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BRIEF COMMUNICATION

Investigation of Nocturnal Hypokinesia and Health-Related Quality of Life in Parkinsonian Patients with the Korean Version of the Nocturnal Hypokinesia Questionnaire

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ABSTRACT

Objective To assess nocturnal hypokinesia using the Korean version of the Nocturnal Hypokinesia Questionnaire (NHQ-K) in Parkinson's disease (PD) patients across disease stages.

Methods We developed the NHQ-K and performed questionnaire-based interviews with 108 PD patients from three referral hospitals. Clinical associations of nocturnal hypokinesia and its impact on health-related quality of life (HRQoL) were also analyzed.

Results The NHQ-K showed acceptable internal consistency (0.83) and interrater reliability (0.95). Nocturnal hypokinesia significantly affected HRQoL in PD patients at both the early and advanced stages (adjusted $p < 0.001$). Increased severity of nocturnal hypokinesia was associated with dyskinesias, off-period disability, apathy, and anxious mood in PD patients (adjusted $p < 0.01$) after controlling for disease severity and medication dose.

Conclusion The NHQ-K is useful for screening nocturnal hypokinesia in PD patients. Given the high impact of nocturnal hypokinesia on HRQoL, comprehensive management of nocturnal disability is needed for PD patients.

Keywords Parkinson's disease; Nocturnal Hypokinesia Questionnaire; Quality of life; Validation study.

Nocturnal hypokinesia is a symptom of Parkinson's disease (PD) and refers to the difficulty of rolling over in bed.[1,2] More than half of PD patients suffer from this symptom.[1,2] A decrease in dopamine levels during the night can contribute to nocturnal hypokinesia in PD patients.[3,4] However, nighttime aggravation of parkinsonism might not be the sole associated factor, and nocturnal symptoms may be associated with quality of life in PD patients.[1,2,5] Nocturnal hypokinesia is often overlooked in clinics, and tools are scarce for evaluating nocturnal symptoms in PD.[6] Recently, a questionnaire-based screening inventory, the

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Nocturnal Hypokinesia Questionnaire (NHQ), was developed to assess nocturnal immobility symptoms in PD, and the original version showed satisfactory reliability and internal consistency.[7]

The relationship between nocturnal hypokinesia and PD patient quality of life has not yet been systematically evaluated, nor have differences by disease stage been well documented. Therefore, we assessed nocturnal hypokinesia in PD patients by developing the Korean version of the NHQ and investigated the impact of nocturnal hypokinesia on health-related quality of life (HRQoL) and its clinical associations in PD patients across disease stages.

MATERIALS & METHODS

Participants

We collected PD patient data from 3 movement disorder clinics at university-affiliated hospitals between December 2018 and July 2019. Patients were eligible if they met the clinical diagnostic criteria of the UK PD Society Brain Bank[8] and had been stably treated with anti-parkinsonian medications. We excluded patients if there was a possibility of secondary parkinsonism, such as drug-induced or structural brain lesions, history of deep brain stimulation, history of psychosis, or cognitive impairment with Korean version of the Mini-Mental Status Exam (K-MMSE) score[9] < 20. Because the NHQ needs to be completed independently by both patient and their caregiver, we also interviewed primary caregivers of the PD patients included in this study. The institutional review board of each participating center approved this study and waived the need for informed consent because this was a retrospective analysis (IRB No. 10-2019-77).

The NHQ-K

The original NHQ comprises ten items for nighttime or early-morning symptoms related to nocturnal immobility. Each item is scored as yes (1) or no (0) based on the symptoms during the past week. The total NHQ score is the sum of all items and ranges from 0 to 10.[7]

We developed Korean version of the NHQ (NHQ-K) by translating the original NHQ into Korean. Two independent bilingual translators translated the original NHQ, and another translator translated it back into English. The translated version was reviewed and modified by an expert panel and then applied to six Korean PD patients after which the NHQ-K was finalized (the questionnaire is available online at www.mapi-trust.org).

Clinical variables

We assessed nocturnal symptoms using the NHQ-K. We collected clinical information, including age, sex, age at PD onset, levodopa equivalent dose (LED),[10] and data regarding the Hoehn and Yahr (H&Y) stage[11] and the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I–IV.[12] We used the motor score (part III) rated at the medication on state and categorized part III into four subdomains: axial (items 1 and 10–13), bradykinesia (items 2, 4–9 and 14), rigidity (item 3), and tremor (items 15–18).[12,13] HRQoL was assessed by the Korean 39-item PD Questionnaire (K-PDQ-39).[14]

Statistical analysis

The Shapiro–Wilk test was performed to assess the normal distribution of the data. We calculated Cronbach's alpha to estimate the internal consistency of the NHQ-K. Interrater reliability between the patients and caregivers was assessed by the intraclass correlation and Cohen's kappa coefficient for continuous variables and ordinal variables, respectively. Correlations between the NHQ-K and clinical variables were analyzed using Spearman's rank correlation, and we performed multiple linear regression analyses to investigate clinical associations of nocturnal disability. We applied Bonferroni correction for multiple analyses across each item of the MDS-UPDRS and K-PDQ-39. SPSS software (version 26.0, IBM Corp., Armonk, NY, USA) was used, with the significance set at 0.05 (two-tailed).

RESULTS

This study included a total of 108 PD patients (age, 66.6 ± 8.7 years; female, 58.3%; PD duration, 7.7 ± 5.0 years). The demographic and clinical characteristics of the patients are summarized in Supplementary Table 1 (in the online-only Data Supplement). Sixty-two pairs of caregivers and patients completed the NHQ-K independently.

Nocturnal disability assessed by the NHQ-K

The average total NHQ-K score of all PD patients was 3.9 ± 2.9 (ranging from 0 to 9). The most frequent nocturnal symptom was 'requiring several attempts to get out of bed' (item 3, 62.0%), followed by 'supine position for most of the night' (item 2, 54.6%) and 'difficulty turning over' (item 1, 51.9%) (Supplementary Figure 1 in the online-only Data Supplement).

Internal consistency and reliability of the NHQ-K

Cronbach's alpha for internal consistency of the NHQ-K total score was 0.83 (Table 1). Four out of 10 items of the NHQ-K showed excellent internal consistency (coefficient > 0.7). Items 2, 5–7, and 9 showed intermediate internal consistency, ranging from 0.32 to 0.47. The NHQ-K total score interrater reliability between PD patients and their caregivers was 0.95 (Table 1). Eight out of 10 items of the NHQ-K showed high interrater reliability, with Cohen's kappa coefficients greater than 0.7.

Table 1. Internal consistency and reliability of the NHQ-K

Item	Internal consistency		Interrater reliability		
	Corrected item total correlation	Cronbach's alpha if item deleted	PD patients	Caregivers	Coefficient
Item 1: Difficulty in turning over or around in bed	0.81	0.78	40 (64.5)	35 (56.5)	0.83
Item 2: Supine position for most of the night	0.34	0.84	34 (54.8)	33 (53.2)	0.97
Item 3: Difficulty in getting out of bed, requiring several attempts to get out of bed	0.70	0.80	45 (72.6)	44 (71.0)	0.96
Item 4: Asking for help or holding onto bed rails to get out of bed	0.76	0.79	39 (62.9)	26 (41.9)	0.54
Item 5: Stiffness in trunk/back during the night or in the early morning	0.47	0.82	26 (41.9)	21 (33.9)	0.76
Item 6: Stiffness in legs or arms during the night or in the early morning	0.46	0.82	34 (54.8)	28 (45.2)	0.74
Item 7: Pain in legs or arms during the night or in the early morning	0.40	0.83	21 (33.9)	15 (24.2)	0.69
Item 8: Unable to take the first step as soon as getting out of bed due to freezing	0.71	0.79	38 (61.3)	38 (61.3)	0.93
Item 9: Dyskinesia during the night	0.32	0.83	9 (14.5)	11 (17.7)	0.88
Item 10: Taking extra PD medication during the night to relieve nighttime symptoms	0.12	0.84	5 (8.1)	6 (9.7)	0.90
Total nocturnal hypokinesia score	0.83	-	4.69 ± 2.92	4.10 ± 2.83	0.95*

Internal consistency based on the corrected item total correlation and Cronbach's alpha coefficient if items were deleted for all PD patients (n = 108). Interrater reliability based on Cohen's kappa coefficient for ordinal variables and *intraclass correlation for continuous variables between PD patients (n = 62) and their caregivers (n = 62). NHQ-K: Korean version of the Nocturnal Hypokinesia Questionnaire, PD: Parkinson's disease.

Relationship between nocturnal disability and clinical features in PD patients

In the correlation analyses, the NHQ-K score increased with H&Y stage, MDS-UPDRS-III total score, and total LED (r = 0.66, 0.55, and 0.50, respectively; $p < 0.001$) (Supplementary Figure 2 in the online-only Data Supplement). Regarding correlation with the MDS-UPDRS-III subdomains, the NHQ-K total score correlated with the MDS-UPDRS-III scores for axial, bradykinesia, and rigidity (r = 0.64, 0.58, and 0.22; $p < 0.001$, < 0.001, and 0.025, respectively), but it did not correlate with the tremor score (r = 0.06, p = 0.554).

We further performed multivariable regression analyses with the MDS-UPDRS items while adjusting for possible confounding factors, including age, sex, disease duration, K-MMSE, H&Y stage, MDS-UPDRS-III total score, and total LED (Table 2). The NHQ-K score was significantly associated with the MDS-UPDRS item scores for anxious mood, apathy, dyskinesias, and off disability (β = 0.246, 0.230, 0.271 and 0.505, respectively; $p < 0.05$ after Bonferroni correction). To explore whether the clinical associations differed according to the disease stage, we performed subgroup analyses in patients with early (H&Y stage, 1–2; n = 60) and advanced stages (H&Y stage, 3–4; n = 32) of the disease (Table 2). In both groups, apathy and off disability showed significant associations with the NHQ-K ($p < 0.05$ after Bonferroni correction).

Impact of nocturnal disability on HRQoL in PD patients

In the multivariable regression analyses with the K-PDQ-39 (after adjusting for confounding factors described above in all PD patients), the NHQ-K was found to be significantly associated with HRQoL (K-PDQ-39 summary index, β = 0.505, adjusted $p < 0.001$) (Table 2). The results from the subgroup analyses in patients with early and advanced stages of the disease were similar to those observed for the total PD patient group (Table 2).

DISCUSSION

The NHQ-K showed high reliability and satisfactory internal consistency, similar to the original NHQ,[7] indicating that it is a reliable assessment tool for nocturnal disability in PD. The present study also demonstrated that nocturnal hypokinesia was common, affecting more than half of the included PD patients and significantly impacting a broad spectrum of HRQoL aspects, including physical, emotional, and social functioning, regardless of the disease stage. Our findings suggest that screening and assessing the severity of nocturnal disability would be valuable for patient care. Several other scales have been used to assess nocturnal symptoms in PD; however, these have not been explicitly validated on nocturnal hypokinesia-related symptoms.[15,16]

We also assessed associations between nocturnal disability and clinical features in PD patients. We found no correlation between nocturnal disability and tremor symptoms, contrary to the correlation with axial and rigidity symptoms. In addition, the NHQ-

Table 2. Multivariable analysis for clinical associations and impact of nocturnal disability on health-related quality of life in PD patients

Scores for independent variables	Total PD patients (*n* = 108)		Early-stage PD (H&Y 1–2) (*n* = 60)		Advanced-stage PD (H&Y 3–4) (*n* = 32)	
	β coefficient	*p* value	β coefficient	*p* value	β coefficient	*p* value
MDS-UPDRS-I items						
Cognitive impairment (item 1)	0.050	0.506	-0.039	0.761	0.373	0.036
Hallucinations and any psychosis (item 2)	0.013	0.868	-0.145	0.250	0.315	0.216
Depressive mood (item 3)	0.076	0.319	0.171	0.142	0.154	0.528
Anxious mood (item 4)	0.246	0.001*	0.383	< 0.001*	0.470	0.007
Apathy (item 5)	0.230	0.002*	0.444	< 0.001*	0.515	0.003*
Dopamine dysregulation syndrome (item 6)	0.177	0.013	0.289	0.009	0.216	0.380
Sleep problems (item 7)	0.100	0.178	0.198	0.102	0.108	0.651
Daytime sleepiness (item 8)	0.073	0.296	0.146	0.211	0.135	0.492
Pain and other sensations (item 9)	0.185	0.015	0.201	0.072	0.264	0.280
Urinary problems (item 10)	0.171	0.024	0.141	0.282	0.402	0.064
Constipation problems (item 11)	0.201	0.008	0.098	0.404	0.140	0.506
Light headedness on standing (item 12)	0.108	0.125	0.084	0.470	0.138	0.480
Fatigue (item 13)	0.110	0.154	0.255	0.034	0.400	0.023
MDS-UPDRS-III items						
Axial (items 1,10–13)	0.269	0.022	0.274	0.026	0.356	0.398
Bradykinesia (items 2, 4–9, 14)	0.220	0.022	0.318	0.006	0.084	0.863
Rigidity (item 3)	-0.101	0.289	-0.055	0.718	-0.091	0.758
Tremor (items 15–18)	-0.072	0.391	-0.188	0.174	-0.045	0.689
MDS-UPDRS-IV items						
Dyskinesias duration and disability (items 1,2)	0.271	< 0.001*	0.060	0.651	0.355	0.116
Off duration and disability (items 3,4)	0.505	< 0.001*	0.394	< 0.001*	0.496	0.004*
Motor fluctuations (item 5)	0.190	0.029	0.178	0.175	0.257	0.334
Painful off dystonia (item 6)	0.180	0.025	0.208	0.076	0.501	0.004*
K-PDQ-39 domains						
Mobility	0.484	< 0.001*	0.434	< 0.001*	0.594	< 0.001*
Activities of daily living	0.310	< 0.001*	0.437	< 0.001*	0.500	0.004*
Emotional well-being	0.324	< 0.001*	0.439	< 0.001*	0.617	< 0.001*
Stigma	0.302	< 0.001*	0.391	< 0.001*	0.403	0.022
Social support	0.164	0.018	0.370	0.001*	0.090	0.668
Cognition	0.196	0.007	0.270	0.021	0.440	0.012
Communication	0.251	0.004*	0.416	0.002*	0.315	0.269
Bodily discomfort	0.308	< 0.001*	0.456	< 0.001*	0.381	0.031
Summary index	0.505	< 0.001*	0.638	< 0.001*	0.623	< 0.001*

Multivariable analysis for the NHQ-K score with the MDS-UPDRS and K-PDQ-39 scores after adjusting for confounding factors including age, sex, disease duration, K-MMSE, H&Y stage, MDS-UPDRS-III total score, and total LED. *significant level after Bonferroni correction; p<0.0038 for the MDS-UPDRS-I items, p<0.0125 for the MDS-UPDRS-III and IV items, and p<0.00625 for the K-PDQ-39 domains. PD: Parkinson's disease, MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale, K-PDQ-39: Korean version of the 39-item Parkinson's Disease Questionnaire, K-MMSE: Korean version of the Mini-Mental State Examination, H&Y stage: Hoehn and Yahr stage, LED: levodopa equivalent dose.

K scores of PD patients with the postural instability/gait difficulty (PIGD; $n = 80$) phenotype tended to be higher than those with the tremor-dominant (TD; $n = 20$) phenotype[17] (4.4 ± 2.8 vs. 3.2 ± 2.7, $p = 0.09$). These results suggest that nocturnal disability may affect PD patients with the PIGD phenotype more than those with the TD phenotype. It may also reflect the necessity of coordinated movements in the trunk and limbs to turn over and get out of bed.[18,19]

The current study has some limitations. We used questionnaires, which are subjective but easily applicable in clinics. Devices such as wearable sensors would provide more valid data on nocturnal disability.[3,4,20] The MDS-UPDRS rating was conducted in the "on" state for purposes of practical application. However, measuring in the "off" state might reflect the patients' night-time status more precisely than measuring in the "on" state. Another limitation was the lack of evaluation of primary sleep disorders

and comorbid musculoskeletal disorders and no consideration of nighttime medication use other than anti-PD drugs (e.g., muscle relaxers, pain relievers, and sedatives). Last, because we excluded patients with significant cognitive impairment or psychosis, their influence on nocturnal disability might be underestimated.

The present study indicates that nocturnal hypokinesia significantly affects HRQoL across the stages of PD. One way of treating nocturnal hypokinesia is to obtain a stable dopamine level during the nighttime by adjusting dopaminergic drugs.[20] Our findings suggest the need for comprehensive management of motor and nonmotor risk factors for nocturnal hypokinesia in PD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20172.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Jee-Young Lee. Data curation: Ji-Hyun Choi, Jee-Young Lee. Formal analysis: Ji-Hyun Choi, Jee-Young Lee. Investigation: all authors. Methodology: Jee-Young Lee. Project administration: Jee-Young Lee. Resources: Jee-Young Lee, Chaewon Shin, Han-Joon Kim, Tae-Beom Ahn, Beomseok Jeon. Supervision: Jee-Young Lee, Tae-Beom Ahn, Beomseok Jeon. Validation: Ji-Hyun Choi, Jin Hee Im. Visualization: Ji-Hyun Choi, Jee-Young Lee. Writing—original draft: Ji-Hyun Choi. Writing—review & editing: Jee-Young Lee, Chaewon Shin, Han-Joon Kim, Tae-Beom Ahn, Jong-Min Kim, Beomseok Jeon.

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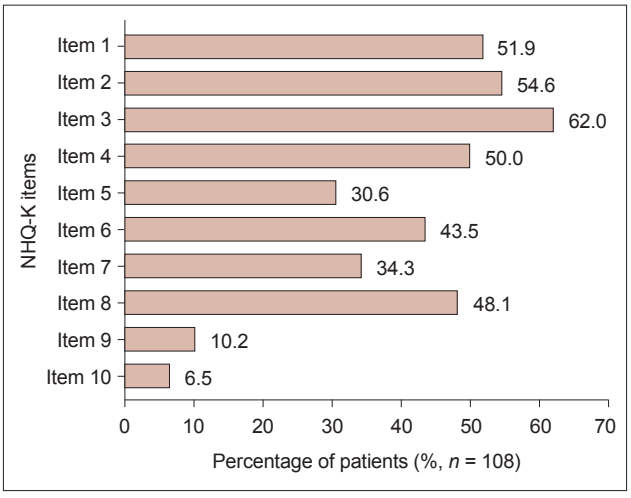
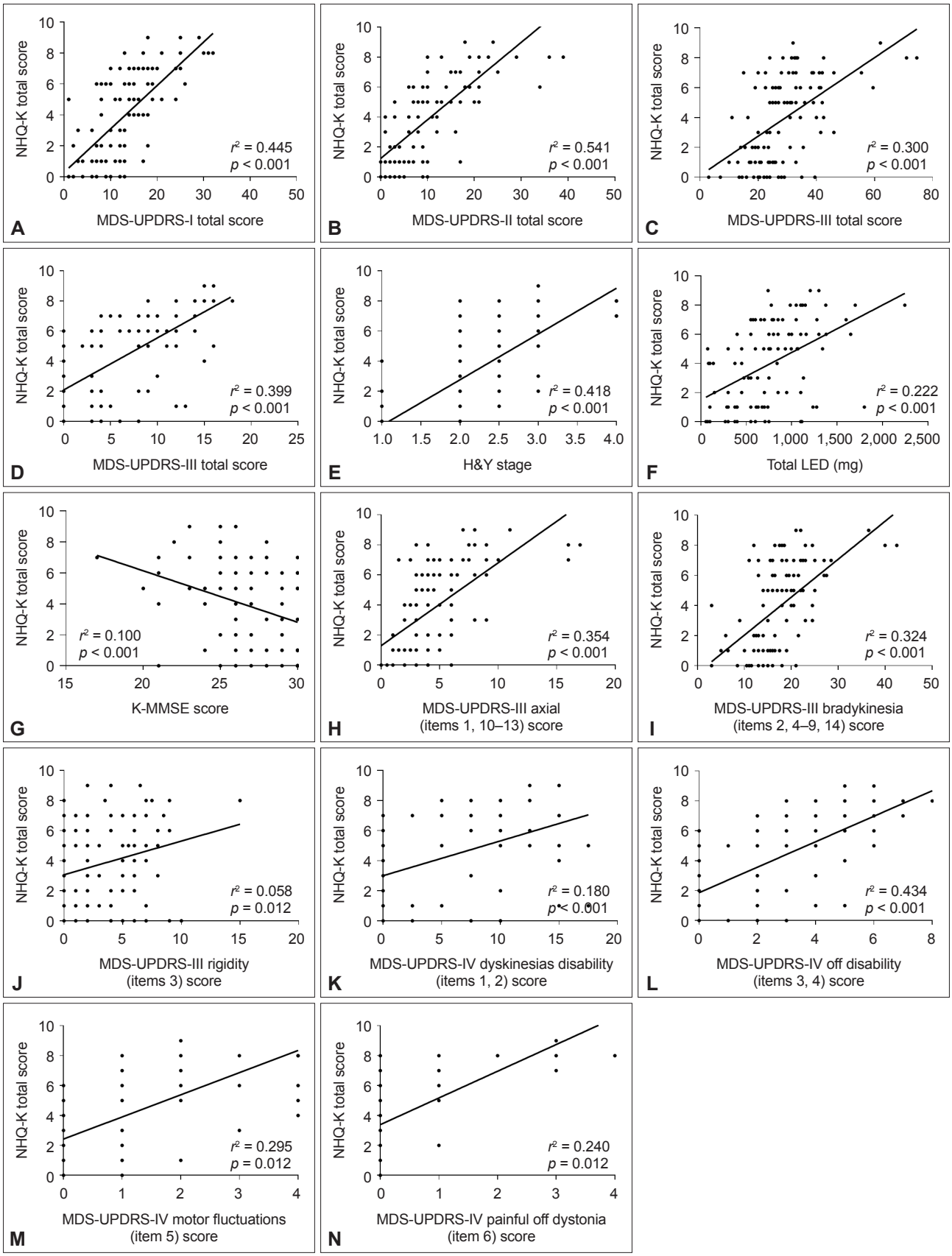
Supplementary Table 1. Demographic and clinical characteristics of the PD patients

Variables	Total PD patients (*n* = 108)
Age at presentation, year	66.6 ± 8.7
Female gender	63 (58.3)
Age at PD onset, year	58.9 ± 9.9
PD disease duration, year	7.7 ± 5.0
K-MMSE score	26.7 ± 2.7
H&Y stage	2.0 (1–4)
Total LED, mg	743.9 ± 416.1
MDS-UPDRS part I total score	12.9 ± 6.8
MDS-UPDRS part II total score	10.4 ± 8.2
MDS-UPDRS part III total score	28.9 ± 11.9
MDS-UPDRS part IV total score	5.3 ± 5.2
K-PDQ-39 summary index	24.3 ± 17.7

The values are expressed as mean ± standard deviation, median (min–max), or number (percentage). PD: Parkinson's disease, K-MMSE: Korean version of the Mini-Mental State Examination, H&Y stage: Hoehn and Yahr stage, LED: levodopa equivalent dose, MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale, K-PDQ-39: Korean version of the 39-Item Parkinson's Disease Questionnaire.



Supplementary Figure 1. Percentage of patients with nocturnal disability as assessed by the NHQ-K. NHQ-K: Korean version of the Nocturnal Hypokinesia Questionnaire.



Supplementary Figure 2. Correlational analysis between nocturnal disability and clinical variables in PD patients (n = 108). (A) MDS-UPDRS-I total score, (B) MDS-UPDRS-II total score, (C) MDS-UPDRS-III total score, (D) MDS-UPDRS-IV total score, (E) H&Y stage, (F) Total LED, (G) K-MMSE score, MDS-UPDRS-III item scores for (H) Axial, (I) Bradykinesia, and (J) Rigidity, MDS-UPDRS-IV item scores for (K) Dyskinesias disability, (L) Off disability, (M) Motor fluctuations, and (N) Painful off dystonia. PD: Parkinson's disease, NHQ-K: Korean version of the Nocturnal Hypokinesia Questionnaire, MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale, H&Y stage: Hoehn and Yahr stage, LED: levodopa equivalent dose, K-MMSE: Korean version of the Mini-Mental State Examination.