Role of Sleep Disturbance in the Trajectory of Alzheimer's Disease

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Sleep disturbances such as insomnia, hypersomnia, and circadian rhythm disturbance are common in normal elderly and Alzheimer's disease (AD) patients. To date, special attention has been paid to sleep disturbance in the clinical course of AD insofar as the interaction of sleep disturbance with the pathogenesis of AD may impact the clinical course and cognitive function of AD patients. This review covers the bidirectional relationship between sleep disturbance and AD pathogenesis; the associations between sleep disturbance and AD-specific neurotransmitters, brain structure, and aspects of sleep disturbance in each phase of AD; and the effects of sleep disturbance on the cognitive functions of patients in each phase of AD. We consider several factors required to exactly interpret the results and suggest a direction for future studies on the role of sleep disturbance in AD.

KEY WORDS: Sleep; Alzheimer disease; Mild cognitive impairment; Aging; Amyloid beta-peptides; Cognition.

INTRODUCTION

Sleep disturbance is a frequent occurrence in the normal aging process, which involves deterioration in sleep quality, represented by increased sleep latency, difficulty with sleep maintenance, and early morning awakening and has been documented to include an increase in the prevalence of circadian sleep disturbance and sleep disordered breathing (SDB).[1]

Sleep affects various domains of cognitive function, including attention and memory consolidation.[2,3] In addition, sleep disturbance is a known risk factor of cognitive dysfunction in elderly.[4-6] Furthermore, recent studies have reported that sleep disturbance deteriorates cognitive function and functional impairment by facilitating the pathogenesis of Alzheimer's disease (AD).[7,8] Reciprocally, lifestyle change and an atrophy of brain structure caused by the progression of AD have been found to accentuate sleep disturbance.[9-12] In this regard, many studies have suggested mechanisms by which sleep disturbance has a relationship with AD pathogenesis.[13-15]

The pathogenesis of AD affects the entire course of AD, including preclinical dementia, minimal cognitive impairment (MCI), and advanced AD.[16] However, most existing studies separately examine sleep disturbance in each phase of AD. Therefore, the existing research is limited in its understanding of sleep disturbance in differing aspects of the entirety of AD progression.

The authors of the current study reviewed the relationship between sleep disturbance and AD pathogenesis from multiple, integrated perspectives, including mechanisms by which sleep disturbance interacts with AD pathogenesis, aspects of sleep disturbance over the entire course of AD, and the effects of sleep disturbance on cognitive functions over the entire course of AD.

RELATIONSHIP BETWEEN SLEEP DISTURBANCE AND AD PATHOGENESIS

Sleep Disturbance as a Risk Factor of MCI or AD

It is well documented that sleep disturbance is a risk factor of MCI or AD. In two community-based studies, poor sleep quality (investigated by self-reported questionnaire) was shown to increase the risk of dementia.[17,18] Furthermore, poor sleep quality has been reported to increase the risk of metabolic and cardiovascular diseases, which are known independent risk factors of AD.[19]

It is widely accepted that circadian rhythm disturbance is associated with increased risk of developing AD. One study that measured circadian rhythms by actigraphy has

shown that decreased amplitude of the sleep-wake cycles and delayed rhythms increase the odds of developing dementia in a community-based population.[20] Excessive daytime sleepiness (EDS) is a common symptom of circadian rhythm disturbance. According to a community-based longitudinal cohort study, subjects who suffer from EDS at baseline were twice as likely to be diagnosed with incident dementia.[21] In another study, disrupted daytime activity was shown to facilitate conversion to MCI or dementia.[22] Sleep fragmentation is another common symptom of circadian rhythm disturbance and has been reported to increase the risk of incident AD in community dwelling, cognitively normal elderly.[23] Moreover, sleep consolidation has been reported to decrease the incidence of AD in community dwelling elderly.[24]

It has been demonstrated that SDB increases the risk of developing dementia.[25] In one prospective study, subjects with SDB confirmed by polysomnography were shown to be prone to develop MCI or dementia with an 85% increased risk.[26] In that study, breathing had an adjusted odds ratio of 1.85 for the development of MCI or dementia in subjects.[26]

In addition, cognitively normal elderly with the apolipoprotein epsilon 4 (APOE E4) allele reporting sleep disturbance have shown a risk level for developing MCI or dementia seven times as high as that of cognitively normal elderly without the APOE E4 allele reporting sleep disturbance.[27]

Furthermore, in circadian rhythm disturbance, poorer rhythm measured by actigraphy has been associated with later stages of dementia.[28] There also is a relationship between the frequency of apnea and the severity of dementia in elderly with SDB.[29] It has been suggested that frontal-subcortical pathology associated with SDB could increase the risk of developing dementia.[29]

Effect of Sleep on AD Pathology

Several studies have reported that sleep disturbance precipitates the accumulation of beta amyloid (Aβ) protein in brain. Poor sleep quality, measured by self-reporting, has been implicated in the accumulation of Aβ measured by positron emission tomography (PET) scanning.[30] Among objective sleep parameters representing sleep quality, longer sleep latency has been shown to be related to the accumulation of Aβ in the prefrontal region of the brain.[31] In addition, subjects with less adequate sleep, more sleep problems, and greater somnolence have greater Aβ burdens measured by PET scanning in prefrontal and insular regions of the brain.[31] Sleep duration has also

been shown to have a relationship with the accumulation of Aβ. Shorter sleep duration was previously associated with greater Aβ burden measured by PET scanning in the precuneus, angular gyrus and frontal medial orbital cortex.[32] Most of these studies had a crossover design. Therefore, all of these results have limitations insofar as they only clarify the causal effects of sleep disturbance on AD pathology. Accordingly, a prospective study was conducted and found that improving sleep quality reduced the incidence of AD and neurofibrillary tangle density in cognitively normal elderly with the APOE E4 allele.[24] Furthermore, in amyloid precursor protein transgenic mice, chronic sleep deprivation promoted formation of amyloid plaque, while orexin receptor antagonists (which induce sleep) decreased formation of Aβ plaque.[7] In addition, it has been suggested that circadian rhythm disturbance could facilitate the accumulation of Aβ by promoting molecular transcription, autophagy, and the formation of reactive oxygen species.[33] Moreover, one recent study assessed the effects of respiratory and non-respiratory sleep variables on the accumulation of Aβ in MCI subjects and showed that respiratory variables, such as the apnea-hypopnea index (AHI) and an oxygen desaturation index, precipitated Aβ deposition.[34] Furthermore, SDB has been reported to be associated with AD-specific cerebrospinal fluid (CSF) biomarkers in cognitively normal elderly.[35]

There are several suggested mechanisms that show how sleep disturbance could precipitate the accumulation of Aβ. One mechanism is that sleep disturbance inhibits the clearance of Aβ. One study measured the volume of brain interstitial space that is supposed to exchange and clear Aβ with CSF in mice by altering the sleep state.[13] The study found that the brain interstitial space was 60% larger in sleeping and anesthetized mice than in awake mice, and that level of amyloid beta was associated with time spent awake.[13]

Another proposed mechanism is that sleep disturbance increases synaptic activity and facilitates the accumulation of Aβ. Among the stages of sleep, the slow wave sleep stage (SWS) is the phase in which synaptic activity is most greatly decreased.[36,37] In this regard, decreased SWS induces increased synaptic activity. In addition, increased synaptic activity releases Aβ into brain interstitial fluid. It has been documented that increased synaptic activity in specific regions is related to region-specific increases of Aβ.[14] In particular, brain regions in the default mode network (DMN) are most active during quiet wakefulness and are known to be most prone to aggravation

with Aβ.[38,39] This DMN has been reported to be deactivated during SWS.[40] In this regard, sleep disturbance could decrease SWS, activate brain components of the DMN, and accelerate the accumulation of Aβ in this region.

A third possible mechanism is that sleep disturbance impairs the response of the endoplasmic reticulum to cellular stress, leading to Aβ misfolding and accumulation.[15] Changes due to this response at the molecular level have been suggested to be common features in neurodegenerative diseases, including AD.[41] Indeed, aging enhances the adverse effects of sleep disturbance on promoting the accumulation of Aβ through synergistic interaction with changes in the response at the molecular level.[42]

Effect of AD Pathology on Sleep

The accumulation of Aβ could directly interfere with neuronal functions in brain regions that regulate sleep.[43] It has been confirmed that Aβ accumulation measured by PET scanning disrupts SWS and memory consolidation in the elderly, and it has been assumed that Aβ accumulation affects the pathways that regulate the sleep-wake cycle.[44] Another study has reported that subjects with Aβ confirmed by PET scanning lack a diurnal variation of Aβ.[45] The design of these studies, however, was cross-sectional. To investigate the causative effects of AD pathology on sleep disturbance, studies with mutant mice have been conducted. Mutant mice that are prone to amyloid plaque deposition have shown a deficiency in the sleep-wake cycle and are shown to lack a diurnal variation of Aβ after the formation of amyloid plaque.[46] Furthermore, active immunization to remove amyloid plaque normalizes the sleep-wake cycle and the diurnal variation of Aβ in mutant mice.[46] Also, a study with APP/PS1 knock-in mice, a model of AD, has indicated that mutant mice have a phase delay in the sleep-wake cycle in comparison to wild-type mice.[47] Another transgenic mice study, in which human-mutated amyloid and tau transgenes were inserted into animal subjects, has shown reduced sleep duration, shorter sleep bouts, and reduced amplitude in the sleep-wake cycle with a decline of multiple cognitive domains.[48]

Effects of Hypnotics on AD Pathology

With the understanding that sleep affects AD pathology, hypnotics acting through γ-aminobutyric acid A (GABA A) receptor could be assumed to impact AD pathology and progression. Although there are few human studies regarding the efficacy of hypnotics on AD pathology and progression, several transgenic mice studies have observed the efficacy of GABA A agonists on AD

pathology. GABA A agonists have been shown to reduce Aβ induced neurotoxicity in hippocampus and cortical neurons, to ameliorate neuronal maturation and neurogenesis, to decrease the deposition of Aβ fibrils in the CA1 area of the hippocampus and to improve cognitive function in AD mouse model.[49-54] Moreover, these researches suggested that the stimulation of GABA A receptor might protect against AD pathology by attenuating the Aβ induced mitochondria dysfunction, enhancing glycogen synthase kinase 3 beta (GSK-3β) pathway and balancing between excitatory and inhibitory systems underlying synaptic function.[54-56] However, there are other evidences of long term adverse effects of GABA A agonists and their relationship with increased risk of dementia.[57]

Associations between Sleep Disturbance and Changes of Neurotransmitters in AD

Changes in the neurotransmitters in AD have been documented to be associated with sleep disturbance. One change involves the cholinergic system. Cholinergic pathways are known to correlate with wake promotion and maintenance, participating in the ascending reticular activating system.[58,59] The cholinergic system also has a major role in modulating electroencephalogram (EEG) activation, which is representative of rapid eye movement (REM) sleep.[60] Due to vulnerability of cholinergic neurons in the nucleus basalis of Meynert to neurodegenerative stress, cholinergic dysfunction by Aβ accumulation has been reported to induce REM deficits in MCI and AD populations.[61] Another neurotransmitter change involves the noradrenergic system. In AD, noradrenergic dysfunction in the brain stem is assumed to decrease REM sleep.[62] Research has shown that noradrenergic dysfunction in the pineal gland provokes the decrease of melatonin level in subjects with preclinical AD and AD.[63] In addition, melatonin regulates the biological clock and the sleep-wake cycle and is supposed to have neuroprotective characteristics.[63,64] Evidence indicating that melatonin is implicated in AD pathogenesis continues to accumulate. AD patients with homozygous APOE E4 alleles have lower melatonin level than those with heterozygous APOE E4 alleles.[65] Furthermore, there is a relationship between level of melatonin and the severity of sleep disturbance in subjects with dementia.[66] In addition, MCI patients treated with melatonin show better cognitive function and sleep quality than patients without melatonin supplement.[67,68]

Association between Sleep Disturbance and AD-specific Brain Structure

There are several studies regarding the relationship between sleep disturbance and AD-specific brain structure. Among self-reported sleep parameters in cognitively healthy elderly, frequency of nocturnal awakening has been negatively correlated with the volume of gray matter in the insular region, known to be vulnerable to AD pathogenesis.[31] Other studies have demonstrated that poor sleep is associated with a decrease in gray matter volume of the frontal cortex and hippocampus and an increased rate of atrophy in the frontal, temporal, and parietal regions of the brains of elderly subjects in community-dwelling populations.[69,70] Additionally, atrophy of brain regions vulnerable to AD pathogenesis, such as the medial prefrontal cortex and cholinergic structures in the forebrain, has been reported to compromise non-rapid eye movement (NREM) sleep and REM sleep, respectively.[9,10]

Bidirectional Relationship between Sleep Disturbance and AD Pathogenesis

Current research has provided evidence that the relationship between sleep disturbance and AD pathogenesis is bidirectional. Sleep disturbance appears to facilitate the progression of AD pathogenesis, including the accumulation of Aβ and tau proteins through dysfunctional clearance of neurotoxins, increased synaptic activity, and impaired molecular response. Consequently, AD patho-

genesis could compromise brain regions that modulate the sleep-wake cycle and affect neurotransmitters implicated in sleep processes. In this regard, sleep disturbance and AD pathogenesis are caught in a vicious cycle whereby sleep disturbance leads to increased AD pathogenesis, which in turn exacerbates sleep disturbance (Fig. 1).

SLEEP IN NORMAL AGING

Changes in Sleep in Normal Aging

Sleep structure changes with aging due to the reduction of SWS and a compensatory increase of the lighter sleep stage.[1] Changes in the REM sleep stage appear to be unremarkable in normal aging, but have a propensity to show a decrease in delta waves and an increase in fast waves.[71,72] Elderly people are prone to awaken less during REM sleep, but more during NREM sleep and are known to have fewer numbers of sleep spindles and K-complexes in NREM than young adults.[73] These changes in sleep with aging have been documented in nearly all people older than 60 years and to worsen in populations of elderly people with the APOE E4 allele.[74] In accordance with impaired sleep structure, sleep quality is also compromised due to aging. Sleep efficiency tends to be decreased, sleep fragmentation tends to be increased, and sleep phases are inclined to advance with aging.[75] Synchronization of circadian sleep disturbance is impaired with aging.[68] Among elderly people, 20-30% complains of EDS.[76,77] In addition, SDB is
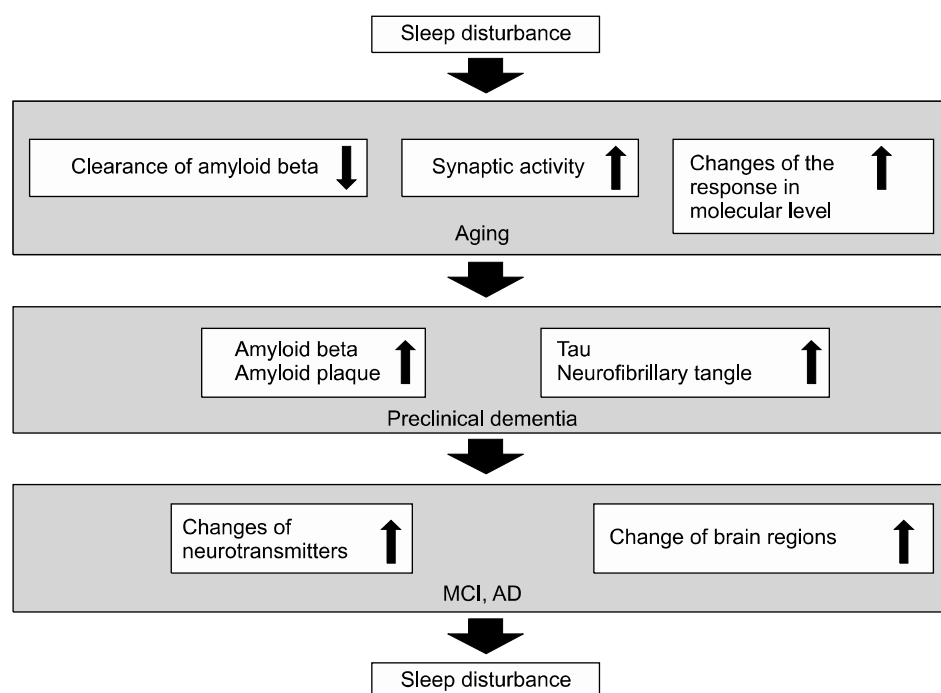
Fig. 1. Bidirectional relationship between sleep disturbance and AD pathogenesis.
MCI, mild cognitive impairment; AD, Alzheimer's disease.

another common symptom of sleep disturbance. Seventeen percent of elderly males and 9% of elderly females are estimated to suffer from moderate to severe SDB.[78] Moreover, a population of subjects with preclinical dementia with amyloid burden has been shown to have worse sleep quality than a population without amyloid burden, including reduced sleep efficiency and frequent napping, as estimated by actigraphy.[79]

Relationship between Sleep Disturbance and Cognitive Function in Normal Aging

The disruption of sleep structure is known to have a correlation with cognitive function in normal elderly. Declarative memories are known to improve after SWS, but the relationship between memory function and SWS has been reported to be more attenuated in normal elderly than in younger adults.[3,80] An increased number of sleep spindles, which are components of stage 2 sleep, have been reported to be associated with verbal memory retention.[81]

During the REM sleep stage, newly encoded memories appear to consolidate. In a cohort study with cognitively normal elderly, REM sleep latency and REM density showed a correlation with decline of cognitive function.[2,82]

There has been a controversy regarding the relationship between sleep quality and cognitive function in normal elderly. Many studies have observed that poor sleep quality by subjective, objective measurement is associated with decline of cognitive function including memory retention, attention and executive function.[4-6,83,84] Conversely, improved sleep quality attenuates the adverse effects of the APOE E4 allele, a high-risk genotype, on cognitive function.[24] In contrast to these findings, it also has been reported in certain other prospective and crossover studies that poor sleep quality has no significant association with cognitive function.[25,85,86]

Some controversy also exists concerning the relationship between sleep duration and cognitive function. In studies with subjective and objective measurements of sleep duration, it has been shown that longer sleep duration impairs cognitive function.[87-90] There are other reports that both short and long sleep durations worsen cognitive function, indicating a U-shaped pattern of the relationship between cognitive function and sleep duration.[25] Three prospective studies have demonstrated that short and long sleep durations measured by self-reported questionnaires precipitate cognitive dysfunction in elderly subjects.[91-93] However, some researchers have reported that sleep duration has no correlation with cognitive

function. Sleep duration measured by actigraphy has been reported to have no association with cognitive function estimated in a cross-sectional study using the Mini-Mental State Examination (MMSE) and a trail-making test.[6,94] Another study has concentrated on the effects of age on the relationship between sleep duration and cognitive function. In a group of patients 50 to 64 years of age, both short and long sleep durations were associated with a decline of cognitive function.[95] However, in a group of patients over 65 years of age, this association remained significant only in those with a long sleep duration.[95]

Sleep fragmentation evaluated by actigraphy has been demonstrated to accentuate cognitive dysfunction and to accelerate the rate of decline in cognitive function.[6,89,96] In a meta-analysis, sleep deprivation by sleep fragmentation was also associated with cognitive decline, including decline of memory and executive function.[97] In addition, sleep consolidation has been shown to lower the rate of cognitive decline in community-dwelling elderly with the APOE E4 allele.[23] EDS has been reported to have a correlation with cognitive decline in community-dwelling elderly.[83,85,98] In an animal study, circadian rhythm disruption induced by frequent phase shifting was correlated with decrements of cognitive function, such as learning and memory.[99]

Evidence continues to accumulate indicating that SDB is associated with cognitive decline in normal elderly. In a prospective study, mild to moderate SDB was associated with cognitive decline evaluated by MMSE in community-dwelling elderly.[100] Additionally, SDB parameters encompassing the AHI and oxygen saturation were correlated with decrements of global cognitive function.[101] Furthermore, this observation was particularly remarkable in a population of subjects with the APOE E4 allele.[101] There is another report that the APOE E4 allele affects the relationship between SDB and cognitive decline.[95] According to that research, higher AHI score aggravated memory function only in subjects with the APOE E4 allele.[102] According to that research, higher AHI score aggravated memory function only in subjects with the APOE E4 allele.[102]

There is some disagreement concerning the relationship between SDB and cognitive decline. Two cross-sectional studies and one prospective study with normal elderly participants have shown no significant association between AHI and cognitive decline.[89,103]

SLEEP IN MCI

Changes in Sleep in MCI

Prevalence of sleep disturbance in MCI subjects has been documented to range from 8.8% to 45.5%.[104,105] In addition, SDB and sleep behavior disorders appear more frequently in MCI patients than in normal patients.[106] In one prospective study, MCI subjects who converted to AD had shown no differences in parameters of sleep disturbance than MCI subjects who remained stable.[107]

Changes in sleep structure in amnestic MCI patients have been demonstrated in respective sleep stages. In the NREM stage of sleep, the duration of SWS is more decreased in MCI patients than in cognitively normal elderly.[108] In addition, the power of both delta and theta waves in the NREM sleep stage were found to be more reduced in amnestic MCI patients than in cognitively normal elderly, and fast sleep spindles in the NREM sleep stage have been reported to be more reduced in amnestic MCI patients than in normal elderly.[108] And fast sleep spindles in NREM sleep stage has been reported to be more reduced in amnestic MCI patients than in normal elderly. The duration of REM has been shown to be remarkably reduced in MCI patients with the APOE E4 allele.[109] In addition, it has been documented that theta waves are diminished during the REM sleep stage in MCI patients.[108]

Relationship between Sleep Disturbance and Cognitive Function in MCI

In amnestic MCI patients, memory functions, such as recall and recognition, have been shown to be improved after sleep consolidation, but were still lower than those in a control group.[110] It has been observed that the impairment of memory functions in MCI patients is associated with reductions in delta and theta power measured by polysomnography.[108] That research also showed that greater variability across nights of sleep predicts an impairment of memory recall.[108] In non-amnestic MCI (naMCI) patients, characteristics of sleep fragmentation are associated with cognitive dysfunction.[111] An increased number of wake arousals after sleep onset (WASO) has been shown to be correlated with an impairment of nonverbal learning, and increased duration of WASO was associated with impairment of several domains of cognitive function, including attention, response inhibition, concept forming, and problem solving in naMCI patients.[111] In MCI patients with the APOE E4 allele, increased duration of REM sleep improves the performance of immediate recall.[109]

SLEEP IN AD

Changes in Sleep in AD

The prevalence of sleep disturbance in AD patients has been reported to range from 25% to 60% according to the categorization of sleep disturbance.[112,113] AD patients complain of subjective sleep problems more frequently than cognitively normal elderly (18.3% vs. 27.6%).[114] The prevalence of SDB was shown to be as high as 60% in AD patients.[113] The prevalence of circadian sleep disturbance has been estimated to be 25% in AD patients.[115] In addition, as many as 25% to 50% of AD patients have been reported to suffer from a nocturnal restlessness known as "sundowning."[112]

Changes in sleep structure in AD patients are perceived as an exaggeration of the changes in sleep due to normal aging and are understood to be aggravated with the progression of the disease. AD patients show reduced sleep efficiency, sleep fragmentation, and decreased total sleep time.[62] Furthermore, stage 1 sleep is increased, sleep spindles are decreased, and SWS is decreased in AD patients.[116,117] Several studies have reported decreased REM sleep in AD patients, which is associated with emotional and behavioral changes.[118-121] Furthermore, EEG slowing in the REM sleep of AD patients has been observed in frontal, parietal, and temporal brain regions.[122] In contrast, another study has observed an unchanged total number of REM sleep episodes and REM sleep latency in AD patients.[123]

Circadian sleep disturbance is also represented in AD patients. AD patients are known to frequently experience sleep fragmentation and EDS.[62,124] In advanced stages of AD, the amplitude of circadian rhythms is reduced, and the phase of circadian rhythms is delayed.[125] These changes have been documented to be aggravated as a function of the severity of dementia.[125]

A Relationship between Sleep Disturbance and Cognitive Function in AD

Several studies have reported that changes in sleep structure are associated with cognitive function in AD patients. It has been suggested that decreased sleep spindles, a feature of sleep changes in AD, are implicated in the pathway of memory consolidation between the hippocampus and neocortical areas of the brain.[3] In mild to moderate AD patients following a challenge with donepezil, increased REM sleep has been associated with improved cognitive function.[126] In addition, sleep duration has also been reported to affect cognitive function in AD

patients.[114] In a crossover study in AD patients, it has been reported that shorter sleep duration was correlated with better cognitive function and longer sleep duration was associated with poor cognition and function.[114]

In mild to moderate AD, EDS is correlated with global cognitive dysfunction including psychomotor and memory impairment.[119] In other research, aberrations of sleep parameters associated with cognitive dysfunction have been reported to have worsened in AD patients without the APOE E4 allele than in AD patients with the APOE E4 allele.[127] The authors of that study concluded that further studies are needed to elucidate the relationships among APOE E4 allele, sleep parameters, and cognitive function in terms of changes in hormones and brain regions of AD patients.[127]

CONCLUSION

The current article reviews numerous studies that support the bidirectional relationship between sleep disturbance and AD pathogenesis. Sleep disturbance affects AD pathogenesis over the entire course of AD from the preclinical phase to advanced phases of AD. Consequently, a decline of cognitive function is induced by accentuated AD pathogenesis. Inversely, an aggravated AD pathogenesis deteriorates sleep, forming a vicious cycle throughout the course of AD.

Current methods of treatment for AD do not target modification of AD pathogenesis, but instead work to slow the rate of the disease. The reality, however, is that AD pathogenesis has already progressed for 10 to 20 years before AD patients reveal symptoms of cognitive dysfunction and functional impairment.[128] Accordingly, it is important to modulate the modifiable risk factors of AD in the preclinical phase for the prevention of AD.[129,130] Delaying symptom onset by as little as one year could reduce AD prevalence by more than nine million cases over the next 40 years.[131] Among variable modifiable risk factors, with the understanding that sleep disturbance directly impacts AD pathogenesis, the treatment of sleep disturbance has a great deal of importance.

The studies presented here need careful interpretation with regard to measurements of sleep and cognitive function, study design, and exogenous factors. There are subjective and objective ways to measure sleep disturbance. It is recognized that subjective measurement of sleep disturbance in AD patients does not exactly reflect an objective measurement of sleep disturbance in the sample.[132] Moreover, some studies use a tool for screening cognitive

dysfunction, such as MMSE, while other studies use a tool for confirming cognitive dysfunction, such as the cognitive assessment battery.

In the analysis herein, the number of cross-sectional studies reviewed was greater than the number of prospective studies. According to the designs of the pertinent studies, the relationship between variables could be associative or causal.

Exogenous factors could affect the relationship between sleep disturbance and AD pathogenesis, which causes cognitive dysfunction. It has been reported that several factors, including cognitive reserve, depression, cardiovascular factors, external zeitgebers, and neurosensory dysfunction, could affect sleep disturbance and AD pathogenesis.[133] Some studies adjust for exogenous factors, while other studies do not consider these factors. Therefore, the results of the relationships between sleep disturbance, AD pathogenesis, and cognitive dysfunction should be interpreted with caution by considering relevant factors. Furthermore, future studies will be required to ascertain the role of sleep disturbance in the understanding and treatment of AD by focusing on the preclinical phase of AD, undertaking more prospective studies with more accurate measurements of sleep and cognitive function, and adjusting for known exogenous factors.

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