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Correlation of Sleep Disturbance and Cognitive Impairment in Patients with Parkinson's Disease

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ABSTRACT

Objective Cognitive impairment is a common nonmotor symptom of Parkinson's disease (PD) and is associated with high mortality, caregiver distress, and nursing home placement. The risk factors for cognitive decline in PD patients include advanced age, longer disease duration, rapid eye movement sleep behavior disorder, hallucinations, excessive daytime sleepiness, and nontremor symptoms including bradykinesia, rigidity, postural instability, and gait disturbance. We conducted a cross-sectional study to determine which types of sleep disturbances are related to cognitive function in PD patients.

Methods A total of 71 PD patients (29 males, mean age 66.46 ± 8.87 years) were recruited. All patients underwent the Mini-Mental State Examination (MMSE) and the Korean Version of the Montreal Cognitive Assessments (MoCA-K) to assess global cognitive function. Sleep disorders were evaluated with the Stanford Sleepiness Scale, Epworth Sleepiness Scale, Insomnia Severity Index (ISI), Pittsburg Sleep Quality Index, and Parkinson's Disease Sleep Scale in Korea (PDSS).

Results The ISI was correlated with the MMSE, and total PDSS scores were correlated with the MMSE and the MoCA-K. In each item of the PDSS, nocturnal restlessness, vivid dreams, hallucinations, and nocturnal motor symptoms were positively correlated with the MMSE, and nocturnal restlessness and vivid dreams were significantly related to the MoCA-K. Vivid dreams and nocturnal restlessness are considered the most powerful correlation factors with global cognitive function, because they commonly had significant correlation to cognition assessed with both the MMSE and the MoCA-K.

Conclusions We found a correlation between global cognitive function and sleep disturbances, including vivid dreams and nocturnal restlessness, in PD patients.

Key Words Cognitive impairment; Parkinson's disease; Sleep disturbance.

Parkinson's disease (PD) is characterized by abnormal motor symptoms such as bradykinesia, tremor, rigidity, and postural instability. However, the nonmotor symptoms of PD, including cognitive impairment, depression, anxiety, psychosis, sleep disorders, and autonomic dysfunction, are also important and could have greater significance for disability, decreased quality of life, and reduced lifespan of the patiens.[1] Sleep disturbances are present in approximately 38% to 98% of PD patients and are more frequent in the advanced stages of the disease.[2-4] Nocturnal sleep of PD patients is interrupted by PD-related motor symptoms, nocturnal behavioral disturbances, and concurrent

sleep disorders. The nocturnal akinesia, painful cramps, tremor, and difficulty turning in bed are common motor symptoms of PD that interfere with nocturnal sleep. The nocturnal behavior disturbances include agitation, confusion, hallucinations, depression, and anxiety, and the concurrent sleep disorders include insomnia, rapid eye movement sleep behavior disorder (RBD), restless leg syndrome (RLS), periodic limb movements in sleep, and excessive daytime sleepiness (EDS).[5]

Cognitive impairment is a common and devastating nonmotor manifestation of PD. The possibility of developing dementia is six times higher in patients with PD compared to the gen-

eral population, and dementia affects 83% of patients after 20 years of PD.[6,7] PD patients with dementia have a 2- to 5-fold higher mortality rate compared to PD patients without dementia.[8] Moreover, dementia can exacerbate caregiver distress and increase the risk of nursing home placement.[9,10] Mild cognitive impairment in PD is associated with increasing age, longer disease duration, non-tremor features of bradykinesia, rigidity, postural instability, and gait disturbance.[1] In previous studies, the development of cognitive impairment in PD patients has been shown to be related to sleep disturbances, such as RBD, hallucinations, and EDS.[11,12]

Few studies have investigated the correlation of sleep disturbances and cognitive impairment of PD patients in Korea. The aim of the present study is to determine the type of sleep disturbances related to global cognitive function in PD patients.

METHODS

Study population

Between November 2010 and May 2011, 71 patients with PD completed this study. Patients were diagnosed with PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria by a neurologist who specialized in movement disorders.[13] Exclusion criteria included atypical parkinsonism, secondary parkinsonism, and dementia as defined by the age- and education-specific reference values of the Mini-Mental State Examination (MMSE), which was validated in Korea.[14] Subjects were required to answer to all questionnaires by themselves or with the assistance of caregivers. The study was approved by the Institutional Review Board at Gachon University Gil Medical Center, and written informed consent was obtained from each patient.

Patient evaluation

Detailed neurological examinations and interviews were performed by a movement disorder specialist. Patients followed their usual medication schedule during the evaluation. Demographic factors, including sex, age, disease duration, and disease onset age, were obtained by interviewing patients in outpatient clinics and reviewing medical records. All participants underwent the MMSE and the Korean Version of the Montreal Cognitive Assessments (MoCA-K) to assess global cognitive function.

Sleep disorders were evaluated with the Parkinson's Disease Sleep Scale in Korea (PDSS), Stanford Sleepiness Scale (SSS), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), and the Pittsburg Sleep Quality Index (PSQI). The PDSS is a visual analogue scale that consists of 15 sleep-associated items. Each item reflects eight sleep symptoms: overall quality of the night's sleep (item 1), sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10−13), sleep refreshment (item 14), and daytime sleepiness (item 15).[15] The scores for each item range from 0 (a severe symptom that is always experienced) to 10 (symptom free). This questionnaire was validated in Korea.[16] The SSS can be applied repetitively to evaluate brief subjective sleepiness and study circadian sleepiness.[17] A score of 4 or below indicates that a patient is suffering from a lack of sleep. The ESS assesses daytime sleepiness; a score > 10 is clinically defined as excessive daytime sleepiness.[18] The ISI measures the severity of insomnia; a cutoff score of 10 is optimally considered as insomnia.[19] The PSQI assesses the quality of sleep; a score > 5 indicates a significant sleep disturbance.[20]

Statistical analysis

Statistical analysis of clinical data was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows. Data for clinical characteristics and sleep profiles of the subjects are expressed as the mean ± standard deviation. The Pearson correlation test was used to evaluate the relationship between sleep disturbances and global cognitive function. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 71 patients participated in the study, including 29 men and 42 women, and the mean age was 66.46 ± 8.87 years. The mean disease duration was 4.15 ± 3.43 years, and the mean age of disease onset was 62.66 ± 9.61 years. The mean MMSE score was 25.89 ± 3.40, and the mean MoCA-K score was 20.39 ± 5.13. Sleep disturbances were observed in the SSS, PSQI, and PDSS items 1, 3, and 8 (mean SSS score 2.93 ± 1.51; mean PSQI score 11.89 ± 4.57; mean PDSS items 1, 3, and 8 scores were 4.85 ± 2.92, 3.54 ± 4.03, and 3.07 ± 4.05, respectively),

which indicates that many PD patients suffer from poor quality of sleep, difficulties with sleep onset and maintenance of sleep, and nocturia (Table 1).

Global cognitive function evaluated with the MMSE showed a positive correlation for sleep disturbances with the ISI (r = -0.254, p = 0.032), and the total PDSS score (r = 0.359, p = 0.002), and the MoCA-K scores were correlated with the total PDSS score (r = 0.239, p = 0.044) (Table 2). Table 3 shows that the MMSE scores were significantly related to the PDSS scores of item 4, 5, 6, 7, and 13, and that the MoCA-K scores were positively correlated with items 5 and 6. Each items indicates nocturnal restlessness (item 4, r = 0.297, p = 0.012 with the MMSE and item 5, r = 0.343, p = 0.003 with the MMSE, r = 0.249, p = 0.036 with the MoCA-K), vivid dreams (item 6, r = 0.369, p = 0.002 with the MMSE, r = 0.334, p = 0.004 with the MoCA-K), hallucinations (item 7, r = 0.308, p = 0.009 with the MMSE), and nocturnal motor symptoms (item 13, r = 0.265, p = 0.025 with the MMSE). Univariate regression analysis revealed that insomnia (ISI, adjusted R^2 = 0.051, p = 0.032 with the MMSE), nocturnal restlessness (item 4, adjusted R^2 = 0.075, p = 0.012 with the MMSE, item 5, adjusted R^2 = 0.105, p = 0.003 with the MMSE, adjusted R^2 = 0.048, p = 0.044 with the MoCA-K), vivid dreams (item 6, adjusted R^2 = 0.123, p = 0.002 with the MMSE, adjusted R^2 = 0.098, p = 0.004 with the MoCA-K), hallucinations (item 7, adjusted R^2 = 0.082, p = 0.009 with the MMSE), and nocturnal motor symptoms (item 13, adjusted R^2 = 0.057, p = 0.025 with the MMSE) had a significant effect on global cognitive function.

DISCUSSION

This study showed that the global cognitive function of PD patients was correlated with sleep disturbances measured with the PDSS. The PDSS is a simple and reliable instrument for assessing sleep disturbances in PD patients.[15] Among individual items of PDSS, items 4, 5, 6, 7, and 13 were correlated with the MMSE, and items 5 and 6 were correlated with the MoCA-K. Each item indicates nocturnal restlessness (items 4 and 5), nocturnal psychosis that includes vivid dreams (item 6), hallucinations (item 7), and nocturnal motor symptoms (item 13). The ISI was also related to global cognitive function, but was only correlated with the

MMSE. However, nocturnal restlessness and vivid dreams are considered more favorable correlation parameters to cognitive function. Two explanations can be offered for these results. First, vivid dreams and nocturnal restlessness were both correlated with

Table 1. Clinical characteristics and sleep profile of subjects

Total	71 patients (mean ± SD)	Range
Age (y)	66.46 ± 8.87	43−80
Disease duration (y)	4.15 ± 3.43	0.08−20.75
Disease onset age (y)	62.66 ± 9.61	35−79
MMSE	25.89 ± 3.40	15−30
MoCA-K	20.39 ± 5.13	8−30
SSS	2.93 ± 1.51	1−11
ESS	4.93 ± 3.11	0−14
ISI	7.89 ± 5.50	0−25
PSQI	11.89 ± 4.57	0−21
PDSS total	109.30 ± 19.99	62−150
Overall quality of night's sleep (item 1)	4.85 ± 2.92	0−10
Sleep onset insomnia (item 2)	6.35 ± 4.02	0−10
Sleep maintenance insomnia (item 3)	3.54 ± 4.03	0−10
Nocturnal restlessness (item 4)	9.06 ± 1.92	3−10
Nocturnal restlessness (item 5)	8.61 ± 2.23	2−10
Nocturnal psychosis (item 6)	7.39 ± 2.49	2−10
Nocturnal psychosis (item 7)	8.87 ± 2.34	0−10
Nocturia (item 8)	3.07 ± 4.05	0−10
Nocturia (item 9)	9.42 ± 1.84	0−10
Nocturnal motor symptoms (item 10)	8.73 ± 2.24	2−10
Nocturnal motor symptoms (item 11)	8.30 ± 2.36	2−10
Nocturnal motor symptoms (item 12)	9.03 ± 2.07	2−10
Nocturnal motor symptoms (item 13)	6.99 ± 3.37	0−10
Sleep refreshment (item 14)	5.65 ± 3.70	0−10
Daytime dozing (item 15)	9.45 ± 1.44	5−10

MMSE: Mini-Mental State Examination, MoCA-K: Korean Version of the Montreal Cognitive Assessments, SSS: Standard Sleep Scale, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, PSQI: Pittsburg Sleep Quality Index, PDSS: Parkinson's Disease Sleep Scale in Korea.

Table 2. Statistically significant Pearson product-moment correlation between global cognitive functions and sleep disturbance (SSS, ESS, ISI, PSQI, PDSS)

	MMSE		MoCA-K	
	r	p	r	p
SSS	-0.032	0.789	-0.096	0.425
ESS	-0.014	0.906	0.013	0.912
ISI	-0.254*	0.032	-0.174	0.146
PSQI	-0.155	0.198	-0.116	0.336
PDSS	0.359*	0.002	0.239*	0.044

*statistically significant correlation (p < 0.05). MMSE: Mini-Mental State Examination, MoCA-K: Korean Version of the Montreal Cognitive Assessments, SSS: Standard Sleep Scale, ESS: Epworth Sleepiness Scale, ISI: Insomnia Severity Index, PSQI: Pittsburg Sleep Quality Index, PDSS: Parkinson's Disease Sleep Scale in Korea.

Table 3. Statistically significant Pearson product-moment correlation between global cognitive functions and sleep disturbance (each items in PDSS)

	MMSE		MoCA-K	
	r	*p*	*r*	*p*
Overall quality of night's sleep (item 1)	0.133	0.267	0.040	0.738
Sleep onset insomnia (item 2)	0.159	0.186	0.063	0.601
Sleep maintenance insomnia (item 3)	0.051	0.670	0.029	0.810
Nocturnal restlessness (item 4)	0.297*	0.012	0.210	0.079
Nocturnal restlessness (item 5)	0.343*	0.003	0.249*	0.036
Nocturnal psychosis (item 6)	0.369*	0.002	0.334*	0.004
Nocturnal psychosis (item 7)	0.308*	0.009	0.199	0.097
Nocturia (item 8)	0.007	0.955	0.130	0.281
Nocturia (item 9)	0.140	0.244	0.006	0.958
Nocturnal motor symptoms (item 10)	0.159	0.184	0.100	0.406
Nocturnal motor symptoms (item 11)	0.159	0.184	0.118	0.328
Nocturnal motor symptoms (item 12)	0.104	0.388	0.094	0.433
Nocturnal motor symptoms (item 13)	0.265*	0.025	0.212	0.077
Sleep refreshment (item 14)	0.156	0.194	-0.024	0.841
Daytime dozing (item 15)	0.182	0.128	0.130	0.280

*statistically significant correlation ($p < 0.05$). MMSE: Mini-Mental State Examination, MoCA-K: Korean Version of the Montreal Cognitive Assessments, PDSS: Parkinson's Disease Sleep Scale in Korea.

the MMSE and the MoCA. Second, the MoCA is a more sensitive method to detect mild cognitive impairment in PD patients compared to the MMSE, and the MoCA assesses a broader range of cognitive domains than the MMSE, which primarily tests memory and language abilities.[21] The results from the present study correspond to the results of earlier studies that reported that risk factors of cognitive decline in PD patients include an older age at the onset of the disease, greater severity of motor symptoms, RBD, and hallucinations.[11,12]

Both RLS and PD are related to dopamine system dysfunction. In PD, the loss of nigral neurons results in a striatal dopamine deficiency. The neuronal loss in the ventrolateral part of the substantia nigra pars compacta that project to dorsal putamen is noticeable in the akinetic-rigid type of PD, while neuronal loss in the medial part of substantia nigra pars compacta is evident in tremor-dominant PD patients.[22] Autopsies of primary RLS patients indicated that a significant decline in the dopamine D2 receptor occurred in the putamen, and the magnitude of the decrease was related to the severity of RLS.[23] The fact that the nigrostriatal dopaminergic system is affected in both RLS and PD supports the etiologic link between them. Other evidence that indicates a link between these disorders includes the effect of dopaminergic agents and deep brain

stimulation (DBS) in RLS. Dopaminergic agents, including rotigotine, ropinirole, and pramipexole, are the first line treatment of RLS, and a recent prospective study showed significant improvement of RLS symptoms at 4 weeks and 6 months after DBS of the subthalamic nucleus.[24,25] There are several evidences that cognitive function correlates with RLS. RLS has common risk factors with Alzheimer disease: advanced age, depression, anxiety, smoking, and hypertension, and plays a role in developing nocturnal agitation in dementia.[26] The prefrontal cortical functions of RLS patients were more impaired, which may represent the cumulative effects of sleep loss.[27]

Psychotic symptoms including vivid dreams, hallucinations, loss of insight, and delusions, affect many PD patients, and the risk of these symptoms is increased in patients with advanced age, cognitive impairment, severe PD symptoms, the need for high doses of dopaminergic drugs, and probable RBD.[28] Although hallucinations are usually induced by dopaminergic therapies, especially dopamine agonists, they can be present in drug-naïve patients. The shared underlying mechanisms of neurotransmitter imbalance and increased cortical Lewy body deposits may explain the correlation between psychotic symptoms and cognitive impairment. One of the features of prodromal PD is RBD, which is a

parasomnia that manifests as vivid, often frightening dreams associated with dream enactment behavior during rapid eye movement sleep.[29] RBD is also associated with a higher risk of dementia in PD, which could be a diffuse, complex disease subtype of PD. The interaction between serotonin and acetylcholine and the dopaminergic system also contributes to the emergence of psychosis in PD. Several agents that reduce serotonergic activity improve the psychotic symptoms; however, serotonergic agonists induce both delirium and psychosis. A cholinergic deficit, specifically in the nucleus basalis of Meynert, is apparent in cognitively impaired and demented PD patients.[30] In this study, vivid dreams and hallucinations were correlated with global cognitive function in both the MMSE and MoCA-K, but hallucinations were not statistically significant in the MoCA-K.

Some limitations of this study should be mentioned. First, we did not conduct polysomnography, which is considered a gold standard of certain sleep disorders, including RBD. However, polysomnography is expensive, time-consuming, and less accessible, whereas questionnaires are simple, clinical, and inexpensive bedside tools. Second, we did not consider the confounding effect of medications. Some anti-parkinsonism drugs induce sleep problems. Anticholinergic agents are related to nocturnal behavioral disturbances such as hallucinations and agitation, and dopaminergic agonists increase the risk of EDS. Third, the PDSS was used in our study; however a revised version of the PDSS (PDSS-2) was created and validated.[31] The PDSS is not designed as a diagnostic method for PD-specific sleep disturbances and is not suitable for screening for EDS, sleep apnea, RLS or RBD, which contribute to major sleep disturbances in of PD patients. However, the PDSS-2 is a reliable, valid, potentially treatment-responsive tool for evaluating sleep disorders in PD. The MMSE and MoCA-K are useful, short screening tests of cognitive function, but they do not assess each domain of cognitive function. The Seoul Neuropsychological Screening Battery (SNSB) is a valid and reliable neuropsychological tool for assessing and monitoring five cognitive domains: attention, memory, language, visuospatial function, and fontal executive function. However, one of its shortcomings includes an excessive length of time required to administer the test.[32] Future studies should incorporate polysomongraphy, the PDSS-2,

and the SNSB to further evaluate the reliability of the correlation between sleep disorders and cognitive function in PD patients.

In conclusion, our study shows that global cognitive function in PD patients is correlated to vivid dreams and nocturnal restlessness. We suggest that physicians evaluate and treat PD patients for the presence of pathological sleep disturbances. Furthermore, studies are needed to identify the early markers of cognitive impairment in PD patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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