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Mini-Review: A potential intervention of Alzheimer disease prevention based on a sleep disturbance monitoring

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Abstract: **This review aimed to demonstrate recent research on the relationship between sleep disturbance and Alzheimer's disease (AD) due to sleep disturbance being determined as a specific modifiable risk factor for AD, but the mechanism is not well comprehended yet. The two main etiologies of AD are an accumulation of amyloid-ß (Aß) and tau protein in the brain. Several studies indicate a strong association between poor sleep and an increase of Aß in cerebrospinal fluid and plasma, signifying that sleep disturbance plays a crucial role in AD onset. Therefore, knowing this relation can help prevent AD through sleep disturbance monitoring and management.**

Keywords: **potential intervention, Alzheimer's disease (AD), sleep disturbance monitoring.**

1. INTRODUCTION

Alzheimer's disease (AD) is one of the best-known illnesses associated with old age. As the world's population increases, the figures for older people with Alzheimer's disease are expected to advance. Over time, this destruction erodes the most vital human abilities, such as language, learning, memory, and judgment. Personality and behavior also are dramatically affected by this so-called disease.

Based on the World Alzheimer reports 2021, the prevalence of 50 million people affected by AD worldwide. It is approximately to 152 million by 2050 (1). AD is a growing global public health problem including in Thailand caused by cognitive impairment in older and a lack of effective treatment. According to the latest WHO data published in 2021 Alzheimer's & Dementia Deaths in Thailand reached 22,851 (5.13%) of total deaths (2). Therefore, a preclinical diagnosis for AD is an urgent effort to prevent and delay the AD onset.

It was clear that the hallmarks of AD pathology are the Aß plaques and intracellular neurofibrillary tangles (NFTs) or tau protein in the brain (3, 4). The excessive accumulation of Aß in the brain resulting from an imbalance between its production and clearance. The clearance of brain Aß has been studied in rodents and found that the clearance of Aß occurs during sleep. There are several clinical studies showing that the highest cerebrospinal fluid Aß levels are found before sleep and the lowest one found after awakening (5-7). Besides, imaging studies in healthy people revealed a relation between poorer self-reported sleep duration and a higher burden of Aß in the brain (8). Thus, effective intervention that prevents Aß accumulation in the brain should be a promising step in prevention and delay AD. Moreover, sleep disturbance monitoring might be a potential non-invasive preclinical diagnosis for AD.

2. PATHOGENESIS OF ALZHEIMER DISEASE

Alzheimer's disease, a neurocognitive disorder, is the most common cause of dementia that causes the degeneration, or loss of neurons in the brain, particularly in the cortex area, leading to the symptoms characteristic of dementia. The two hallmark neuropathologic changes of AD are diffuse and neuritic plaques, marked by extracellular Aß deposition and neurofibrillary tangles comprised of the intracellular accumulation of hyperphosphorylated tau (p-tau) protein. (9)

A particular molecule called amyloid precursor protein, or APP, would be in a cell membrane. This specific protein was tucked into the cell membrane with both ends outside and inside the cell. To be more precise, it is researched that APP is in charge of helping the neuron grow and repair itself after an injury, and similarly to other kinds of proteins, it gets used, and over time, it gets broken down and recycled (10). Commonly, this protein gets chopped up by alpha-secretase and gamma-secretase enzymes and is soluble; however, if another enzyme, beta-secretase, comes in place of alpha-secretase and teams up with gamma-secretase, this creates a monomer called Aß, which is a leftover fragment that is not soluble. These leftover monomers tend to be more chemically sticky, resulting in the bonding of each other beside the neurons, forming beta-amyloid plaques, a clump buildup of several amyloid-beta monomers. These newly modified plaques can potentially get between the neurons, disrupting the pathway of a neuron to another neuron and blocking the neurons from signaling to one another, resulting in impairment of the brain function. In addition, these plaques can also trigger an immune response, which causes inflammation and damages the surrounding neurons. Amyloid plaque can also deposit around blood vessels in the brain, called amyloid angiopathy, which weakens the walls of the blood vessels and increases the risk of hemorrhage or rupture in the blood vessel that causes blood loss (10, 11).

Another main pathological feature of AD is the tangles inside the cell instead of the beta-amyloid plaques. Like other cells, neurons are held together by their cytoskeleton formed by microtubules. Its function is to maintain cell structural shape and provide a mechanical asset that enables cells to carry out essential functions. More significantly, there is a particular phosphorylated tau (ptau) protein, its role is to support the stability of microtubules in axons. Furthermore, it is not yet confirmed, but it is thought that the beta-amyloid plaque build-up initiates pathways inside the neuron that leads to the activation of kinase, which is an enzyme that transfers phosphate groups to the ptau. As the kinase leaves the phosphate group to the track, this ptau transforms its shape. It stops supporting the microtubules, which clump up with other ptau or are tangled and leads to other characteristic findings of AD— neurofibrillary tangles (12). As the neurons with tangles and non-3 microtubules lose their ability to signal, they undergo apoptosis or programmed cell death. While the neurons are dying, the brain atrophies and shrinks, resulting in the gyri getting narrower, which are the characteristic ridges of the brain. As the gyri became narrower, the sulci, the grooves between the gyri, became more expansive. With atrophy, the ventricles and fluid-filled cavities in the brain get more extensive (13) caused a traumatic brain injury lead to AD.

3. SLEEP DISTURBANCE IN ALZHEIMER DISEASE

Disturbance in sleep seems to be a significant causing component of Alzheimer's disease and its pathophysiology. Research has suggested that chronically poor sleep quality was associated with amyloid plaques in cognitively healthy individuals and that sleep deprivation can increase the levels of amyloid in the cerebral spinal fluid (CSF), the fluid that bathes the brain (14). When sleep is improper, it starts accumulating Aß; in early-stage, it potentially triggers the memory decline and then converts it further to AD; from the result of considerable research, it has been found that Sleep patterns directly or indirectly affect Alzheimer. Associations and plausible mechanisms link non-rapid-eye-movement (NREM) sleep disruption, Aß, and AD. Disruption in NREM sleep is a novel factor relating cortical A to impaired hippocampus-dependent memory consolidation. In older age, proper sleep is a new treatment target, affording anticipatory and therapeutic remuneration (15).

Regular sleep has been reported to contribute to tissue repair, thermoregulation, homeostatic restoration, memory consolidation processes, and preservation of neuroimmune-endocrine integrity. During sleep, the brain switches periodically between different activity states, which are non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. REM sleep is considered necessary for learning, memory consolidation, neurogenesis, and regulation of the blood-brain barrier function, while non- REM sleep has been related to the regulation of hormonal release, the lowering of the thermal set point, and is characterized by a reduction of cardiovascular parameters such as blood pressure (16).

Having trouble sleeping can lead to Insomnia, which is a sleep disorder in which patients have dissatisfaction with sleep quality or duration, difficulty in falling asleep at night, or waking up too early in the morning, and it can lead to daytime fatigue, low energy, difficulty in maintaining attention, and formation of long-term memory. The human immune system follows diurnal patterns like circadian rhythm. Cytokines and immunoglobulins are highest during the night, while immune cells in the blood are at their highest levels in the early evening and their lowest in the morning. Sleep disturbance disrupts this regulation by increasing proinflammatory cytokines such as IL-6, TNF-α, IL-1, and CRP levels. Indeed, sleep duration is directly correlated with lower levels of inflammatory markers and hence with a predisposition to AD (17).

The bidirectional, causal interaction between REM sleep and Aß pathophysiology may contribute to AD risk and progression. Disruption of NREM sleep acts as a new biomarker of AD and may represent a new pathway through which cortical Aß impairs hippocampus-dependent memory consolidation. In addition, the disruption of NREM sleep physiology

offers potential diagnostic utility in the form of a non-invasive biomarker of Aß pathology, AD risk, and AD pathophysiological progression. Evidence implicates sleep disturbance as a consequence and cause of AD progression; modifiable one, offering preventative and treatment potential (17).

4. CONCLUSION

In summary, this review suggests evidential correlations between sleep disturbance and Alzheimer's on memory impairments, AD neuropathogenesis, and development by exacerbating necessary biochemical processes. Consequently, correcting sleep disorders, including insomnia and sleep deprivation, could be a potential therapeutic strategy for individuals with a risk of AD.

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