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ORIGINAL ARTICLE

Assessing the relationship between non-motor symptoms and health-related quality of life in Parkinson's disease: a retrospective observational cohort study

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Abstract

Objectives Non-motor symptoms (NMSs) negatively impact the health-related quality of life (HrQOL) of patients with Parkinson's disease (PD). The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a comprehensive scale for evaluating PD. It remains unclear whether the NMSs evaluated with MDS-UPDRS are predictive of HrQOL. This study aimed to investigate whether NMSs, as evaluated with the MDS-UPDRS, could predict the HrQOL of patients with PD.

Materials and methods We conducted a 2-year retrospective observational cohort study assessing 108 patients with PD who were recruited from a single tertiary center between January 2015 and December 2017. MDS-UPDRS was used to assess NMSs and motor symptoms and Parkinson's Disease Questionnaire-39 (PDQ-39) to measure patients' HrQOL.

Results The median age of patients was 69 years, and 65.7% were female. The median MDS-UPDRS part I, part II, part III, and PDQ-39-summary index scores were 8, 10, 22, and 25, respectively. The final stepwise multiple linear regression model showed that female sex (standard partial regression coefficient $\beta = 0.131$, $P < 0.05$) and baseline MDS-UPDRS part I ($\beta = 0.272$, $P < 0.01$) and part II ($\beta = 0.571$, $P < 0.01$) scores significantly predicted the PDQ-39-SI scores at the 2-year follow-up.

Conclusions In addition to motor symptoms, NMSs at the 2-year follow-up may be useful for predicting the HrQOL of patients with PD. In clinical practice, MDS-UPDRS-guided assessment and treatment of motor symptoms and NMSs may contribute to improving HrQOL in patients with PD.

Keywords Non-motor symptoms · Parkinson's disease · Health-related quality of life · Longitudinal study · MDS-UPDRS

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which involves the disruption of multiple neurotransmitter pathways in the brain and autonomic nervous system [1, 2]. PD is characterized by motor symptoms such as bradykinesia, rigidity, and resting tremor. In addition, PD causes non-motor symptoms (NMSs) such as cognitive impairment, autonomic dysfunction, sleep disorders, depression, and hyposmia, which contribute to an impaired health-related quality of life (HrQOL) [3, 4].

In previous cross-sectional studies, NMSs and NMS fluctuations were reported to negatively correlate with HrQOL in patients with PD [5–8]. However, because cross-sectional studies cannot assess causal relationships, longitudinal studies are needed to better evaluate the relationship between NMSs and HrQOL. Importantly, recent longitudinal studies have shown that NMSs were negatively associated with HrQOL, while motor symptoms had no association with HrQOL [9–11].

The aforementioned studies evaluated NMSs using various methods [9–11]. The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which has been translated and validated in many languages, is a globally applicable and comprehensive scale for assessing PD and can likewise be used to evaluate NMSs [12, 13]. However, it remains unclear from longitudinal

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data whether the NMSs evaluated with MDS-UPDRS are predictive of HrQOL. Therefore, we conducted a retrospective longitudinal cohort study to determine whether NMSs evaluated with MDS-UPDRS is predictive of impaired HrQOL in Japanese patients with PD.

Materials and methods

This retrospective observational cohort study was conducted among patients with PD assessed between January 2015 and December 2017. The subjects were outpatients undergoing treatment in a PD clinic in the neurology department of the Aomori Prefectural Central Hospital. Subjects were required to meet the following inclusion criteria: (1) their diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank Criteria [14]; (2) they were followed up for at least 2 years; (3) they were 20–80 years old at the time of their first visit; and (4) they scored > 23 on the Mini-Mental State Examination (MMSE). Patients with incomplete data were excluded.

We used the MDS-UPDRS and the Japanese version of the Parkinson's Disease Questionnaire-39 (PDQ-39) to evaluate NMSs [12, 13] and patients' HrQOL, respectively [15]. The MDS-UPDRS part I scores 13 items, from 0 to 4, on "non-motor experiences of daily living (nM-EDL)," such as cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome, nighttime sleep problems, daytime sleepiness, pain and other sensations, urinary problems, constipation, lightheadedness when standing, and fatigue [12, 13]. MDS-UPDRS part II assesses the "motor experiences of daily living (M-EDL)," which are comprised of 13 self-assessment items: speech, salivation and drooling, chewing and swallowing, eating, dressing, hygiene, hand writing, preforming activities, turning in bed, tremor, getting out of bed, car or deep chair, walking and balance, and freezing [12, 13]. In MDS-UPDRS part III, a neurologist evaluates 18 motor examination items, as previously reported [12, 13]. The PDQ-39 is scored from 0 to 5 points and consists of 39 items addressing 8 dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort [15]. PDQ-39 is the most widely used and validated disease-specific instrument for the self-reported health status of patients with PD [16]. In this study, the clinical subtypes of PD were classified based on a previous report [17].

We evaluated the following variables: sex, age, disease duration, modified Hoehn and Yahr stages, clinical subtype (tremor dominant [TD], postural instability/gait difficulty [PIGD], and intermediate), wearing off, dyskinesia (non-troublesome and troublesome), MMSE, levodopa equivalent daily dose (LEDD) [18], MDS-UPDRS parts I–III scores [12, 13], and PDQ-39 scores [15]. Clinical variables were assessed at baseline and at the 2-year follow-up. For each item in the MDS-UPDRS part I, we defined ≥ 2 points as positive for an NMS. Items of the MDS-UPDRS part I were recoded and analyzed as binary variables (< 2 points, ≥ 2 points).

All statistical analyses were conducted using SPSS version 25 (SPSS Japan, Tokyo, Japan). To assess within-subject differences in a given patient (i.e., comparing baseline to the 2-year follow-up), we used the McNemar test for categorical variables and the Wilcoxon signed-rank test for continuous variables. The non-parametric Wilcoxon signed-rank test was used since not all continuous variables were normally distributed (based on the Shapiro–Wilk test results). We considered $P < 0.05$ to be statistically significant. To predict the PDQ-39 score at the 2-year follow-up, we used stepwise multiple regression analysis. The factors of age, female sex, disease duration, Hoehn and Yahr stages, MMSE score, MDS-UPDRS parts I–III scores, wearing off, dyskinesia, and LEDD were analyzed for multiple collinearity at baseline by using a correlation matrix table and variance inflation factor. As no set of factors showed multiple collinearity, we included all variables for stepwise multiple regression analysis.

For multiple regression analysis, the sample size should exceed the number of variables by 10 times. Therefore, since the multiple regression analysis included 11 independent variables in this study, 110 participants were required. This number was inflated by 40% to consider the possibility that some patients might not complete all the measures in this study. The target sample size was set at 154 participants.

Results

Of 177 patients recruited over the 2-year study period, 69 patients were excluded who did not meet the inclusion criteria. Therefore, we analyzed a final subset of 108 patients with PD. The patients' clinical characteristics at baseline are shown in Table 1. The median age was 69 years (interquartile range (IQR), 64–75 years), and 65.7% were female. The median MDS-UPDRS part I and PDQ-39-summary index (SI) scores were 8 and 25, respectively.

After 2 years, modified Hoehn and Yahr stages, MDS-UPDRS part II scores, and PDQ-39-SI scores were significantly worse than those at baseline ($P < 0.01$) (Table 2). However, the MDS-UPDRS part I scores at 2 years were not significantly different from the baseline (Table 2). In addition, at 2 years, PDQ-39 scores, mobility, activities of daily living, emotional well-being, cognition, bodily discomfort, and communication were significantly increased from baseline levels (PDQ-39 scores, mobility, activities of daily living, emotional well-being, cognition, bodily discomfort; $P < 0.01$, communication; $P < 0.05$). LEDD and dyskinesia were likewise increased from baseline levels ($P < 0.01$), while the MDS-

Table 1 Patients' characteristics

	Total number ($n = 108$)
Age, yrs., median [IQR]	69 (64–75)
Female, *n* (%)	71 (65.7)
Disease duration, yrs., median [IQR]	5 (3–10)
Hoehn and Yahr stage, median [IQR]	2.5 (2–3)
MMSE, median (IQR)	28 (26–29)
MDS-UPDRS part I, median [IQR]	8 (5–13)
MDS-UPDRS part II, median [IQR]	10 (5–18)
MDS-UPDRS part III, median [IQR]	22 (12–33)
LEDD (mg/day), median [IQR]	523 (329–770)
PDQ-39 SI, median [IQR]	25 (9–53)
Wearing off, *n* (%)	42 (38.9)
Dyskinesia, n (%)	18 (16.7)

MMSE, Mini-Mental State Examination; *MDS-UPDRS*, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; *LEDD*, levodopa equivalent daily dose; *PDQ-39*, Parkinson's Disease Questionnaire-39

UPDRS part III scores did not significantly differ from those at baseline (Table 2).

In univariate analysis, disease duration, Hoehn and Yahr stages, the MMSE scores, MDS-UPDRS parts I–III scores, wearing off, dyskinesia, and LEDD were associated with the change in the PDQ-39-SI score between the baseline and 2-year follow-up (Table 3). Final stepwise multiple regression model predicting QOL (PDQ-39) showed that female sex (standard partial regression coefficient (β) = 0.131, $P < 0.05$) and the MDS-UPDRS part I ($\beta = 0.272$, $P < 0.01$) and part II ($\beta = 0.571$, $P < 0.01$) baseline scores were significant predictors of the PDQ-39-SI scores at the 2-year follow-up. However, age, disease duration, Hoehn and Yahr stages, the MMSE scores, the MDS-UPDRS part III scores, wearing off, dyskinesia, and LEDD did not correlate with PDQ-39-SI scores (Table 3). Adjusted R^2 of the final model was 0.577.

Discussion

In this 2-year longitudinal retrospective cohort study, we showed through stepwise multiple regression analysis that female sex and the baseline MDS-UPDRS part I and part II scores were significant predictors for the PDQ-39-SI scores at the 2-year follow-up.

Transition of NMSs and motor symptoms after 2-year follow-up

At the 2-year follow-up, while the PDQ-39-SI scores had worsened, the MDS-UPDRS part I scores had not changed in the univariate analysis (Table 2). The MDS-UPDRS part I measures NMSs that include cognitive, mood, and behavioral dysfunctions. A similar 2-year cohort study found more significant changes in NMSs related to MDS-UPDRS part I scores and also reported that sleep, gastrointestinal, attention/memory, and skin disturbances were more common in patients with PD at the 2-year follow-up; however, psychiatric, cardiovascular, and respiratory symptoms were less frequent [9]. In another 2-year prospective study in patients with de novo untreated PD, NMSs such as "sex difficulties," "pain," and "weight change" deteriorated, while depression and concentration improved over the study period [19]. In addition, a similar 2-year prospective study showed that sleep/fatigue and mood/apathy increased, while attention/memory, sexual function, and miscellaneous NMSs decreased in patients with PD [11]. Another 2-year longitudinal study measured MDS-UPDRS part I scores in patients with PD and found on follow-up that all NMS items, with the exception of anxious mood and sleep problems had deteriorated [20]. These results demonstrated that the course of NMSs differs in each study.

In our analysis, we only evaluated NMSs that impacted daily life. Therefore, for each item of the MDS-UPDRS part I assessment, we selected a threshold score of ≥ 2, as 1 point indicates a slight NMS, which does not affect daily life. As a result, changes in NMSs at follow-up may have been underestimated, which may explain differences between our study and previous reports [20]. Another explanation for these differences is that the population of this study had higher MDS-UPDRS part I scores than previous studies [20]. Because NMSs are severe, the treatment during the course of the study may affect these differences.

Previous studies have evaluated NMSs using different scales, including the original instrument for the Parkinson and NMSs study [9], the non-motor symptoms questionnaire (NMSQ) [19], and the non-motor symptoms scale (NMSS) [11]. The MDS-UPDRS part I and NMSS assessments have been shown to have similar validity. However, transformed scores estimated from weighted regression models have shown that the MDS-UPDRS part I scores and NMSS are not concordant for patients with severe NMSs [21]. As a result, given that our study only considered NMSs, which impacted daily life, our assessment of more severe NMSs only may explain why the slight change in NMSs may have been underestimated.

We also found that the MDS-UPDRS part III scores did not change at the 2-year follow-up, whereas the MDS-UPDRS part II scores and the Hoehn and Yahr stage deteriorated compared with baseline. Furthermore, LEDD, usage of selegiline, and dyskinesia were more frequent at 2 years than at baseline (Table 2). Oral administration of levodopa is the most effective therapy for PD, and long-term treatment with levodopa can lead to levodopa-induced dyskinesia [22]. Our results

Table 2 Changes in MDS-UDPRS, and PDQ-39 at 2 years after presentation

	Baseline	2-year	*P* value
Clinical subtype, *n* (%)			<0.01
Tremor dominant	56 (51.9)	27 (25.0)	
PIGD	43 (39.8)	72 (66.7)	
Intermediate	9 (8.3)	9 (8.3)	
LEDD (mg/day), median [IQR]	523 (329–770)	668 (420–828)	< 0.01
Levodopa, *n* (%)	101 (93.5)	104 (96.3)	NS
Dopamine agonist, *n* (%)	54 (50)	60 (55.6)	NS
Istradefylline, *n* (%)	6 (5.6)	10 (9.3)	NS
Selegiline, *n* (%)	26 (24.1)	37 (34.3)	< 0.05
Amantadine, *n* (%)	21 (19.4)	22 (20.4)	NS
Entacapone, *n* (%)	9 (8.3)	11 (10.2)	NS
Trihexyphenidyl, *n* (%)	5 (4.6)	1 (0.9)	NS
Hoehn and Yahr stage, median (IQR)	2.5 (2–3)	2.5 (2–3)	< 0.01
MMSE, median (IQR)	28 (26–29)	28 (25–30)	NS
MDS-UPDRS part I, median (IQR)	8 (5–13)	8 (5–13)	NS
Cognitive impairment, *n* (%)	1 (0.9)	3 (2.8)	NS
Hallucinations and psychosis, *n* (%)	3 (2.8)	2 (1.9)	NS
Depressed mood, *n* (%)	4 (3.7)	3 (2.8)	NS
Anxious mood, *n* (%)	9 (8.3)	3 (2.8)	NS
Apathy, *n* (%)	2 (1.9)	2 (1.9)	NS
Features of DDS, *n* (%)	0	0	NS
Nighttime sleep problems, *n* (%)	31 (28.7)	39 (36.1)	NS
Daytime sleepiness, *n* (%)	64 (59.3)	59 (54.6)	NS
Pain and other sensations, *n* (%)	36 (33.3)	30 (27.8)	NS
Urinary problems, *n* (%)	29 (26.9)	35 (32.4)	NS
Constipation problems, *n* (%)	45 (41.7)	45 (41.7)	NS
Lightheadedness on standing, *n* (%)	23 (21.3)	17 (15.7)	NS
Fatigue, *n* (%)	22 (20.4)	29 (26.9)	NS
Number of NMS, median (IQR)	6 (4–8)	6 (4–7)	NS
MDS-UPDRS part II, median (IQR)	10 (5–18)	13 (6–21)	< 0.01
MDS-UPDRS part III, median (IQR)	22 (12–33)	23 (13–31)	NS
Wearing off, *n* (%)	42 (38.9)	53 (49.1)	NS
Dyskinesia, *n* (%)	18 (16.7)	29 (26.9)	< 0.01
PDQ-39 SI, median (IQR)	25 (9–53)	44 (17–70)	< 0.01
Mobility, median (IQR)	8 (1–21)	17 (4–27)	<0 .01
Activities of daily living, median (IQR)	2 (0–9)	5 (1–10)	<0 .01
Emotional well-being, median (IQR)	4 (2–10)	6 (3–12)	<0 .01
Stigma, median (IQR)	1 (0–4)	(0–6)	NS
Social support, median (IQR)	1 (1–2)	1 (1–3)	NS
Cognition, median (IQR)	3 (1–6)	4 (2–7)	< 0.01
Communication, median (IQR)	0 (0–2)	0 (0–2)	< 0.05
Bodily Discomfort, median (IQR)	2 (1–4)	3 (1–7)	< 0.01

MMSE, Mini-Mental State Examination; *MDS-UPDRS*, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; *DDS*, dopamine dysregulation syndrome; *NMS*, non-motor symptom; *LEDD*, levodopa equivalent daily dose; *PDQ-39*, Parkinson's Disease Questionnaire-39; *PIGD*, postural instability/gait difficulty; *NS*, not significant

suggest that augmentation of dopamine replacement therapy simultaneously increased levodopa-induced dyskinesia and prevented the exacerbation of motor symptoms. However, the MDS-UPDRS part II scores pertaining to M-EDL worsened despite patients receiving dopamine replacement therapy. Similar to our findings, a previous longitudinal study

Table 3 A stepwise multiple regression model predicting the PDQ-39 score 2 years after presentation

	Standard partial regression coefficient	P value	Standard partial regression coefficient	P value
	Unadjusted	Unadjusted	Multivariate model	Multivariate model
Age (years)	0.043	NS	-	-
Female	0.151	NS	0.131	< 0.05
Disease duration (years)	0.207	< 0.05	-	-
Hoehn and Yahr stage	0.338	< 0.01	-	-
MMSE	− 0.19	< 0.05	-	-
MDS-UPDRS I	0.616	< 0.01	0.272	< 0.01
MDS-UPDRS II	0.718	< 0.01	0.571	< 0.01
MDS-UPDRS III	0.32	< 0.01	-	-
LEDD (mg/day)	0.313	< 0.01	-	-
Wearing off	0.261	< 0.01	-	-
Dyskinesia	0.255	< 0.01	-	-

Final model, adjusted $R^2 = 0.577$

Dependent variables, age, female, disease duration, Hoehn and Yahr stages, MMSE, MDS-UPDRS parts I–III, wearing off, dyskinesia, LEDD

PDQ-39, Parkinson's Disease Questionnaire-39; *MMSE*, Mini-Mental State Examination; *MDS-UPDRS*, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; *LEDD*, levodopa equivalent daily dose

reported that the M-EDL scores in patients treated with pharmacological therapy increased by an average of 0.80 points per year over a 4-year study period [23]. Moreover, M-EDL scores were shown to increase by 0.99 points per year in patients with de novo PD [24]. In this study, the median MDS-UPDRS part II scores increased by 1.5 points per year, which is higher than what has been previously reported. This may be due to the fact that, in our study, the median age of participants was higher than that in previous studies [23, 24].

In examining the clinical subtypes of PD, PIGD was more prevalent than TD after 2 years. Previous reports have shown that the conversion from TD to PIGD was more common than the conversion from PIGD to TD [25]. As greater nigral degeneration is expected in PIGD cases [26], the increased frequency of PIGD in our study may reflect the progression of the pathology of PD. These results suggest that subjective improvement is difficult with pharmacological treatment alone. Therefore, to achieve subjective improvement, a neurologist may need to consider treatments other than drug therapy, such as rehabilitation.

Predictors of HrQOL after 2 years

Our study showed that MDS-UPDRS part I and part II scores, as well as female sex, were predictors of HrQOL at the 2-year follow-up in patients with PD. MDS-UPDRS part I scores were not significantly different at the 2-year follow-up, but this score was the important predictor of HrQOL. These findings indicate the important contribution of confounding factors to HrQOL in PD.

The association between sex and HrQOL remains controversial [27]. However, our results are consistent with previous work, which demonstrated that female sex was associated with a worse HrQOL among patients with PD [28]. Different evaluation instruments, sociocultural differences, and sample size issues may affect the detection of a relationship between sex and HrQOL.

In previous cross-sectional studies, the main determinant for predicting HrQOL was the MDS-UPDRS part II scores, followed by the MDS-UPDRS part I scores [29, 30]. Analogously, NMSs assessed in longitudinal studies by either NMSS or the NMSQ predicted changes in the PDQ-39-SI scores [10, 11]. We evaluated NMSs using a different instrument than that used in previous longitudinal studies [10, 11], and our final multiple regression model showed that M-EDL and nM-EDL, as estimated by the MDS-UPDRS, were good predictors for future HrQOL. NMSS and NMSQ can enable a more detailed confirmation of non-motor symptoms than MDS-UPDRS part I. Although MDS-UPDRS part I involves evaluation of only 13 items, it is simpler and more clinically usable because fewer evaluation items are required.

MDS-UDPRS part III scores did not predict future HrQOL, and this was consistent with the findings of previous studies [10, 11]. While the MDS-UPDRS part I and part II scores quantify subjective symptoms, the MDS-UDPRS part III scores assess objective motor problems as evaluated by a

neurologist [12]. Since the PDQ-39 scores also address subjective issues, MDS-UPDRS part I and part II scores may be more related to PDQ-39 than MDS-UDPRS part III scores. Moreover, MDS-UDPRS part III scores were evaluated in the "ON" state, while MDS-UPDRS part I and part II scores were evaluated in all states of everyday life; this may also have affected the results, especially in patients with wearing off and dyskinesia.

Strengths and limitations

To the best of our knowledge, this is the first longitudinal study to evaluate the association between the MDS-UPDRS and HrQOL. This allowed us to better investigate the longitudinal association between MDS-UPDRS scores and HrQOL. However, this study also had several limitations. First, we could not evaluate the efficacy of treatments for addressing NMSs. This is because patients with PD may be receiving care from a primary physician, such as treatment for constipation, which would not have been included in the survey of our clinic. Primary care may be an unaddressed confounding factor in our analysis. Second, this study did not include patients with dementia (MMSE score ≤ 23). Thus, our results may not be generalizable to cases of PD with dementia. Third, due to the small sample size, a few cases are missing in multiple regression analysis. We could also not evaluate which MDS-UPDRS I and II subitems were related to QOL in our regression model. Fourth, given that this retrospective cohort study was conducted in a single tertiary center, there is a risk of selection bias impacting our results. Further prospective studies are necessary to clarify the external validity of our findings.

Conclusions

MDS-UPDRS part I and part II scores and female sex were found to be predictors of HrQOL 2 years after clinical presentation. In clinical practice, MDS-UPDRS-guided assessment and treatment of motor symptoms and NMSs may contribute to improving HrQOL in patients with PD.

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Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study protocol was approved by the institutional review board of the Aomori Prefectural Central Hospital. Since this study was a retrospective observational study, written informed consent was not obtained from the patients, and requirement for informed consent was waived by the institutional review board. However, we gave patients an opportunity to opt out of the study.

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