce the disease progression and delay its symptoms by having effects in neuropathology.

Keywords: Alzheimer's disease; memory deterioration; sleep impairments; catecholinaminergic imbalances; insulin signaling; vascular cognitive impairment.

ABBREVIATIONS

Aβ: Amyloid-βeta peptide; Ach: Acetylcholine; AD: Alzheimer's disease; APOE: Apo lipoprotein E; BBB: Brain blood barrier; CRP: C-reactive protein; CSF: Colony stimulating factor; DHEA: Dehydroepiandrosterone; DHES: Dehydroepiandrosterone Sulfate; ECG: Electrocardiogram; EEG: Electroencephalogram; EMG: Electromyogram; EMO: Electrooculogram; GF: Growth factor; IFN: Interferon; IGF: Insulin like growth factor; IL: Interleukin; Irs: Insulin receptor substrates; MMSE: Mini-Mental-State-Examination; MT: Metallothionein; NFT: Neurofibrillary tangle; OSAY: Obstructive sleep apnea syndromes; PSG: Polysomnography; REM: Rapid Eye Movement sleep; SCN: Suprachiasmatic nucleus; SOB: Sleep disordered breathing; SWS: Slow-wave sleep; TGF: Transforming growth factor beta.

1. INTRODUCTION

Alzheimer's disease (AD) is a devastating progressive neurodegenerative disorder, which disables patients gradually. It is standing on the sixth leading cause of death in the United States. AD deteriorates over time and impairs memory process and other intellectual abilities. It interferes with daily life, personal communication and person's responses to the environment [1]. It also decreases the life quality of both patients and their caregivers while the behavioral symptoms grow and get more signified. There is a worldwide effort to find better ways to prevent and postpone AD from regression. Circadian impairments, such as abnormal sleep patterns, increase gradually in patients consists of measures taken for disease prevention could be a good start for delaying the degeneration of central nervous system that is problematic to repair and cost at least their function. They were previously considered as senile processes since AD onset usually occurs after the seventh decade of life. Thus, understanding the changes that occur within circadian rhythm in older population is important. It is also known that genes play a significant role in AD. Research studies reveal clues about the interaction of some lifestyle management factors, such as sleep pattern, with genes which may influence health conditions [2]. According to the oldest cholinergic hypothesis, it is assumed that there is a decrease of synthesis of acetylcholine in AD. Acetylcholine (Ach) is an important neurotransmitter in both AD and scheduling of REM sleep. In other words, during waking cycle and REM sleep, the release of Ach in the cortex will be increased [3]. However, the treatment of Ach deficiency has not been very effective in patients. Therefore, this hypothesis has not been maintained.

The aim of this present review is clarifying whether these circadian system alterations can be used for early neurodegenerative prediction. For example, chronic sleep deprivation can predispose person to have neurodegenerative disease. We review five main areas in AD: 1) Changes in sleep quality and pathology in cerebral cortex of brain; 2) Vascular cognitive impairment due to cerebrovascular disease caused by the lack of sleep; 3) Comparing memory deterioration in AD with abnormal sleep pattern, based on existing reviews on changes in sleep-dependent memory processing; 4) The effect of melatonin [4]; 5) Neuroinflammation and activation of microglia along with catecholinaminergic imbalances; 6) And finally, the role of sleep in insulin resistance and defective insulin signaling in AD [5]. This memory processing can be characterized by neuromodulatory and electrophysiological events in sleep stages [6]. Fig. 1 represents all known possible causes, which are explained in this paper.

Fig. 1. Known possible causes of Alzheimer's disease

2. SLEEP QUALITY ASSESSMENT

Sleep disturbances often occur in AD which affect both patients and their care givers. These changes in sleep schedule also include the changes in memory and behavior which most of patients without dementia notice in the primitive period of disease onset. However, these changes are more common in later stage of AD and will be presented by increased or decreased total sleep time, nocturnal arousal, daytime napping, and other changes in circadian cycle [7]. The evidences from recent prospective cohort study over 5 year period have showed that the sleep pattern changes are associated closely with cognitive impairment which evaluates by Mini-Mental-State-Examination (MMSE) [8]. MMSE examines the functions including registration, attention and calculation, recall, language, ability to follow simple commands, and orientation. Thus, sleep pattern as a risk factor across the life course from early to mid and late adulthood has an essential role in AD onset and progression.

In a research study, quantity of sleep was measured by self-administrated total sleep time. Furthermore, wake time after sleep onset, naps during daytime, bedtime hours, awaking during night, sleep latency was gathered by next morning diaries for another aspects of sleep quality [9]. In some articles, the quality of sleep was explained by polysomnography (PSG). Polysomnography is a multi-parametric comprehensive recording of the physiological changes, which usually occur during sleep and used to diagnose or rule out many types of sleep disorders in the adults. The PSG screens body functions, such as brain by electroencephalogram (EEG), eye movements by electro-oculogram (EOG), skeletal muscle activity by electromyogram (EMG) and heart rhythm through a typical electrocardiogram (ECG) during sleep. Furthermore, nasal and oral airflow can be measured by pressure transducers with or without a thermocouple to detect diminished airflow in hypopnea or obstructive apnea. After the test is accomplished, the data is analyzed with score. This score

contains some the useful information including sleep onset latency (onset of sleep from the time the lights are turned off), sleep efficiency (total sleep time divided by time spend in bed) and sleep stages (1,2,3 and REM or rapid eye movement sleep), breath irregularities, arousals (sudden shifts in brain wave activity), cardiac rhythm abnormalities, and even limb movements and body position during sleep [10,11].

In some articles, actigraphy is also used for gross motor activity during sleep. Actigraphy is a non-invasive method of monitoring activity cycles. It is a wrist-watch-like device worn on the wrist of the non-dominant arm for detecting motor activity. Contrary to polysomnography, the patient does not necessarily need to be located in a laboratory while the required data is being recorded. Sleep actigraphy is also more affordable than performing a polysomnography [12,13].

2.1 Change in Sleep Quality and Pathology in Cerebral Cortex

The major change in AD patient is the shrinkage in brain, which is apparent in brain imaging. The brain shrinks dramatically and it affects approximately all its functions. It is especially severe in the hippocampus, an area of the cortex that plays a main role in formation of new memories. In consequence of its reduction followed by cell death and tissue loss, ventricles passively grow larger significantly [14]. Ventricular enlargement defines hemispheric atrophy rates which is apparently associated with changes on cognitive tests in AD progression and it correlates more strongly with temporal lobe atrophy rates [14,15]. Furthermore, [14] revealed that the progression of AD after six months was confirmed nearly twice than the rate of ventricular enlargement compared to stable mild cognitive impairment.

But the question is what pathology is known for this! It seems that it is mostly associated with age related brain atrophy in the hippocampus and entorhinal cortex [16]. The prominent temporal changes and also amyloid neuropathology are considered as important factors in chasing brain pathology in these known fields.

It was shown that short sleep duration could be associated with faster deterioration in global cognitive performance [17]. It was also revealed that every one hour decrease in sleep duration was associated with an increase in total cognitive decline by 0.67%.

The neurofibrillary tangle (NFT) and the senile plaque were two principal identifiable neuropathological lesions since Alois Alzheimer first described:

- Abnormal accumulations of phosphorylated tau protein as NFT
- Senile plaque with a basic core of beta-amyloid

It is important to note that these lesions can be confirmed only after biopsy of cerebral cortex of dead advanced old-aged patients' brain. Thus, its diagnosis, especially in its early stages, is beneficial for finding a way to prevent further progress in AD. Over the past years, much more details and explanations were studied and added to this field but it still is very difficult to define constitutional therapy for preventing the progression or keeping neural work normal [18].

The relation between changes in sleep and changes in AD was hypothesized for many years. In a recent longitudinal study, the consequence of the risk of all-cause dementia incidents, including AD, on sleep problems was shown and explained by interfering neuronal health. A population of dementia-free adults, aged over 75, was considered and then the results were compared with the follow-up data, gathered 3 years later [19]. Their results revealed an increase of dementia incidents with the changes in sleep duration after 6 to 9 years later in three quarters of the cases.

Another study used sleep-wake cycle as an objective in pathogenesis of AD through another pathway related to cortico-subcortical network. In this study, an apoptosis Increase, cytoskeletal disintegrating along with neuronal synaptic failure, was detected in AD brain cortex [20].

Another research study focused on the dysregulation of the secreting of stress hormones, like cortisol, with changing in sleep pattern [21]. A later study investigated decreasing of cellular tolerance to oxidative factors and reducing DNA repair due to cellular loss of neuroprotective functions and stem cell proliferations [22].

Microscopic bundles of a protein fragment, i.e. plaque, are hallmark of Alzheimer's brain abnormalities. These accumulations of amyloid-β

peptide (Aβ) occur in the extracellular space of the brain and get deposited later in the brain. The data revealed by [23] suggested that Aβ aggregation could interrupt the sleep cycle and the fluctuation of Aβ in vivo in the model of AD associated with amyloid deposition. This result suggested that amyloid deposition in the brain was associated with poor sleep quality, but not its quantity. A later study [9] hypothesized that the changes in sleep quality or quantity, or both, were related to the amyloid deposition. They used the biological marker of ADs from longitudinal studies in memory and aging from cognitively normal volunteers at the Washington University Knight Alzheimer Disease Research Center. Any amyloid depositions were classified as a preclinical stage of AD. They claimed that poor sleep quality, and not sleep quantity, could be originated from amyloid deposition in the brain. Soluble Aβ was also released during physiological neuronal activity. It was shown that increases of Aβ depositions during periods of wakefulness were associated with increases in synaptic and neuronal activity [24].

Frequent naps were also related to amyloid deposition. The results were stated in a cohort study performed among elderly females with preclinical cognitive decline [25]. However, in recent studies, the daytime napping could be associated with a lower risk of cognitive decline in the Mini Mental Status Exam score after 10 years [26].

Another area of study is the confluence of genetic contribution, as an important risk of AD, besides environmental factors. These studies have explained some genetic risk factors such as Apo lipoprotein E (APOE) related with sleep disruption [27,28] which indicates the controlling role of endogenous circadian genes in sleep patterns by causing insomnia [29]. These results suggest that sleep changes can modify the APOE effect on Neurofibrillary Tangle (NFT) density, which is not related to Aβ pathology.

2.2 Vascular Cognitive Impairment and Sleep Deprivations

Pathophysiological relations between obstructive sleep apnea syndromes (OSAS) and AD have been reviewed in Epidemiological studies. However its mechanism is not clearly understood [30].

One of the most common forms of sleep disordered breathing (SDB), which affects nearly17% of the US population, is Obstructive sleep apnea. A relationship between SDB and cognition was already known but found to be associated with cognitive deficit related to APOE4 carriers [31]. They performed overnight polysomnography studies at the Clinical Research Unit at University of Wisconsin Hospitals and Clinics. At the first stage, they invited patients in the range of 30-81 years old, predominantly males, to have baseline studies for about 12 years and then followed up every four years for cognitive evaluation and blood sample for genetic analysis. After analyzing five stages of the study on about 1,843 of the remaining participants, they stated results based on Cross-sectional analysis of a community-dwelling cohort. High-risk APOE4 genotype was identified in 200 of 500 participants. They found SDB to be associated with cognitive deficit only in APOE4 carriers and that it might affect the nervous system through hypoxia, oxidative stress, sleep fragmentation and cerebrovascular changes. Accordingly, it could intensify cognitive impairment in high-risk patients for Alzheimer disease [32]. Thus, the variety of underlying brain pathology, such as hypoperfusion, oxidative stress and inflammation, can cause endothelial damage, brain blood barrier (BBB) breakdown and immune system activation. The major target of these vascular fluctuations happens in the white matter part of brain which emphasizes the role of the immune system in the brain and, furthermore, the contribution of neurons, glia cells and myelin. Axonal loss and demyelination lead to misappropriate corporation between neurons and subsequently cognitive impairment and gradually cerebral atrophy [33].

Various types of vascular lesions can be seen in AD which contributes to cognitive impairment, such as large cortical infarcts, lacunar infarcts and subcortical white matter disease. Vascular lesions can make the disease hard to control because of different clinical manifestations of AD [34]. The results of this study, along with a later one, showed a high prevalence of neuropsychiatric symptoms in AD with vascular lesion. It also revealed that the sleep disturbance was more severe in patients with cortical lesions [35].

2.3 Memory Deterioration in Abnormal Sleep Pattern in AD

There are several mechanisms showing the cause of sleep disturbance and cognitive impairment in AD, such as impaired amyloid-β

clearance, due to increases of Tau protein from disassemble microtubule in neurons, neurotransmitter changes, and hypoxia or vascular changes [36]. There are also different functional connectivity maps involving different parts of the brain in AD versus healthy elderly patients. Anterior and ventral functional connectivity are dominant in AD in contrast to posterior connectivity [37]. Furthermore, it should be noted that memory consolidation happens during sleep time. Slow-wave sleep (SWS) and rapid eye movement (REM) sleep support system consolidation and synaptic consolidation, respectively. During SWS, at minimum cholinergic activity, the hippocampus-dependent memories are re-activated and organized to neocortical sites, whereas during REM sleep it has higher cholinergic activity, resulting in consequent synaptic consolidation of memories that occur in the cortex [38].

Amyloid-β concentration is defined to be increased in sleep deprivation and poor quality sleep [39]. Increased wakefulness and altered sleep patterns depend on high accumulation of amyloid-β [40]. Neurogenesis and neurodegeneration can consequently happen in order to endorse neuroinflammation, especially in the learning and memory region [41].

2.4 The Effect of Melatonin

The center of the suprachiasmatic nucleus (SCN), a tiny region in the hypothalamus which is above the optic chiasm, is responsible for wakefulness and sleep state and it generates the circadian rhythm measured on a 24-hour scale [42]. The most important timing signal, produced by the SCN, is melatonin. It is synthesized from serotonin which is converted to N-acetyl-5-methoxytryptamine mainly in the pineal gland during the dark phase of the circadian cycle [43]. Melatonin gets released into the CSF and it controls circadian rhythm through an indirect inhibitory pathway. When the SCN is active in daytime, the melatonin production is suppressed and in dark cycle, it is reversed.

Although several interactions for promoting the effect of melatonin have been discovered, it still remains a mystery. However, the relationship between two subtypes of human melatonin binding receptors (MT1 and MT2) is known. MT1 suppresses the circadian wakefulness by affecting the SCN that promotes sleep. Beside this direct effect, melatonin improves the endogenous circadian rhythm in humans, through expression on the MT2 receptors in the SCN [44]. This result is in consensus of previous studies which indicate that theta and delta waves increase significantly and spindle bursts propagate with oral administration of melatonin [45].

Because the rhythmic expression of noradrenergic receptors in pinealocyte is lost in AD, the regulation of the pineal gland by the SCN may also be interrupted [46]. Furthermore, in the earliest preclinical AD stages, the melatonin precursor serotonin is already depleted and patients with AD show more profound decreases in total melatonin levels [47]. During the progression of the disease, the wakefulness and sleep rhythm disappear exhibiting the severity of the pineal glands affect through impaired control of the SCN. In summary, the melatonin levels decrease in early stages of the disease, while its diurnal rhythm vanishes at a later stage [48].

2.5 Neuroinflammation with Catecholaminergic Imbalances

The catecholamine neurotransmitters include dopamine, epinephrine (adrenaline), and norepinephrine (noradrenaline). Catecholamine causes general physiological changes for physical activity (fight-or-flight response) and a general reaction of the sympathetic system. High catecholamine levels in blood are associated with stress and act as neuromodulators in the central nervous system. The neuromodulators which are neurotransmitters in the nervous system trigger neuroinflammation in brain.

The associations between neuroinflammation and AD and the role of inflammatory responses in AD have been broadly studied. The basal-cholinergic system expresses mutation in genes PS1 and APP. Cholinergic processes trigger the change of distribution patterns by accumulation of amyloid as cortical plaques [49].

The acute neuroinflammatory response precedes the activation of immune cells (microglia) resulting in a phagocytic phenotype and is also responsible for the release of inflammatory mediators such as cytokines. Activated microglia, in the presence of inflammatory cytokines cannot phagocytose amyloid-beta, which may contribute to the accumulation of plaque [50]. The main role of cytokines is to promote differentiation of T cells to T-helper 1 and 2, regulatory T cells, and T-helper 17 cells [51]. Transforming growth factor beta (TGF-β), interleukin 6 (IL-6), interleukin 21

(IL-21) and interleukin 23 (IL-23) contribute to this formation as regulatory proteins. These regulatory proteins include ILs, interferons (IFNs), colony stimulating factors (CSFs), TNFs, and certain growth factors (GFs). Many of these cytokines have already been shown to be produced by neurons or glia and there are a number of reports indicating changes in their levels in the AD brain, blood, and cerebrospinal fluid.

The presence of IL-1β greatly increases the secretion of cytokines IL-6 and IL-8 in response to Aβ by astrocytes while IL-1α and IL-1β both up-regulate the expression of APP, which consequently up-regulates the production of Aβ [52]. It can be explained that cytokine dysregulation with age advancing has come from IL-6 secretion inhibition by dehydroepiandrosterone (DHEA) from human mononuclear cells in vitro [53]. Therefore, with advancing age, the increase of IL-6 owes to a loss of DHES inhibition [54].

IL-6 and its receptors are in several regions of the normal brain, including the hippocampus, hypothalamus, neocortex, and brainstem [55]. However it is interesting to find a significantly elevated levels of IL-6 in the CSF and the serum of AD patients [56]. One of the main sources of synthesis and secretion of IL-6 in the CNS is astrocytes. Previous studies also revealed stimulation of microglia and astrocytes by IL-6 and that it mediates the synthesis of acute phase proteins and phosphorylation of tau protein in neurons. Thus, leading to the release of inflammatory cytokines and acute-phase proteins, such as C-reactive protein (CRP) ultimately causing brain inflammation [57,58].

Further, it was confirmed that IL-6 could not induce hyperphosphorylation of tau protein in neurons [59]. Therefore, it was anticipated that IL-6 from astrocytes could induce a calcium excess in neurons through the N-methyl-D-aspartate receptors (a glutamate receptor) and initiate the JAKs/STATs pathway. Activation of this pathway leads to tau protein phosphorylation and neurofibrillary tangle formation [60].

Activity-dependent secretion of neurotransmitters is identified to provoke biosynthesis of neurotransmitters to reload these molecules for neurotransmission. Thus, regulated neuronal activity participates in the release of both Aβ and neurotransmitters. The regulated co-secretion of Aβ suggests participation of those neurotransmitters that modulate cognition and memory.

2.6 Insulin Resistance Abnormal Sleep Pattern; Role of Defective Insulin Signaling in AD

Recent exploration of biochemical, molecular, and cellular abnormalities [61] confirmed that Insulin resistance could affect cell destiny in AD by changing cerebral glucose utilization and energy metabolism. However, these changes cannot be considered as a single primary pathogenic mechanism in AD but can promote neurodegenerative disease and trigger a developmental cascading of all other known abnormalities [62]. Insulin resistance, hyperinsulinemia, attracts the attention of scientists to find any connection. A physiological condition, known as Insulin resistance, is responsible for normal actions of hormone insulin. In this situation, the body produces insulin, but the cells become resistant to insulin and are unable to use it as effectively.

Several recent studies have shown the association of hyperglycemia, due to Insulin resistance, as a possible risk of cognitive dysfunction and dementia despite some uncertainty. Several mechanisms are identified on the metabolic state of body and can explain the vascular etiology of cognitive defect, like dyslipidemia or hypertension. Some intercellular mechanisms are considered as moderators of high-level glucose through the polyol and hexosamine pathways, and disturbances of intracellular second messenger pathways [63].

The brain is involved in cerebral insulin receptor signaling, as a peripheral insulin resistance. Otherwise, insulin may interfere with Aβ and tau metabolism and simplify amyloid plaques and neurofibrillary tangles formation. In addition, insulin seems to act as a neuromodulator for release and reuptake of neurotransmitters in order to improve learning and memory [64].

Tyrosine kinases, the receptor of insulin and IGF-1, intervene in the phosphorylation of insulin receptor substrates (Irs), including Irs1, Irs2, Irs3, and Irs4. The Irs's contain a phosphotyrosine binding-domain [65]. For example, Irs-1 plays an important biological function for both metabolic and mitogenic pathways or the decrease of Irs-2 in a neural cell may be attributed to apoptosis [66]. Moreover, brain aging is protected by Irs-2 from accumulation of phosphorylated tau [61].

Furthermore, previous studies reveal that IGF-1 signaling inhibits neuronal apoptosis [67]. Many proinflammatory signaling pathways inhibit the activity of Irs proteins, specifically amyloid inhibits Irs-2 signaling. These findings suggest that insulin and IGF-1 are necessary for neural cell survival and have a critical role in human brain atrophy and cognitive impairment. Thus, defects in insulin and subsequently decreases in Irs2 signaling causes the neurodegenerative disorder, such as Alzheimer's progression by deregulated peripheral nutrient homeostasis and finally neurodegeneration.

Plasma glucose levels during nocturnal sleep can increase 20% to 30% and the maximum range occurs during the middle of the sleep cycle. During the first half of sleep, there is an increase in plasma glucose due to decreased glucose uptake and certainly its metabolism in cells, which is followed by a 50% increase in insulin secretion. The decrease in glucose levels is because of a decrease of brain metabolism during slow wave sleep (SWS). The body is subsidized to this decrease in peripheral glucose uptake by reducing muscle tone during sleep and its effects on growth hormone (GH) pulse during sleep [68]. Glucose tolerance begins during the later stage of the night and not during REM sleep. As glucose levels progressively decrease, it causes an increase in glucose uptake and facilitates the wake and rapid eye movement (REM) stages with increasing insulin sensitivity [69].

Sleep deprivation affects glucose metabolism through multiple pathways and insufficient sleep increases the risk for insulin resistance. Whereas brain glucose utilization is 10 times more than predicted on a mass basis, sleep-deprived brain is shown to reduce the uptake of glucose by 7-8 % of normality as compared to the rested brain [70]. Thus, this can easily induce the neurodegenerative cascade in neural cells.

3. CONCLUSION

Research studies in recent years have significantly made forward-thinking pathways to better understand the role of preventive approaches in disorders that still have no definitive effective treatments. Sleep deprivation is becoming a more apparent contributor in the pathology of neurodegenerative disorders, such as AD, along with other multiple factors such as genetics and environmental conditions.

In summary, sleep deprivation hastens the onset of Alzheimer's and its progression. Poor sleep has been tied to increased levels of beta-amyloid in neural cells and consequently making higher Aβ levels in the CSF, which are toxic to neurons and synaptic endings. The accumulation of insoluble Aβ forms plaques in the brain and contributes to neuronal death, which in turn stimulates a local inflammatory response that can result in further cell injury. The presence of Aβ also provokes the increase of phosphorylation of tau, causing tangles through the neuronal microtubule binding protein which is used for restructuring axons in to dendrites, finally leading to neuronal dysfunction and cell death.

Two main known processes in neuronal cells include extracellular deposition of Aβ and intracellular accumulation of Tau protein, both playing a pathologic change in the patients' brain. The circadian rhythm regulates the neuronal activity, which is responsible for the change of soluble Aβ to unsolvable depositions [71], leading to an association between Aβ accumulation and sleep-wake cycle disruption. Furthermore, Aβ fluctuation in CSF levels followed by amyloid deposition due to the changes in Aβ metabolism correlates with the presence of presenilin mutations, a transmembrane protein that are responsible for familial AD.

This review article gathers basic and recent findings of sleep loss, which effects memory deterioration and its pathophysiology in cognitively dysfunctional brains. Beside other factors, like ageing and genetics, we consider that changes in sleep patterns by improving sleep quality could reduce the disease progression and delay its symptoms. Therefore, this review suggests that improving sleep quality may reduce neurodegenerative risk. It can be introduced as a new strategy from health providers to their clients, such as maintaining healthy weight. In conclusion, sleep is affected in early- and moderate-stages of AD, and progressively gets worse during the end-stage in elderly [72]. Thus, it indirectly supports the directional hypothesis that sleep quality and disruption assessment by care providers may help in identifying early onset of the disease when there is still opportunities to interrupt the degeneration process of the irreversible symptoms.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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