Low Sleep Efficiency in Patients with Cognitive Impairment

Jia-Ming Yu[1], Ing-Jy Tseng[2], Rey-Yue Yuan[2], Jau-Jiuan Sheu[2], Hsing-Cheng Liu[3], and Chaur-Jong Hu[1,4,5,6]

Abstract- Alzheimer's disease (AD) is the most common cause of dementias. Mild cognitive impairment (MCI) indicates the situation that a person has memory complaints and mild objective cognitive impairment but no evidence of dementia. Sleep disturbance, one of the behavioral and psychological symptoms of dementia (BPSD), frequently occurs in patients with AD or MCI. The alteration of sleep architectures in AD patients remains inconclusive. In this study, we conducted the polysomnography (PSG) examination among patients with mild AD with cholinesterase inhibitors (N=10) or MCI (N=12) and age-matched non-demented controls (N=13). The results showed sleep efficiency, which was one of the important parameters for sleep quality was significantly lower in patients with MCI and AD (N=22), 79.14±11.06 % vs. 67.07±19.10 %, p=0.046. There were no statistic differences of sleep architecture but a trend of REM insufficiency in patients with MCI or AD. The mean scores of geriatric depression score (GDS) and Epworth sleepiness scale (ESS) did not differ among the three groups. Our study implicated maintenance of sleep was impaired in patients with cognitive impairment and it was independent with depressive symptoms.

Key Words: Dementia, Alzheimer's disease, Mild cognitive impairment, Sleep, Polysomnography

Acta Neurol Taiwan 2009;18:91-97

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease, characterized by insidious onset, memory deterioration, cognitive functions impairment, behavioral disturbances and various kinds of psychiatric manifestations[(1)]. AD is the most common cause of dementias. The etiology of AD is still obscure. The neuropathological landmarks of AD include neuritic senile plaques, neurofibrillary tangles, and neuronal loss. Only a few drugs are approved for AD therapy. One group is cholinesterase inhibitor and the other group is N-methyl D-aspartate (NMDA) receptor inhibitor. Unfortunately, these medications only could slow down the progression

From the [1]Department of Neurology, Taipei Medical University; [2]College of Nursing, Taipei Medical University; [3]Department of Psychosomatic Medicine, Taipei City Psychiatric Center, Taipei City Hospital; [4]Sleep Center, Taipei Medical University Hospital; [5]School of Medical Technology, Taipei Medical University, Taipei, Taiwan; [6]Department of Neurology, Taipei Medical University, Shuang Ho Hospital, Taiwan.
Received March 25, 2008. Revised May 14, 2008.
Accepted October 6, 2008.

Reprint requests and correspondence to: Chaur-Jong Hu, MD. Department of Neurology and Sleep Center, Taipei Medical University Hospital, No. 252, Wu-Hsing Street, Taipei 110, Taiwan.
E-mail: chaurjongh@tmu.edu.tw

of AD so their cost-effective is still controversial[2].

Mild cognitive impairment (MCI) usually defines a transitional stage between normal ageing and dementia, usually in terms of AD. MCI indicates the clinical situation of subjective memory complaints and objective evidence of mild cognitive impairment but no evidence of dementia[3]. The disease validity of MCI has been supported by conversion rates to AD of about 12% annually and 80% at 6 years follow-up[4,5]. MCI could be the preclinical or very early stage of AD. But, the diagnosis criteria for MCI are still controversial[6].

Sleep disturbance and circadian disarrangement are both common manifestations of behavioral and psychological symptoms of dementia (BPSD)[7]. BPSD also commonly occurs in patients with MCI[8]. During sleep, there usually are one or few cycles containing rapid eye movement (REM) sleep and non-REM sleep in each cycle. REM sleep is linked to dreaming and it is with characteristic physiological presentations, including rapid eye movement, generalized hypotonia and alteration of autonomic nervous tone[9]. Recent researches have raised the association between REM sleep and some specific forms of memory, especially in sleep deprivation studies[10]. Sleep disturbance could be an indicator for poor outcome of dementia and it usually causes a heavy burden for care-givers of dementia[8,11]. In AD animal models, sleep disturbance was found to be associated with the brainstem cholinergic neurons degeneration. These implicate that sleep disturbance is an important manifestation of AD[12,13]. The compelling evidence supports memory consolidation during sleep. Especially, rapid eye movement (REM) stage is crucial for some visual-spatial memory and specific task-learning[14]. The initiation of REM sleep is mainly acetylcholine-dependent[15]. Cholinesterase inhibitors which can increase intracerebral acetylcholine levels have become the standard therapy of Alzheimer's disease (AD) for improving cognitive function[16]. Therefore, theoretically, REM sleep should be insufficient in AD or MCI patients. However, the changes of sleep architectures among AD or MCI patients are still inconclusive[17-19]. In this study, we conducted polysomnography examinations for age-matched controls and patients with cognitive impairment, in terms of AD and MCI to explore whether sleep disturbed in the patients with cognitive impairment.

METHODS

Patients and controls

Ten AD patients with mild dementia, whose minimental status examination (MMSE) scores between 18 and 22, 12 MCI patients with MMSE scores 27-29 and 13 controls without cognitive impairment were recruited (Table). This study was approved by the Interstitial Review Board of Taipei Medical University Hospital (TMUH) and all the participants gave written informed consents. The diagnosis of AD is according to the criteria of NINCDS-ADRDA for probable AD[20]. All the AD patients were taking cholinesterase inhibitors. None of them had sleep complaints at the study time. The diagnosis of MCI was made by the consensus of neurologists (H.C. Liu and C.J. Hu) according to the diagnostic criteria including: (1) the person is neither normal nor demented; (2) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (3) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired[21]. In summary, the MCI patients were diagnosed if their Clinical Dementia Rating (CDR) was 0.5 (memory box 0.5-1) and minimal mental status examination (MMSE) ≥24. All the AD and MCI patients took laboratory tests to exclude other dementia causes, including complete blood count, folic acid, vitamin B12, VDRL, thyroid function test and CT of brain[4]. Thirteen healthy volunteers who received routine health examinations at TMUH were subjects for controls. Each control was given clinical, mental, and neurological examinations, and none of them showed any cognitive defects or sleep complaints. None of them was taking hypnotics.

Questionnaires associated with day time sleepiness and depression

To understand the day time activities and mood situ-

ation, the questionnaires of Geriatric depression scale (GDS) and Epworth sleepiness scale (ESS) were performed before the polysomnography[22,23].

Polysomnography (PSG)

All the participants took PSG in the Sleep Center of TMUH by use of Sandman Elite (Tyco Healthcare, Canada). The scoring of PSG examination was based on the Rechtschaffen & Kales rules[24].

Statistical analyses

SPSS 13.0 for Windows was used for all statistical analyses. Descriptive statistics were expressed as mean ±standard deviations as well as frequencies in the AD, MCI and control groups. Multiple comparisons among AD, MCI and control groups were examined using the Kruskal-Wallis test. AD and MCI groups are merged into a group of cognitive impairment to compare with control group by using two-tailed values of the Mann-Whitney U test. *P* values below 0.05 were considered statistically significant.

RESULTS

Demographics

A total of 22 patients with cognitive impairment (AD ＝10, MCI＝12) and 13 healthy controls were included in this study. Mean age of the patients was 77.14±8.93 years (range：63-90 years). Controls were age-matched with the mean age of 76.38±8.31 years. Further characteristics of the patients are listed in Tables.

Polysomnographic results

The data of total sleep time, time in bed, sleep efficiency, sleep onset (latency), REM onset (latency), percentage of REM, periodic limbs movement index (PLMI), and number of REM obtained from PSG and subjective questionnaire data, including ESS and GDS are summarized in Tables. The PSG parameters in the three groups, in terms of controls, MCI and AD, are not statistically different from each other (Table 1). The patient group showed a disturbed sleep efficiency (67.07 ±19.10%). Time in bed was 436.82±29.21 minutes. Total sleep time was 293.45±86.52 minutes. Sleep onset was 1061.68±1428.00 seconds. REM onset was 149.45 ±72.67 minutes. The percentage of REM sleep was 13.52±7.37%. PLMI was 30.77±35.87/h. Number of REM sleep was 2.68±1.36. In the Control group, sleep efficiency was 79.14±11.06 %. Time in bed was 421.00 ±48.95 minutes. Total sleep time was 333.54±61.40 minutes. Sleep onset was 803.31±997.65 seconds. REM onset was 134.38±73.04 minutes. The percentage of REM sleep was 15.33±7.77%. PLMI was 30.77± 35.87/h. Number of REM sleep was 2.85±0.80. Only the sleep efficiency was significantly different among all the sleep variables between cognitive impairment group and control group. There were no statistically significant differences in the scores on the ESS and GDS.

There were no differences in sleep architecture between controls and patients with cognitive impairment, in terms of MCI and mild AD. Sleep efficiency, which was one of the important parameters for sleep quality was significantly lower in patients with cognitive impairment than in controls. Low sleep efficiency usually results from poor maintenance of sleep and it was probably associated with depression neurosis. However, the geriatric depression scores (GDS) were not different between controls and patients. These results implicate maintenance of sleep was impaired in patients with cognitive impairment and it was independent from depressive symptoms.

DISCUSSION

In a meta-analysis of quantitative sleep parameters, among adults, total sleep time, sleep efficiency, percentage of slow-wave sleep, percentage of REM sleep, and REM latency significantly decreased with age. Sleep latency, percentage of stage 1 sleep, percentage of stage 2 sleep, and wake after sleep onset significantly increased with age. Only sleep efficiency continued to significantly decrease after 60 years of age[25]. Sleep efficiency which represents the ratio of total sleep time to the total time in bed, is a parameter of sleep maintenance. Sleep efficiency of lower than 85% usually indicates one of the diagnostic criteria of insomnia[26]. Although low sleep efficiency has been associated with excessive day time sleepiness in Parkinson's disease, the

Table 1. *Comparison of means of sleep variables between MCI, AD and control group*

Variable	Controls (n=13)	MCI (n=12)	AD (n=10)	χ^2 or KW test	*p*
Age (yrs.)	76.38± 8.31	75.08±10.66	79.60±5.87	2.433	.469
Gender					
Male	9 (69.2)	7 (41.7)	5 (50.0)	.892	
Female	4 (30.8)	5 (58.3)	5 (50.0)	.640	
Time spend in bed (min.)	421.00±49.00	426.58±33.27	449.10±18.17	3.417	.190
Total sleep time (min.)	333.54±61.40	279.67±79.24	310.00±96.10	3.725	.245
Stage I (%)	18.57± 9.59	26.16±13.92	21.54±11.90	1.596	.207
Stage II (%)	61.70±11.56	54.24±12.94	59.26±11.15	1.157	.282
Stage III (%)	4.35± 5.71	6.26± 6.83	4.56± 7.95	0.301	.583
Stage IV (%)	0.10± 0.28	0.71± 1.54	0.33± 1.04	0.010	.922
Sleep efficiency (%)	79.14±11.06	65.70±18.16	68.71±21.04	4.168	.129
Sleep onset (min.)	13.47±16.62	14.85±19.60	21.11±28.78	.179	.914
REM onset (min.)	134.38±73.04	155.92±67.37	141.70±81.55	.859	.763
REM(%)	15.33± 7.77	12.97± 8.46	14.19± 7.46	.690	.742
PLMI (%)	15.09±19.18	27.62±27.70	34.56±45.12	1.512	.324
PLMAI (/h)	2.39± 3.31	10.77±14.36	8.22±11.72	3.21	.201
RERAI (/h)	21.24±17.91	10.68± 9.60	22.88±24.26	2.51	.286
Number of REM (/h)	2.85± 0.80	2.42± 0.90	3.00± 1.76	1.180	.324
AHI (/h)	27.27±19.62	14.01±12.42	26.52±28.30	2.726	.256
Arousal Index (/h)	27.71±15.13	22.54± 7.21	33.57±18.54	1.815	.404
Geriatric Depression Scale (0-15)	7.09± 4.28	6.25± 4.17	5.00± 2.73	.939	.377
Epworth Sleepiness Scale (0-24)	7.23± 6.11	5.27± 6.62	6.60± 5.04	1.233	.692
Mini Mental State Exam (0-30)	29.46± 0.97	27.80± 2.04	20.80± 2.49	23.249	.000*
Education (year)	12.00± 4.27	9.60± 7.46	8.00± 5.06	1.854	.396

Data are presented as mean ± Standard deviation (SD). Significance was determined by nonparametric statistics (Kruskal-Wallis (KW) test for three groups). PLMI: Periodic limbs movement index; AHI: Apnea hypopnea index; PLMA: PLM arousal index; RERAI: Respiratory arousal index. *P < 0.05.

clinical consequence of low sleep efficiency in other neurodegenerative diseases still lacks detailed studies[27]. On the other hand, decreased sleep efficiency has been found in many mental diseases, such as depression, psychosis and alcoholism[28-30]. In this study, sleep efficiency of patients with cognitive impairment was significantly lower than that of controls. There was no increase of day time sleepiness based on the Epworth sleepiness scale. These results implicates that sleep maintenance might be impaired in the patient group but the impairment did not impact their day time sleepiness. Since depression is common in patients with cognitive impairment, geriatric depression scale questionnaire (GDS), which is feasible even in mild dementia population, was performed to explore the role of mood in the decrease of sleep efficiency[7,31]. The study found depression was not associated with the decrease of sleep efficiency. Therefore, the causes and the consequences of decreased sleep efficiency in patients with cognitive impairment need further investigation.

Table 2. *Comparison of means of sleep cariables between cognitive impairment group and control group*

Variable	Control group (n=13)	Cognitive Impairment group (n=22)	Z	P
Age (yrs.)	76.38±8.31	77.14±8.93	- .188	.851
Gender				.311
Male	9 (69.2)	12 (54.5)		
Female	4 (30.8)	10 (45.5)		
Time in bed (min.)	421.00±48.95	436.82±29.21	-1.007	.314
Total sleep time (min.)	333.54±61.40	293.45±86.52	-1.417	.157
Stage I (%)	18.57± 9.59	24.06±12.95	-1.263	.216
Stage II (%)	61.70±11.56	56.52±12.14	-1.076	.287
Stage III (%)	4.35± 5.71	5.49± 7.23	-0.549	.601
Stage IV (%)	0.10± 0.28	0.54± 1.32	-0.098	.960
Sleep efficiency (%)	79.14±11.06	67.07±19.10	-1.997	.046*
Sleep onset (min.)	13.47±16.63	17.69±23.80	- .171	.864
REM onset (min.)	134.38±73.04	149.45±72.67	- .597	.550
REM (%)	15.33± 7.77	13.52± 7.37	- .632	.528
PLMI (%)	15.09±19.18	30.77±35.87	-1.200	.230
PLMAI (/h)	2.39± 3.31	9.68±13.04	-1.677	.094
RERAI (/h)	21.24±17.91	15.91±18.01	-1.347	.178
Number of REM	2.85± 0.80	2.68± 1.36	- .733	.464
AHI (/h)	27.27±19.62	19.70±21.56	-1.434	.152
Arousal index (/h)	27.71±15.13	27.23±14.05	- .301	.763
Geriatric depression scale (0-15)	7.09± 4.28	5.38± 3.78	- .870	.366
Epworth sleepiness scale (0-24)	7.23± 6.11	5.45± 5.57	- .733	.384
Mini mental state exam (0-30)	29.46± 0.97	24.30± 4.22	-3.821	.000*
Education (year)	12.00± 4.72	9.00± 6.52	-1.317	.188

Data are presented as mean ± Standard deviation (SD). Significance was determined by nonparametric statistics (Mann-Whitney U test for two groups) as a result of data that were not normally distributed. PLMI: Periodic limbs movement index; AHI: Apnea hypopnea index; PLMA: PLM arousal index; RERAI: Respiratory arousal index. *P < 0.05.

There have been many polysomnographic (PSG) reports about changes of sleep architectures in AD patients with or without cholinesterase inhibitors[17-19]. The initiation of REM sleep depends on the activation of cholinergic neurons in lateral dorsal tegmental nuclei (LDT) and pedunculo-pontine tegmental nuclei (PPT)[13,15,32]. The acetylcholine (ACh) levels are relatively low in patients with AD and deficiency of ACh is considered to be symptomatic for AD[33]. Based on these findings, it is speculated that REM sleep is suppressed in AD. This study did show a tendency that the number or percentage of REM decreased and REM latency increased in patients with cognitive impairment but not reaching the significance. These results might support the defects of acetylcholine-REM axis in AD. Because of the consideration of ethical issue and the compliance of PSG examination, the AD participants of this study were all at mild degree of severity and all of them were

taking cholinesterase inhibitors. Those factors might mask or underestimate the REM changes in cognitive-impaired patients.

One-night PSG is always challenged by the first night effect. Although it has been questioned and the studies showed no difference of sleep efficiency between the first night and second night, the first night effect obviously is a limitation of this study[34]. In AD, sleep disordered breathing (SDB) occurred less frequently than in non-demented elderly subjects. The causal relationship between AD and SDB remains controversial[35]. The mean apnea-hyponea-indexes (AHI) were 27.27± 19.62, 19.70±21.56 in control, and cognitive impairment groups respectively (p=0.152). These results demonstrate SDB is a common disorder among the aged population. The gender distributions in the controls and cognitive impairment group were not the same in this study. However, the differences did not reach statistic significance and the gender effect on sleep architecture, especially in the elder populations, is largely unknown[36]. Arousal index and causes of arousals roughly reflex the impacts of SDB, periodic limb movement and arousal status on the sleep. The arousal patterns in controls and cognitive impairment group need further analysis. Without statistic significance, the mean education years in controls were higher than it in the cognitive impairment group. This phenomenon might result from that the people with higher education year are easier to become a volunteer for the clinical study. There was a tendency that the PLMI of cognitive impairment group was higher than it of the control group. High PLMI usually reflexes the deficiency of dopamine levels in the brain and that could occur in the AD brain[37,38]. PLMI might be a predictor of total sleep time in cognitive impaired elders. Therefore, further investigation by larger sample size might be warranted.

In summary, the number and percentage of REM decreased and REM latency increased at borderline degree in patients of cognitive impairment. That might reflect the low brain ACh levels in these patients. The sleep efficiency significantly reduced but was without significant impacts on day time sleepiness and that was not associated with depressive symptoms. These results might imply that the patients with cognitive impairment could be under the hyper-arousal status. The causes and consequences of low sleep efficiency among patients with cognitive impairment need further investigation.

REFERENCES

1. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159-65.
2. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479-86.
3. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-92.
4. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397-405.
5. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002;59:1594-9.
6. Chong MS, Sahadevan S. Preclinical Alzheimer's disease: diagnosis and prediction of progression. Lancet Neurol 2005;4:576-9.
7. Chiu MJ, Chen TF, Yip PK, et al. Behavioral and psychologic symptoms in different types of dementia. J Formos Med Assoc 2006;105:556-62.
8. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 2002;288:1475-83.
9. Markov D, Goldman M. Normal sleep and circadian rhythms: neurobiologic mechanisms underlying sleep and wakefulness. Psychiatr Clin North Am 2006;29:841-53.
10. Fogel SM, Smith CT, Cote KA. Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. Behav Brain Res 2007;180:48-61.
11. Fuh JL, Wang SJ, Liu HC, et al. The caregiving burden scale among Chinese caregivers of Alzheimer patients. Dement Geriatr Cogn Disord 1999;10:186-91.
12. Vloeberghs E, Van Dam D, Engelborghs S, et al. Altered circadian locomotor activity in APP23 mice: a model for

BPSD disturbances. Eur J Neurosci 2004;20:2757-66.
13. Zhang B, Veasey SC, Wood MA, et al. Impaired rapid eye movement sleep in the Tg2576 APP murine model of Alzheimer's disease with injury to pedunculopontine cholinergic neurons. Am J Pathol 2005;167:1361-9.
14. Stickgold R, Walker MP. Sleep-dependent memory consolidation and reconsolidation. Sleep Med 2007;8:331-43.
15. Hobson JA. Sleep and dreaming: induction and mediation of REM sleep by cholinergic mechanisms. Curr Opin Neurobiol 1992;2:759-63.
16. Fillit H, Hill J. Economics of dementia and pharmacoeconomics of dementia therapy. Am J Geriatr Pharmacother 2005;3:39-49.
17. Bahro M, Riemann D, Stadtmüller G, et al. REM sleep parameters in the discrimination of probable Alzheimer's disease from old-age depression. Biol Psychiatry 1993; 34:482-6.
18. Dykierek P, Stadtmüller G, Schramm P, et al. The value of REM sleep parameters in differentiating Alzheimer's disease from old-age depression and normal aging. J Psychiatr Res 1998;32:1-9.
19. Cooke JR, Loredo JS, Liu L, et al. Acetylcholinesterase inhibitors and sleep architecture in patients with Alzheimer's disease. Drugs Aging 2006;23:503-11.
20. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-44.
21. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-6.
22. Chan AC. Clinical validation of the Geriatric Depression Scale (GDS): Chinese version. J Aging Health 1996;8:238-53.
23. Chen NH, Johns MW, Li HY, et al. Validation of a Chinese version of the Epworth sleepiness scale. Qual Life Res 2002;11:817-21.
24. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human sleep. Los Angeles: Brain Information Service/ Brain Research Institute, UCLA, 1968.
25. Ohayon MM, Carskadon MA, Guilleminault C, et al. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27:1255-73.
26. Morin CM, Hauri PJ, Espie CA, et al. Nonpharmacologic treatment of chronic insomnia. An american Academy of Sleep Medicine review. Sleep 1999;22:1134-56.
27. Shpirer I, Miniovitz A, Klein C, et al. Excessive daytime sleepiness in patients with Parkinson's disease: a polysomnography study. Mov Disord 2006;21:1432-8.
28. Argyropoulos SV, Wilson SJ. Sleep disturbances in depression and the effects of antidepressants. Int Rev Psychiatry 2005;17:237-45.
29. Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev 2003;7:523-39.
30. Benson KL. Sleep in schizophrenia: impairments, correlates, and treatment. Psychiatr Clin North Am 2006;29: 1033-45.
31. Montorio I, Izal M. The Geriatric Depression Scale: a review of its development and utility. Int Psychogeriatr 1996;8:103-12.
32. Stenberg D. Neuroanatomy and neurochemistry of sleep. Cell Mol Life Sci 2007;64:1187-204.
33. Schliebs R, Arendt T. The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. J Neural Transm 2006;113:1625-44.
34. Kader GA, Griffin PT. Reevaluation of the phenomena of the first night effect. Sleep 1983;6:67-71.
35. Janssens JP, Pautex S, Hilleret H, et al. Sleep disordered breathing in the elderly. Aging (Milano) 2000;12:417-29.
36. Sakakibara S, Kohsaka M, Kobayashi R, et al. Gender differences in self-evaluated sleep quality and activity of middle-aged and aged subjects. Psychiatry Clin Neurosci 1998;52:184-6.
37. Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. Sleep 1993;16:713-6.
38. Rossor MN. Neurotransmitters and CNS disease. Dementia. Lancet 1982;2:1200-4.