Amyloid Burden in Alzheimer’s Disease Patients Is Associated with Alterations in Circadian Rhythm

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ABSTRACT

Background and Purpose: In this study we evaluated the relationship between amyloid-beta (Aβ) deposition and 3 aspects of sleep quality in a group of clinically diagnosed Alzheimer’s disease (AD) patients.

Methods: We used self-report questionnaires to assess the quality of sleep using 3 previously established surveys: the Glasgow Sleep Effort Scale (GSES), the Pittsburgh Sleep Quality Index (PSQI), and the Morningness-Eveningness Questionnaire (MEQ). These questionnaires focused on the sleep effort, sleep efficiency, and circadian rhythm patterns of each participant. Also, we evaluated the regional distribution of Aβ in the brain by amyloid positron emission tomography-computed tomography (PET-CT) standardized uptake value ratios (SUVRs) in healthy normal (HN), mild cognitive impairment (MCI), and AD dementia groups. The MCI and AD dementia groups were combined to form the group with cognitive impairment due to AD (CIAD).

Results: GSES and MEQ scores differed significantly between the HN, MCI, and AD dementia groups (p<0.037), whereas PSQI scores were similar across the groups (p=0.129). GSES and MEQ scores also differed between the HN and CIAD groups (p<0.018). Circadian rhythm scores positively correlated with amyloid PET-CT SUVR in posterior cingulate cortices (p<0.049).

Conclusions: Sleep effort and abnormal shifts in circadian rhythm were more significant in the CIAD group than in the HN group. At the same time, HN subjects had minimal sleep disturbance, irrespective of clinical status. Thus, alterations in circadian rhythm may be indicative of neurodegeneration due to Aβ deposition.

Keywords: Alzheimer's Disease; Amyloid Plaques; Sleep; Mild Cognitive Impairment; Sleep Quality

INTRODUCTION

Alzheimer’s disease (AD) is one of the most prevalent neurodegenerative diseases.1 Although it is associated with various clinical risk factors, recent studies have suggested a possible correlation between sleep disruption and the outbreak of AD. AD patients often complain about fragmented sleep or struggling to fall asleep.2-4
Aggregation of insoluble amyloid-beta (Aβ) peptide in various brain regions is a hallmark of AD. Clinical studies have reported the association between Aβ burden and poor sleep. In addition, reduced glymphatic cerebrospinal fluid (CSF) inflow into the brain during awakening results in an insufficient exchange of CSF with interstitial fluid, raising the risk that neurodegenerative disease may occur. Poor sleep quality detected by self-reported sleep parameters showed a close relationship with amyloid burden in various cohorts.

Amnestic mild cognitive impairment (MCI) is thought to represent a preclinical stage of AD. MCI patients revealed physiological sleep abnormalities than did controls; these included less time in slow-wave sleep and lower delta and theta power during sleep, which may interfere with sleep-dependent memory consolidation. However, although it is well known that the cognitive decline in MCI can cause AD, the role of sleep in amnestic MCI and its relationship to the Aβ burden is not well understood.

In this study we investigated whether sleep quality—measured by self-report sleep questionnaires—differs between healthy normal subjects (HN) and patients with MCI or AD dementia itself. Moreover, we tried to find a correlation between sleep quality and patterns of Aβ aggregation in different brain regions.
participant’s circadian-rhythm type by considering their preferred wake-up and bedtime, as well as how they felt during their most active hours of the day.23

**Amyloid PET-CT imaging**
Each participant underwent amyloid PET-CT imaging with fluorine-18 (18F) florbetaben. Images were acquired 90 minutes after intravenous injection of 300±3.75 MBq 18F-florbetaben. The parameters for image acquisition were as follows: matrix size=336×336; Gaussian filter, full-width at half-maximum=2.0; zoom=2.0; and 1 bed per 20 minutes. Three-dimensional images were reconstructed with CT-based attenuation correction and 6 iteration steps with 8 subsets. We used the Syngo.via server and client software v.04.01.0000.0001 (Siemens Healthcare GmbH, Erlangen, Germany) to obtain mean standardized uptake value (SUV\textsubscript{mean}) on bilateral frontal, temporal, parietal, and posterior cingulate cortices (PCC) of the brain using its automatic recognition and drawing feature for those 8 different regions as the volume of interest. Then, we calculated each SUV ratio (SUVR) for the 8 brain regions with cerebellar SUV\textsubscript{mean} as the reference in a hemisphere-dependent fashion (e.g., left frontal SUV\textsubscript{mean} compared to left cerebellar SUV\textsubscript{mean}).24 we compared these SUVRs across the 3 clinical groups (the HN, MCI, and AD dementia groups).

**Data analysis**
We used descriptive statistics to analyze the background of participants in each group. We used a 1-way analysis of variance test and Kruskal-Wallis test to detect the presence of statistically significant differences in age, sex, and education level across the clinical groups. We also used the Kruskal-Wallis test to evaluate the statistical significance of sleep questionnaire scores across the groups. We assessed the difference between the HN group and the CIAD group by the Mann-Whitney \( U \) test. Finally, we evaluated the relationship between sleep quality and the abundance of A\( \beta \) plaques by using Spearman’s Rho tests. We analyzed data using IBM SPSS statistics v.22.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Characteristics of the study population**
Of the 96 elderly participants in this study (mean age: 68.2±10.7 years), 21.9% were considered to be HN, 51.0% to have MCI, and 27.1% to have AD dementia; 46% were male and 54% were female (n=96). Demographic information of each group is described in Table 1. The groups showed statistically significant differences in age, education level, and sex ratio (\( p<0.001 \), \( p<0.001 \), and \( p=0.025 \), respectively). MMSE and CDR-SB differed significantly between the groups (\( p<0.001 \)), consistent with AD clinical criteria.

| Variables          | HN      | MCI     | AD dementia | \( p \)-value |
|--------------------|---------|---------|-------------|--------------|
| Sex ratio (male:female) | 15:6    | 20:29   | 9:17        | 0.025 \( ^* \) |
| Age (yr)           | 60±9.33 | 68±10.04| 75±8.39     | <0.001 \( ^* \) |
| Education (yr)     | 20±4.75 | 12±5.89 | 10±5.61     | <0.001 \( ^* \) |
| MMSE               | 29±1.80 | 26±3.44 | 19±6.41     | <0.001 \( ^* \) |
| CDR-SB             | 0.12±0.27 | 2.77±4.73 | 4.5±5.24   | 0.004 \( ^* \) |

Data are shown as mean±standard deviation.
MMSE: Mini-Mental State Examination, CDR-SB: Korean Clinical Dementia Rating Sum of Box, HN: healthy normal, MCI: mild cognitive impairment, AD: Alzheimer’s disease.
\( ^* \)Total number of patients: 96 (Hanyang University Seoul Hospital); \( ^* \)Mean difference is significant at the 0.05 level.

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https://doi.org/10.12779/dnd.2021.20.4.99
Sleep quality in study subjects

Table 2 presents the correlations of the 3 sleep questionnaires between the different groups. GSES and MEQ scores differed significantly between the groups of HN, MCI, and AD dementia subjects (p=0.037 and p=0.005, respectively). In contrast, there were no differences in PSQI scores (Fig. 1). A comparison of mean scores in each of the 3 tests between the groups showed that HN subjects had the lowest mean scores; MCI patients had moderate scores, and AD dementia patients had the highest scores (GSES: 1.762±1.79, 3.306±3.20, and 4.885±4.79, respectively; PSQI: 4.429±1.50, 5.286±3.12, 7.154±4.54, respectively; MEQ: 54.048±5.71, 59.306±8.79, and 60.653±6.67, respectively). When participants were sorted into 2 groups based on the amyloid burden, GSES and MEQ scores still showed statistically significant differences, whereas PSQI scores did not (Fig. 2).

Relationship between sleep quality and Aβ accumulation

SUVRs derived from the amyloid PET-CT results differed between the HN, MCI, and AD dementia groups (p<0.038; Fig. 3). In addition, we tried to find out the correlation between individual sleep questionnaire scores and each SUVR for different brain regions. Although not all questionnaire scores were statistically correlated to brain scan results, there was a weak correlation between MEQ scores and Aβ deposition within the bilateral PCC (p<0.05) (Table 3).

DISCUSSION

The extracellular aggregation of Aβ peptide is a hallmark of AD; it leads to neurodegeneration and sleep disorders. A previous study reported that shorter sleep duration and poorer sleep quality
are associated with greater Aβ burden among community-dwelling older adults. An association of sleep and the clearance of Aβ plaques has previously been established; it was partly explained by the glymphatic system’s action to clear the waste proteins during sleep. We hypothesized that neurodegeneration due to Aβ deposition could be related to the circadian rhythm.

We found that patients with AD dementia reported higher stress and anxiety resulting from sleeplessness than did HN subjects. In addition, the abnormal early-morning awakenings...
were frequent in the AD dementia subjects, as is consistent with the previous study, demonstrating that circadian-rhythm changes are expected in AD patients.\textsuperscript{25}

Significant differences in GSES scores between the HN, MCI, and AD dementia groups suggest that individuals without AD pathology had no difficulty falling asleep. In contrast, AD dementia patients reported higher stress and anxiety when they had no control over falling asleep. The same trend was observed in the score between the HN group and the CIAD, suggesting that the presence of clinically diagnosed AD pathology is associated with greater sleep effort. Because sleep is an involuntary physiological process, any “efforts to sleep” are likely to fail and exacerbate insomnia for AD dementia patients.\textsuperscript{21} This problem may contribute to the etiology of AD, resulting in a rapid progression of the disease.\textsuperscript{7}

Morningness-eveningness scores measured by MEQ differed significantly between HN, MCI and AD dementia subjects, indicating that each group is characterized by distinct sleep patterns. Most of the HN subjects showed an intermediate-type sleep pattern, whereas MCI and AD dementia patients were of the morning type. Disruptions in circadian rhythm have been apparent among AD dementia patients, suggesting that the deposition of A\textsubscript{\beta} peptide in specific brain regions might affect circadian-rhythm regulation even at preclinical stages.\textsuperscript{25-27} Our findings support this model, because patients that experience neuropathological changes show a shift of the circadian cycle to the morning type.

Although past studies showed that AD dementia patients experienced some sleep quality changes in sleep duration and frequent discontinuation of sleep, our data showed that the 3 different groups (HN subjects, MCI, and AD dementia patients) had relatively similar sleep quality as measured by PSQI.\textsuperscript{28,29} Longer sleep latency was associated with a more significant A\textsubscript{\beta} burden in prefrontal areas in asymptomatic middle-aged participants and older adults. The negative correlation between nocturnal awakenings and gray-matter volume in the insular region was also reported.\textsuperscript{20} Moreover, lower self-reported sleep quality was associated with greater A\textsubscript{\beta} burden and lower volume in brain areas relevant in aging and AD.\textsuperscript{10} PSQI generally covers various categories of sleep quality, which might have generated an inconclusive result. Failing to show significance in the composite measure of sleep efficiency in PSQI does not detract from the fact that specific surveys, such as of sleep effort and circadian rhythm, showed statistically significant differences.

We observed a positive correlation between MEQ scores and regional differences in SUVRs from the amyloid PET-CT scans. Increased levels of insoluble A\textsubscript{\beta} neurofibrils in the PCC...
may be the indicative marker of the abnormal function of the sleep-wake cycle, which often occurs with fragmented sleep.\textsuperscript{26,28} Our findings are biologically relevant, since the anatomical coordinates of Aβ deposits and circadian alterations were ascertained in clinically diagnosed AD dementia patients. The PCC is part of the medial prefrontal system, which represents a novel brain system of the default-mode network.\textsuperscript{30} Some studies have shown that the brain’s default- network activity was lowered during the awake time, whereas PET images showed a high metabolism rate in the PCC in the rested brain.\textsuperscript{31,32} Imbalance in regulating the brain’s default system attributable to the posterior cingulate hypometabolism can be consistent with our finding that abnormal sleep-cycle shifting proven by MEQ correlates with the degree of PCC affected by Aβ deposits. This finding can support the previous study revealing the association between shorter sleep duration and Aβ burden.\textsuperscript{9} Future studies would be valuable to reveal the correlation of alteration in circadian rhythm and molecular pathomechanisms caused by Aβ depositions.

There are several limitations to this study. First, we did not consider covariates, such as age, education years, and sex, which showed statistically significant differences between the 3 groups. The bias of having older individuals in the AD dementia group was anticipated because of the known association between AD progression and aging.\textsuperscript{33,34} In addition, education level in the HN group was higher than in the AD dementia group, as is consistent with the reported indirect relationship between educational level and incidence of AD.\textsuperscript{34} Sex distribution was not as significant as the age or the education level.

Second, we used only subjective measures of sleep quality (self-report sleep questionnaires). Moreover, subjective data collected in patients with cognitive deficits can arouse doubt about reliability. Including polysomnography or actigraphy in the assessment could have provided a more objective measure of sleep disruption or sleep/wake patterns. Also, we relied solely on amyloid PET-CT scans to diagnose AD pathology. Analyses of insoluble Aβ peptide and tau protein levels in the cerebral spinal fluid may have been more accurate in measuring AD pathology.

Next, a longitudinal study could be used to observe the worsening of sleep quality in AD dementia groups. Also, we did not measure the individual progression of sleep problems but focused on a cross-sectional study using the 3 groups in PSQI analysis. We analyzed only the final scores of the PSQI to measure poor sleep from each group. The difference in data analysis would have resulted in the opposite conclusion, since the previous study classified PSQI into 7 different sections, analyzing these scores individually.\textsuperscript{7}

Last, the 3 administered tests (GSES, PSQI, and MEQ) had different score ranges; normalization of the scores is required to improve statistical analyses combined with SUVRs from PET-CT images.

Despite these limitations, our results suggest that alterations in circadian rhythm may have a close relationship with neurodegeneration due to Aβ burden. Increased sleep effort is a co-occurring problem in the preclinical and clinical stage of AD. Also, disturbance in circadian rhythm increases with Aβ plaque abundance in specific regions of the brain. The mean scores from each questionnaire indicated that AD dementia patients are more likely to experience poor-quality sleep than are HN subjects. We identified the correlation between circadian rhythm and the level of Aβ in the PCC, indicating a possible explanation for the altered sleep patterns of AD dementia patients. The biological significance of the disturbed circadian cycle...
observed in AD dementia patients can be further addressed by examining the production of hormones that regulate the sleep cycle and their relationship to excessive Aβ aggregation in specific brain regions.

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