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Alterations in Rapid Eye Movement Sleep Parameters Predict for Subsequent Progression from Mild Cognitive Impairment to Alzheimer's Disease

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Abstract

Objective: Mild cognitive impairment (MCI) refers to the clinical condition between normal aging and Alzheimer's disease (AD). Heterogeneity in this entity has also been recognized, and an accelerated rate of progression to AD was documented in some individuals diagnosed with MCI. It is important for the early detection of and intervention for AD to determine the clinical subtype of MCI with a high risk of progression to AD. Studies have demonstrated that deceased glucose metabolism or regional cerebral blood flow in the posterior cingulate may be associated with a higher risk of such progression. The aim of this study was to investigate whether any polysomnography (PSG) variables support the prediction of progression from MCI to AD.

Methods: Twenty-four subjects with MCI were enrolled in this study. Clinical evaluation, cognitive screening tests, and PSG were carried out at the baseline. A diagnosis of MCI was made with standard criteria. Outcome measures were carried out to examine whether: 1) there was a significant cognitive decline, and 2) it progressed to AD according to the standard criteria for it. After a 2-year follow-up, subjects were divided into 2 groups. The MCI-AD group included subjects who progressed to AD, and the MCI-MCI group included those who did not meet the criteria for dementia. Basal PSG variables were compared between the groups.

Results: Nineteen subjects completed the study. Six subjects (32%) progressed to AD within 2 years. Subjects in the MCI-AD group showed a shorter stage REM sleep (p=0.043), and a reduced REM density (p=0.043) at the baseline.

Conclusion: Subjects who progressed to AD demonstrated altered REM sleep variables, yet they did not meet the criteria for clinically probable AD in the examination period. We consider that these properties may be associated with a higher risk of progression from MCI to AD.

Keywords: Alzheimer's disease; Mild cognitive impairment; Polysomnography; Progression; REM sleep; Risk factor; Sleep architecture

Introduction

Mild cognitive impairment (MCI) refers to the clinical condition between normal aging and Alzheimer's disease (AD) [1]. Individuals with MCI have memory impairment greater than what one would expect for their age, yet the general cognitive function is preserved. Similarly, activities of daily living are normal. Heterogeneity in this entity has also been recognized, and an accelerated rate of progression to AD was documented in some individuals diagnosed with MCI. A high percentage of patients with MCI develop clinical AD within 1 year. It is, therefore, important for the early detection of and intervention for AD to determine the clinical subtype of MCI with a high risk of progression to AD. Previous studies demonstrated that a higher risk of AD progression may be involved with an altered function in specific regions such as the posterior cingulate, which are characteristic of AD. Subjects with MCI who developed AD had already exhibited significantly decreased volumes [2-6], decreased levels of regional cerebral blood flow [7,8] and glucose metabolism [5,9-12] at the posterior cingulate compared to those who remained in a non-dementia state, when they did not meet criteria for dementia.

Studies on sleep architecture in AD have demonstrated that sleep disturbance is more prevalent in subjects with AD than elderly subjects without dementia. Significant changes in sleep/wake patterns, particularly loss of slow wave sleep (SWS) and increased amount and frequency of nighttime awakenings, apparently occur even at an early stage of the AD process [13]. These disruptions of nighttime sleep increase in magnitude with increasing severity of dementia. AD patients present with significant losses of REM sleep and the breakdown of the sleep/wake circadian rhythm with significant amounts of sleep occurring during the day. While the characteristics of sleep architecture in AD and the influence of normal aging on the sleep architectures have been well documented, it has not been discussed whether there are predictors of progression from MCI to AD in terms of somnology.

The aim of this study was to investigate whether there are any polysomnography variables in subjects with MCI that are associated with progression to AD. A shortened REM sleep is one of characteristic PSG variables in AD [13], which has been reviewed to be associated

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with the decrease in cholinergic neuronal activity. We hypothesized that an alteration of REM sleep parameters in MCI may be associated with conversion to AD.

Methods

Study design

This study had a prospective design to investigate whether any PSG variables at the baseline (in the stage of MCI) may be predictive of progression to AD. This study was conducted at Kagawa University Hospital. Data were collected between April 2011 and September 2015.

The local institutional review boards approved this study. All patients gave informed consent according to institutional guidelines and the tenets of the Declaration of Helsinki.

Patients

Twenty-four patients with amnestic MCI were enrolled in this study. Patients were eligible if: (i) they had never been treated with acetylcholine esterase inhibitors (AChIs), and (ii) were able to understand the aim of this study.

Patients were excluded if: (i) they had medical illnesses that may affect sleep quality or daytime alertness, (ii) they met criteria for any other psychiatric disorders such as schizophrenia, mood disorders, or delirium, and (iii) they were being treated with psychotropic agents or psychostimulants. To exclude the influence of sleep-disordered breathing on the sleep architecture, the subjects who had been diagnosed with sleep apnea syndrome were excluded. Even though symptoms or manifestations of sleep apnea such as snoring and excessive daytime somnolence were not presented, we excluded a subject whose apnea-hypopnea index (AHI) was over 10. Patients with potential vascular impairment were also excluded if they had a Hachinski Ischemic Scale [14] over 4, or magnetic resonance imaging (MRI) showed evidence of white matter lesions identified through consensus by experts in neuroimaging.

Diagnosis

Experienced, research-trained clinicians conducted semi-structured interviews with the subjects including the medical and psychiatric history, medication, an aphasia battery, and neurological examination. Families or next-of-kin were also interviewed. In all subjects, the cognitive function was assessed with Mini-mental State Examination (MMSE) [15]. The Clinical Dementia Rating (CDR) [16] was used to determine whether dementia was present and, if present, to stage its severity. Subjective sleep quality was assessed with Pittsburgh Sleep Quality Index (PSQI) [17]. BPSD was evaluated using the Neuropsychiatric Inventory (NPI) score [18]. MRI and technetium-99m ethyl cysteinate dimer (Tc-99m-ECD) single photon emission computed tomography (SPECT) were also carried out as supplementary diagnostic methods.

A diagnosis of amnestic MCI was made according to the criteria established by Petersen [1]. Patients with amnestic MCI of either single or multiple domains impaired were included. Criteria for MCI were: subjective complaint of memory deficit; absence of dementia according to the diagnostic examination (CDR =/< 0.5), and normal daily functioning of ADL; and abnormal memory functioning for age.

Polysomnography

Each patient received a standardized evaluation including a medical history as well as physical and neurological examinations. At the baseline, polysomnography (PSG) was carried out following the adaptation night. Electrodes for PSG were attached till 16:30. We performed overnight PSG by means of standard procedures [19] that included recording a sleep electroencephalogram (C3-A2, C4-A1), bilateral eye movements, submental electromyography (EMG), an electrocardiogram, pulse oximetry, bilateral tibialis anterior EMG, nasal air flow by a pressure sensor, as well as rib cage and abdominal excursions. The sleep stage was scored according to standard criteria. The total sleep time, sleep efficiency, and lengths of stages I, II, III, IV, and REM were obtained. Stage III plus stage IV were calculated as slow wave sleep (SWS). REM sleep was defined and analyzed according to the scoring criteria by Lapierre and Montplaisir [20]. REM sleep latency was calculated as the time from sleep onset to the first occurrence of REM. REM density was defined as the number of ocular movements per minute during REM sleep. PLMS and the apnea-hypopnea index (AHI) were also calculated with a standard guideline [21].

Outcome evaluations and grouping

After baseline examinations, donepezil was prescribed. Initially, 3 mg/d of donepezil was prescribed for 14 days with the assessment of adverse effects such as nausea. If no adverse effects were presented, 5 mg/d of donepezil was prescribed from the 3rd week onward.

On every visit, clinical evaluations were carried out. We also collected information on activities of daily living from their caregivers and/or responsible family members. We investigated how regularly they took donepezil. Two years after the baseline examinations, we evaluated the cognitive function and CDR to determine whether the subjects met the criteria for AD.

Probable AD was diagnosed according to the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [22].

After the 2-year follow up, subjects were divided into 2 groups. One included subjects who progressed to AD (MCI-AD group). The other included those who continued to show MCI (MCI-MCI group). Basal PSG variables and other baseline parameters were compared between the two groups.

Data analysis

We used Mann-Whitney's *U* test to examine the differences in PSG variables and other baseline parameters between the two groups. All analyses were performed with software PASW Statistics 18.0™. When the *p* value was less than 0.05, we considered the difference significant.

Results

Demography of subjects (Table 1)

Of the 24 participants, 19 subjects completed this study. They were 9 males and 10 females, and the mean age was 70.8 ± 7.1 years old. Three patients were excluded because their AHI indices were higher than 10. Two patients were withdrawn due to medical illnesses.

The basal MMSE and body mass index (kg/m^2) were 25.9 ± 1.3 and 21.3 ± 3.0, respectively. Mean PSG variables of the 19 patients are presented in Table 1.

Outcomes after 2-year follow-up

Of the 19 subjects, 6 patients (31.6%; 3 males and 3 females) had progressed to AD within 2 years. There were no differences in the age, body mass index, or basal MMSE between the MCI-MCI and MCI-AD groups (Table 2).

No. of Subjects (Female/Male)	19 (10/9)
age (y.o.)	70.8 ± 7.1
MMSE	25.9 ± 1.3
Education (years)	11.6 ± 2.5
Body mass index (kg/m^2)	21.3 ± 3.0
Pittsburgh Sleep Quality Index	5.2 ± 1.8
Polysomnography variables	
Total sleep time (TST) (min)	356.6 ± 27.7
Sleep efficiency (%)	74.6 ± 5.6
Sleep latency (min)	23.5 ± 8.5
Stage I (%TST)	23.3 ± 8.6
Stage II (%TST)	51.7 ± 6.8
Stage III+IV (%TST)	9.8 ± 3.5
Stage REM (%TST)	15.2 ± 2.9
REM sleep latency (min)	88.7 ± 15.5
REM density (REM/min)	8.5 ± 1.7
PLMS index (No./hr)	21.5 ± 7.5
Apnea-hypopnea index	7.0 ± 2.2

MMSE: Mini-Mental State Examination, REM: rapid eye movement, PLMS: periodic limb movement during sleep

Table 1: Demography of subjects and polysomnography variables at the baseline.

	MCI-MCI	MCI-AD	p value
No. of subjects (Female/Male)	13 (7/6)	6(3/3)	
age (y.o.)	70.2 ± 6.5	70.2 ± 9.1	0.76
body mass index (kg/m^2)	21.5 ± 3.2	20.7 ± 2.9	0.6
Education (years)	11.5 ± 2.5	12.0 ± 2.8	0.66
Pittsburgh Sleep Quality Index	4.8 ± 1.8	6.0 ± 1.5	0.15
At the baseline			
MMSE	26.2 ± 1.4	25.2 ± 0.8	0.13
CDR	0.18 ± 0.25	0.20 ± 0.27	0.87
2-year follw up			
MMSE	25.4 ± 1.3	17.8 ± 1.3	**<0.01
CDR	0.27 ± 0.26	1.42 ± 0.38	**<0.01

MCI: Mild Cognitive Impairment, AD: Alzheimer's Disease, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating

Table 2: Comparison of characteristics at the baseline and 2-year follow-up.

	MCI-MCI	MCI-AD	
	n=13	n=6	p value
Total sleep time (TST) (min)	362.4 ± 28.5	343.9 ± 22.9	0.16
Sleep efficiency (%)	75.7 ± 6.2	72.2 ± 3.1	0.15
Sleep latency (min)	21.9 ± 6.9	27.0 ± 11.2	0.27
Stage I (%TST)	21.7 ± 8.2	26.9 ± 9.1	0.16
Stage II (%TST)	51.4 ± 6.1	52.2 ± 8.8	0.79
Stage III+IV (%TST)	10.7 ± 3.5	7.8 ± 2.7	0.095
Stage REM (%TST)	16.2 ± 2.6	13.1 ± 2.6 *	0.043
REM sleep latency (min)	84.5 ± 12.8	97.7 ± 18.2	0.124
REM density (REM/min)	9.1 ± 1.6	7.3 ± 1.4*	0.043
PLMS index (No./hr)	19.4 ± 7.4	26.0 ± 5.8	0.086
Apnea-hypopnea index	7.1 ± 2.3	6.7 ± 2.3	0.76

Participants were divided into two groups. The MCI-AD group included subjects who developed AD within 2 years. The MCI-MCI group included subjects who maintained MCI for 2 years.
Polysomnography (PSG) was carried out at the baseline. Variables obtained from the basal PSG were compared between the two groups. *p<0.05
MCI: mild cognitive impairment, AD: Alzheimer's disease, REM: rapid eye movement, PLMS: periodic limb movement during sleep

Table 3: Comparison of polysomnography.

PSG variables obtained at the baseline were compared between the 2 groups (Table 3). Times spent in stage REM (% of total sleep time) were 13.1 ± 2.6 and 16.2 ± 2.6% in the MCI-AD and the MCI-MCI groups, respectively (p=0.043). REM density in the MDI-AD group (7.3 ± 1.4 REM/min) was reduced compared to that in the MCI-MCI group (9.1 ± 1.6 REM/min) (p=0.043). Subjects in the MCI-AD group had already presented with a shorter REM sleep and a reduced REM density in the stage of MCI. While significant differences in these REM sleep parameters were demonstrated, the difference in REM sleep latency was not significant (p=0.124). Time spent in SWS in the MCI-AD group (7.4 ± 2.8 %) was shorter than that in the MCI-MCI group (10.9 ± 3.8%), but the difference was not significant (p=0.095). The PLMS index and Pittsburgh Sleep Quality Index (PSQI) score also tended to be high, but the differences were not significant (p=0.086 for PLMS index; p=0.080 for PSQI).

Discussion

The aim of this study was to investigate if any alterations in sleep architecture or sleep parameters may be associated with progression from MCI to AD. We demonstrated that subjects who progressed to AD had a decreased percentage of time spent in REM sleep, and a reduced REM density at the baseline compared to those who did not progress to AD.

Age-dependent alterations in the sleep architecture have been well documented. The total sleep time, sleep efficiency, and times spent in SWS and REM sleep have been demonstrated to significantly decrease with age. The sleep latency, time spent in stage I, and waking after sleep onset were reported to increase with age [23]. In addition, specific disorders such as sleep-disordered breathing and periodic limb movement disorder are prevalent in the elderly. These alterations result in sleep fragmentation and a poorer sleep quality, and may contribute to sleep disturbances in the elderly. Therefore, we set inclusion and exclusion criteria with careful deliberations to exclude the influence of the age, sex, BMI, psychiatric disorders, medications, and sleep-disordered breathing.

Because these features are noticeable in patients with AD [13], they are troubled by sleep disturbances. The prevalence of sleep disturbance in AD has been estimated to be 25% in mild to moderate cases, and about 50% in moderate to severe cases [13]. Disruption of the melatonin rhythm might be caused by a dysfunction in sympathetic regulation by the suprachiasmatic nucleus (SCN) of pineal melatonin synthesis [24]. The SCN may be under the modulatory influence of the nucleus basalis of Meynert, which degenerates in an early stage of AD. Due to these conditions, patients with AD nap excessively in the daytime, have difficulty falling asleep at night, exhibit frequent nocturnal awakenings, and wake up too early.

Subjects with MCI have memory impairment beyond that expected for their age and education, and yet they are not demented. The entity of MCI is heterogeneous, and some subjects with MCI develop AD within a couple of years and others continue with MCI for several years. Therefore, it is mandatory for early detection and adequate intervention to specify the subjects with higher risks of progressing to AD. Evidence has been accumulated to elucidate the predictors of progression to AD in subjects with MCI, which includes investigations of biomarkers obtained in cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), SPECT, and PET. Previous MRI studies have demonstrated that MCI subjects with a smaller volume of the hippocampus [3,4,6] or medial (and inferior) temporal lobe [2,3,5] are at a high risk of progressing to AD. Decreases in regional cerebral blood flow at the precuneus, posterior cingulate [7], or medial temporal lobes [7,8] have been reported to be associated with AD conversion. FDG-PET studies demonstrated that hypometabolisms in the medial temporal [5],

temporoparietal [9,11], or posterior cingulate [9-12] were predictors of progression to AD. These studies suggest that MCI subjects who develop AD begin to exhibit morphological changes (atrophy) and reduced cerebral blood flow and glucose metabolism at the AD-specific lesion sites.

Recently, some reports on somnological features of subjects with MCI have become available. Patients with amnestic MCI have been demonstrated to show reduced REM sleep, disrupted SWS, and a higher prevalence of self-reported sleep problems when compared to age-matched control subjects [25]. Furthermore, shortened REM sleep in MCI has been demonstrated to be correlated with the thinning of canonical AD regions such as the posterior cingulate and precuneus [26]. In the study [26], the relationship between disrupted SWS and increased plasma levels of amyloid-β42 (Aβ42) was also reported.

The cholinergic system plays important roles in generating REM sleep as well as the cognitive function. Neurons of the pedunculopontine and laterodorsal tegmentum are essential for the generation of REM sleep. These neurons send cholinergic projections to the nucleus basalis of Meynert. The basal forebrain cholinergic territories and their cortical projections have been reported to be decreased in MCI subjects, which was further associated with impairment of the cognitive function such as the recall ability [27]. As a previous study [28] demonstrated, REM deficits may indicate the level of AD pathology in the basal forebrain cholinergic system.

Several studies and reviews suggested that patients with AD spent a shorter time in REM sleep [13]. REM densities have also been reported to be reduced in AD patients compared with those in elderly depressed subjects [28,29] and elderly controls [28]. The length of REM latency in AD patients compared to controls is controversial. Some studies reported that AD patients had a longer REM latency [30,31], but others reported no significant differences [28,29]. At any rate, the alteration of REM sleep parameters may be specific to AD, while non-REM stage II may be related to declarative memory formation in dementia independent of subtypes [31]. Our data demonstrated that subjects who developed AD presented with shortened REM sleep and reduced REM density when they were in the stage of MCI. They had a longer REM latency, which was not a significant difference.

In the present study, we demonstrated that there were significant differences in REM parameters (time spent in REM sleep and REM densities) between subjects who developed AD and those who maintained MCI when they did not yet meet diagnostic criteria for AD. We conclude that alterations in REM sleep parameters may be predictors of progression from MCI to AD.

There have been no studies investigating the prediction of progression to AD from a somnological point of view. To our knowledge, this is the first study to demonstrate the association between altered REM sleep parameters and progression to AD. Our study, however, has some limitations. We did not enroll gender- and age-matched subjects without cognitive declines as a control group to exclude the influence of normal aging on PSG. Further studies with a larger sample size are recommended.

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