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Review

Alzheimer's Disease Pathology and Sleep Quality

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ABSTRACT

Alzheimer's disease (AD), which is an advanced dementia progression, is one of the neurodegenerative disorders that result from the accumulation of amyloid plaques and neurofibrillary tangles in the brain. There are several risk factors that can be caused by AD such as genetic and epigenetic factors. Apart from this, factors such as aging, stress, and sleep disturbance are closely associated with AD. The biological clock also called the circadian rhythm, optimizes the day-night cycle so that living things adapt to their basic needs such as nutrition, sleep, and fertility, as well as external factors such as heat and light from the environment. Disturbances in the circadian rhythm, associated with the melanin hormone, trigger sleep disorders, obesity, cardiovascular diseases, and neurodegenerative disorders. In this review, sleep disorders caused by circadian rhythm disturbance and the relationship between sleep and AD were discussed.

Keywords: Aging, Alzheimer's disease, amyloid precursor protein, circadian rhythm, sleep, stress

Dementia is the progressive and irreversible loss of mental function, especially memory.[1,2] Cognitive decline is closely related to mood changes that lead to a complete loss of personality. It mainly occurs in elderly patients, and Alzheimer's disease (AD) appears in its advanced phases.[3] In 1907, German neurologist Aloysius Alzheimer discovered AD while examining his 51-year-old woman patient, Auguste Deter, who had suffered from memory loss, language and disorientation, and hallucinations. The term "Alzheimer" was first used by Emil Kraepelin.[4,5]

The clinical symptoms of Alzheimer's disease:[6-9]

Stage 1: It is the initial stage of the disease and cognitive weakness begins in the patients.

Stage 2 (very mild cognitive weakness): Patients start losing stuff and forgetting where they are. There is no decrease in communication abilities at this stage.

Stage 3 (mild cognitive weakness): Patients have difficulty in choosing words and forming sentences during speech. The planning skills of the patients' are decreased.

Stage 4 (moderate cognitive weakness): The patient begins to be unable to recall relevant memories in his/her personal history. Disruptions begin to occur in the social lives of patients, they start to isolate themselves, and they begin to exhibit symptoms of depression.

Stage 5 (moderate to severe cognitive weakness/early dementia): Confusion of place and time, as well as deterioration in motor functions (apraxia) and perception (agnosia), occur in patients. Patients need help to do their daily activities (such as eating, toilet, and dressing).

Stage 6 (severe cognitive weakness/moderate dementia): The patients cannot find the appropriate words while speaking and their speaking skills regress. Since they are unable to hold their toilet, they need additional support in their daily lives.

Stage 7 (very severe cognitive weakness/late dementia): The speech abilities of the patients become progressively worse or totally disappear.

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Patients constantly need help.

The pathophysiology of AD is based on two basic hypotheses. One of these hypotheses is the amyloid hypothesis. This concept involves extracellular beta-amyloid (Aβ) deposits. Beta-amyloid molecules play a critical role in AD which is triggered by both genetic and environmental factors, and there is an increasing accumulation of Aβ in the brain in AD. Increasing Aβ mass causes neuronal cell death, and loss of synapses, and leads to a progressive course of the disease.[10-12]

The second hypothesis is the deposition of neurofibrillary tangles resulting from hyperphosphorylation of tau, a microtubule-associated protein that stabilizes microtubules.[13] Accumulation of hyperphosphorylated tau protein leads to loss of cellular and neuronal function and ultimately to apoptosis.[14]

Along with these two hypotheses, it has recently been generally argued that the decrease in cognitive functions due to relatively high levels of inflammatory response in the brain in AD and high immune gene activation increases the susceptibility to neurodegeneration.[15]

Aging is another important risk factor for AD formation. When we classify AD according to age: Early-onset AD is observed in people under 65 years of age, while late-onset AD affects patients aged 65 and over.[16] Early and late AD differs in clinical, neuropsychological, neuropathological, and neuroimaging techniques.[17] In the brains of early AD patients, amyloid precursor protein (APP) causes the formation of amyloid plaques (APs). As a result of mutations in presenilin 1 and 2 (PSEN1 and PSEN2) genes, gamma-secretase, the enzyme that degrades APP, cannot be regulated in the brains of patients with early AD, and consequently, amyloid deposits increase. In late AD patients, apolipoprotein E (APOE), a protein that provides lipid transport between tissues or cells, controls the production and function of Aβ and regulates lipid homeostasis.[18-21] In peripheral tissues, ApoE is produced primarily by the liver and macrophages and mediates cholesterol metabolism in an isoform-dependent manner. ApoE4 is also associated with hyperlipidemia and hypercholesterolemia leading to atherosclerosis, coronary heart disease, and stroke.[20,22] In the central nervous system, ApoE is primarily produced by astrocytes and transports cholesterol to neurons via ApoE receptors, which are members of the low-density lipoprotein receptor (LDLR) family.[23] Literature shows that APOE genotypes strongly influence the accumulation of Aβ to form plaques and cerebral amyloid angiopathy in AD brains.[24]

EPIGENETIC FACTORS

Epigenetics is the study of changes in gene function that are inherited mitotically or meiotically and do not require changes in the deoxyribonucleic acid (DNA) sequence. The initiation and progression of AD occur with the interaction of various factors, including aging, genetic mutations, metabolic activity, and nutritional disorders, as well as environmental and social variables.[25] Decreased DNA methylation in the brain impairs neural plasticity, prevents memory formation, and leads to memory loss with aging in AD patients.[19,26] In addition to aging, cerebrovascular diseases, which are other epigenetic risk factors, are the most frequently reported precursor factors of AD. In addition to all of these, the risk of AD is further enhanced by variables including smoking, diabetes, hypertension, obesity, dyslipidemia (increasing blood cholesterol level), traumatic brain injury, marital status, stress, and depression.[27,28]

CIRCADIAN RHYTHM

Living organisms adapt to their environment in order to meet their basic needs such as protection, nutrition, mating, and survival. They also adjust their biological clocks by optimizing their night-day cycles.[29] The circadian system manages various physiological functions such as sleep-wake, temperature, physical activity, and cognitive activity.[30,31]

The circadian rhythm is controlled by transcriptional-translational negative feedback. The transcription factors BMAL1 and CLOCK form heterodimers and the transcription of genes is repressed by promoters containing enhancer box (E-box) elements throughout the genome. The combination of PERIOD (Per) and CRYPTOCHROME (Cry) repressor genes inhibits BMAL1 and CLOCK transcription. The Per and Cry gene generates the biological clock by setting the circadian rhythm to a 24-hour period by creating negative feedback on Bmal1 and Clock.[31-33]

The biological clock is regulated and synchronized by the suprachiasmatic nucleus (SCN) of the hypothalamus.[34,35] The SCN regulates the timing of humoral controls including sleep-wake, temperature, hunger-fullness, and cognitive function by sending

signals to numerous hypothalamic nuclei.[35,36] The SCN regulates output pathways that affect a variety of physiological functions using both neuronal and humoral signals. The proper timing of hormone release, feeding behavior, and body temperature fluctuations is determined by these output pathways.[30]

Photoreceptors containing melanopsin in the retinal layer of the eye sense the external environment and transmit it to the SCN. It regulates the secretion of melanocyte-stimulating hormone (MSH) by stimulating the pineal gland in the SCN. The MSH secretion is low during the day and increases at night. In this situation, the upregulated MSH levels indicate that it is time to sleep in the body. When MSH secretion increases rapidly while we are sleeping, it decreases in the morning, which is the signal to wake up.[37-39] Melatonin can control the timing of the circadian rhythm for up to 24 hours by flowing back into the SCN.[40] Negative factors in our daily life, such as poor quality nutrition, stress, decreased physical activity, night shift work, and jet lag, cause disruptions in circadian rhythm and cause cognitive dysfunction.[41,42] Anomalies in the biological clock as a result of irregularities in the circadian rhythm pose a risk for numerous diseases.[43] These include sleep disorders, depression, bipolar disorder, cognitive function, memory formation, neurodegenerative disorders such as AD, Parkinson's Disease, Huntington's disease, obesity, and cancer.[44]

SLEEPINESS FACTOR

Sleep is characterized by two general sleep states non-rapid eye movement (NREM) sleep which consists of three stages, N1, N2, and N3, and rapid eye movement sleep (REM). As NREM sleep deepens, electroencephalography (EEG) brain frequencies slow down. In the deepest sleep phase (N3) EEG or slow-wave sleep (SWS), a high slow wave activity is seen.[45] The SWS heals the brain itself after prolonged wakefulness, goes to rest, and maintains sleep homeostasis.[46] On the other hand, REM sleep is associated with dream states.[45]

Many regions of the brain are involved in the management of the sleep-wake process. Ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus, hypocretin neuropeptide neurons in the lateral hypothalamus, and locus coeruleus (LC) in the pons are brain regions that regulate sleep and wakefulness. The VLPO is the active area during sleep and contains galaninergic and GABAergic inhibitory neurons.[46] Lesions in VLPO cause sleep problems.[47,48] Hypocretins are neuropeptides that are expressed in neurons during awakening.[49,50] Hypocretins send intense stimuli to multiple nuclei, including the LC, which is the noradrenergic nucleus that amplifies arousal.[51,52] The VLPO and hypocretins send impulses to the brainstem, which regulates REM sleep.[53,54] Sleep-active VLPO and wake-active monoaminergic nuclei mutually inhibit each other, resulting in a rapid transition between sleep-wake states. Wake-active lateral hypothalamic neurons strengthen the arousal system and stabilize the balance between sleep-wake.[55]

ALZHEIMER'S DISEASE AND SLEEP

Aging is the primary risk factor for many neurodegenerative disorders, and with aging, the daily function of the biological clock in the human body decreases.[56] Disruptions in the circadian rhythm affect sleep and misalignment of other physiological rhythms.[57-60] AD patients frequently have circadian rhythm and sleep-wake cycle abnormalities.[61-64] Compared to older individuals who are healthy, people with AD spend more time awake in bed and have more interrupted sleep.[65,66] In a study, it was shown that sleep disruption increases the risk of cognitive decline and AD.[58,66] In another study, a decrease in REM sleep time and slow-wave sleep fragmentation was observed in individuals with AD.[65,67,68] The deposition of Aβ plaques is thought to be interrelated between sleep disturbance and AD progression.[69-73] To determine whether sleep disturbance is associated with AP accumulation before cognitive impairment in AD, cerebrospinal fluid (CSF)[74] Aβ levels and sleep measures were performed in cognitively normal individuals. As an output of this analysis, the scientists found that low CSF Aβ levels were associated with poor sleep quality.[75] Another study found that poor sleep quality is associated with shorter sleep duration and greater Aβ formation.[76] These studies showed that poor sleep quality occurs when there is AP formation and before cognitive dysfunction.[77]

It is known that impairments in sleep duration and circadian rhythm happen with AP formation. These impairments negatively affect sleep quality and cause other bodily rhythms to go out of sync which in turn increases stress. Poor sleep increases stress and stress causes interrupted sleep. Different types of stress create changes in our sleep cycle and activate the hypothalamic-pituitary-adrenal (HPA) axis.[78]

The study, which was done to show how the increased amyloid production caused by sleep dysfunction promotes AP formation, showed that a

key regulator of the sleep cycle, orexin, promoted staying wake in transgenic rats which caused increased AP formation and accumulation.[79,80] The increased AP load disrupts slow-wave sleep, which impairs the consolidation of human memory.[81] Slow-wave sleep is important for cleansing the human body. Inadequate sleep, inability to obtain sufficient wave sleep, and the elevation of oligomeric forms of APs are associated with AD.[82]

In conclusion, multiple factors may affect AD pathology including sleep habits, age, gender, and sleep disorders. It has been known that sleep disorders raise levels of cerebral Aβ and hyperphosphorylated tau accumulation, thus it increases the risk of AD. In addition, damage to neuronal pathways such as cholinergic pathways that initiate and maintain sleep are thought to contribute to sleep changes in AD. Regression analysis revealed that the severity of the impaired slow release-sleep cycle connection predicted a greater medial temporal lobe tau burden. In studies, sleep-wake disorders are observed before AD is clinically diagnosed. Before cognitive disorders, sleep-wake abnormalities such as daytime sleepiness are frequently encountered in patients. In fact, sleep pattern changes that create problematic issues in patients' life cycles are directly associated with the accumulation of tau and Aβ. Extended wakefulness may increase soluble Aβ levels in the brain and both exacerbate and accelerate the development of AD pathology.

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