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Nonmotor Symptoms Are Independently Associated With Impaired Health-Related Quality of Life in Chinese Patients With Parkinson's Disease

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Abstract: We performed a cross-sectional study of 82 Chinese patients with Parkinson's disease (PD) enrolled during an 18-month period using a clinical interview to assess the prevalence of nonmotor symptoms (NMS), the association with disease severity and motor status, and the impact on patients' health-related quality of life (Hr-QoL). The patients' NMS, Hr-QoL, disease severity, and motor status were assessed by the Nonmotor Symptoms Scale (NMSS), the 39-item Parkinson's Disease Questionnaire (PDQ-39), the modified Hoehn and Yahr staging scale (H&Y) and the Unified Parkinson's Disease Rating Scale part III (UPDRS III), respectively. We found that 100% of patients with PD presented with NMS. The NMSS significantly correlated with disease duration (Spearman's $r_S = 0.276$, $P = 0.012$), H&Y ($r_S = 0.230$, $P = 0.038$), and UPDRS III ($r_S = 0.350$, $P = 0.001$). Similarly, the PDQ-39 SI significantly associated with the disease duration ($r_S = 0.258$, $P = 0.019$), H&Y ($r_S = 0.340$, $P = 0.002$), and UPDRS III ($r_S = 0.453$, $P < 0.001$). NMS domains that influenced the PDQ-39 SI were sleep/fatigue, mood, gastrointestinal, urinary, and miscellaneous symptoms. This strongly suggested that the five domains played a key role in the manifestation of Hr-QoL. NMSS explains more of the variability in Hr-QoL than UPDRS III, when both are the model (stepwise multiple linear regression analysis R^2 change, 47.8% vs. 5.87%, respectively). Therefore, these findings demonstrate that NMS are independently and negatively associated with Hr-QoL in PD and that improving NMS should be viewed as an important part in the management of PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; NMS; PDQ-39; Hr-QoL

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease, with disturbance of the central dopaminergic system. It affects approximately 1.5% of the worldwide population aged older than 60 years.[1,2] PD is characterized by typical motor symptoms (MS) such as bradykinesia, resting tremor, and rigidity, as well as nonmotor symptoms (NMS),[3] which are also highly prevalent. Patients normally show increasing severity of NMS as the disease develops, although some of the NMS such as depression and impaired cognition may occur in the premotor stage of this disease. NMS normally include 30 items distributed in nine different domains: gastrointestinal, urinary, attention/memory, perceptual problems/hallucinations, mood (depression/anxiety), sexual function, cardiovascular, sleep/fatigue disorder, and miscellaneous. Although PD is rarely diagnosed before the appearance of MS, NMS appear throughout the disease course and may even precede MS.[4,5] Some PD patients can even recall a prodromal phase with NMS. Two studies by O'sullivan et al. and Shulman et al.

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showed that NMS occurred with a prevalence ranging from 21% at the initial diagnosis of PD to 88% after 7 years of onset.[6,7] Since a variety of NMS may precede typical MS features,[8,9] the correct identification and management of NMS will help neurologists identify PD in the very early stages when the motor signs are not obvious, delay PD progression, and alleviate PD clinical syndromes.

Health-related quality of life (Hr-QoL) measures the impact of chronic disorders such as PD and Alzheimer's disease in their patients, allowing better understanding of how the diseases interfere with a person's day-to-day life. It usually refers to an individual's emotional well-being, social and physical support, mobility, cognition, and bodily discomfort. In PD, numerous factors influence the Hr-QoL of patients, including disease severity, disease duration, motor complications, constipation, depression, anxiety, pain, sleep disorder, declined cognition, and hallucinations.[10,11] Therefore, improving the Hr-QoL becomes a major task in the management of patients with PD,[12] and the evaluation of Hr-QoL after drug or surgical therapy has been widely used in prognosis treatment strategies in clinical practice.[13,14]

Recently, complaints of NMS and their association with Hr-QoL in PD patients have received increasing attention. Some neurologists view NMS, rather than MS, as the primary cause of poor Hr-QoL.[15–17] Because few studies have provided a unified and integrated scale for the assessment of NMS in PD, NMS have not been regularly used to assess PD, especially in China. Recently, the Nonmotor Symptoms Scale (NMSS) for Parkinson's disease was developed to quantify the overall prevalence of NMS[18,19] and was validated in a population of Chinese patients with PD.[20,21]

The primary purpose of this cross-sectional study was to use the NMSS and the 39-item Parkinson's Disease Questionnaire (PDQ-39)[22] to investigate the association between NMS and different dimensions of Hr-QoL in Chinese patients with PD. An evaluation of the influence of disease duration, severity and MS on NMS, and Hr-QoL was also performed.

METHODS

Patients

This cross-sectional study was carried out at the Department of Neurology of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China. From July 2008 to December 2009, 82 patients with PD with mean age (and SD) was 65 ± 9.7 years, including 46 males and 36 females (Table 1), were recruited from the outpatient clinic and identified according to the United Kingdom PD Society Brain Bank (UK-PDSBB) criteria for the diagnosis of idiopathic PD.[23] The local Ethics Committee approved the study, and the patients gave informed consent for the investigation.

TABLE 1. *Demographic, motor and nonmotor parameters, and PDQ-39 SI*

Clinical parameters	Total		
	Mean (SD)	Minimum	Maximum
Demographic			
Gender (n)	82		
Male, n (%)	46 (56.1)		
Female, n (%)	36 (43.9)		
Age at examination (yr)	65.0 (9.7)	38	82
Disease duration (yr)	5.1 (4.9)	0.04	26
Daily L-dopa dosage (mg)	429.7(233.1)	0	1200
H&Y (median)	2	1	4
Motor			
UPDRS III	16.9 (7.0)	4	33
Nonmotor			
MMSE	27.0 (2.2)	22	30
NMSS total	133.2 (47.5)	43	234
Cardiovascular	1.9 (3.5)	0	12
Sleep/fatigue	29.2 (13.1)	0	48
Mood	27.6 (18.0)	0	64
Perceptual problems	5.2 (6.9)	0	29
Attention/memory	13.4 (9.0)	0	36
Gastrointestinal	11.2 (9.1)	0	33
Urinary	16.4 (11.0)	0	36
Sexual function	10.1 (11.2)	0	24
Miscellaneous	18.3 (11.1)	0	48
Hr-QoL			
PDQ-39 SI	43.0 (14.7)	7.7	78.9
Mobility	48.4 (21.9)	7.5	95.0
Activities of daily living	58.9 (16.6)	4.2	87.5
Emotional well-being	47.9 (29.6)	0	100.0
Stigma	46.5 (45.8)	0	100.0
Social support	7.8 (15.9)	0	66.7
Cognition	34.1 (18.5)	0	75.0
Communication	35.3 (32.9)	0	100.0
Bodily discomfort	32.8 (29.5)	0	100.0

SD, Standard deviation; MMSE, Mini-Mental State Examination; UPDRS III, the Unified Parkinson's Disease Rating Scale part III; H&Y, the modified Hoehn and Yahr staging scale; NMSS, Nonmotor Symptoms Scale for Parkinson's disease (range of possible scores from 0 to 360); PDQ-39 SI, the 39-item Parkinson's Disease Questionnaire (range of scores from 0 to 100).

Study Design

Evaluations and complete neurological examination from outpatients were performed by experienced neurologists. All patients with idiopathic PD in this study fulfilled the criteria of the UK-PDSBB.[23] Exclusion criteria were: (1) PD patients with disability due to neurological disorders other than PD, such as cerebro-

vascular disease or sequelae or psychosis[24]; (2) PD patients with somatic diseases that could have a potential effect on NMS and Hr-QoL (e.g., pain syndromes, advanced diabetes mellitus, malignancy, renal, hepatic or heart failure, severe anemia, or any other acute or chronic debilitating or life-threatening disease/state)[24]; (3) PD patients with moderate/severe cognitive impairment that may interfere with the reliability of the Hr-QoL self-assessment, as determined by a Mini-Mental State Examination (MMSE) (the Chinese version of the MMSE) score lower than the median value determined in a reference population-based sample of corresponding age and education[25,26]; and (4) individuals who refused to participate in the study. All subjects completed the following battery of standard assessment measures: a standard demography form, the Unified Parkinson's Disease Rating Scale part III (UPDRS III-motor)[27] and the modified Hoehn and Yahr staging scale (H&Y).[28] The UPDRS III-motor and H&Y scales were used to evaluate motor dysfunctions and disease severity. The degree of NMS in every patient was measured by the NMSS,[18] and the level of Hr-QoL was assessed by PDQ-39.[29] The translation and validation of the Chinese version of the PDQ-39 was referenced from the work by Tsang et al.[21] Cognitive abilities were evaluated with the MMSE.[25] Summary indices were calculated for both the total scale (PDQ-39 SI) and the subscales (including mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort), and the higher numerical values (maximal score of 100) indicated the worse level of complications. All scales were available and validated for the Chinese population. The demographics and clinical data of subjects are shown in Table 1.

Statistical Analysis

All data for the continuous variables [age, disease duration, daily levodopa (L-dopa) dosage, UPDRS III, MMSE, NMSS, and PDQ-39 SI] are shown as the means ± standard deviation, and the categorical variable (gender) is shown as a percentage. The total scores of UPDRS III, MMSE, NMSS, and PDQ-39 were calculated by summing single items. The strength of the association for correlation coefficients was interpreted as follows: $\leq$ 0.19, negligible; 0.20 to 0.39, weak; 0.40 to 0.59, moderate; 0.60 to 0.79, strong; and $\geq$ 0.80, very strong.[30] Spearman's rank correlation coefficient was used to evaluate the association among demographic and clinical variables, nine different NMSS domains and PDQ-39 SI, and NMSS and PDQ-39 SI. Stepwise multiple linear regression analysis (methods = stepwise, F-to-enter = 0.05, F-to-remove = 0.1) was carried out to test the independent effects of the selected variables on PDQ-39. The variables tested included age, disease duration, H&Y, MMSE, NMSS, and UPDRS III. The SPSS 13.0 software (Chicago, IL) was used for statistical analyses. *P* values of less than 0.05 were regarded as statistically significant.

RESULTS

Patient Characteristics

In total, 82 PD subjects, including 46 males (56.1%) and 36 females (43.9%), were enrolled in this cross-sectional study. The mean age of all patients was 65 ± 9.7 years (range, 38–82 years). Mean duration of PD symptoms was 5.1 ± 4.9 years (range, 0.04–26 years), and H&Y stages ranged from 1 to 4. With respect to the L-dopa therapy, the average dosage was 429.7 mg daily. Details of the demographics of all 82 patients are listed in Table 1.

Prevalence of NMS

The mean NMSS score was 133.2, with a range from 43 to 234. The maximum score (standardized to a percentage of the maximum possible score) was recorded for all domains: cardiovascular problems (6 patients); sleep/fatigue (14); mood (3); perceptual problems (1); attention/memory (36); gastrointestinal (1); urinary (12); sexual function (29); and miscellaneous cardiovascular issues (1). Among the PDQ-39 dimensions, patients had the best Hr-QoL in social support (7.8), while higher values of PDQ-39 scores (meaning lower Hr-QoL) were recorded in the activities of daily living (58.9), followed by mobility (48.4), emotional well-being (47.9), and stigma (46.5; Table 1).

Correlations Between Demographics and Clinical Variables, NMSS and PDQ-39 SI, and NMSS Domains and PDQ-39 SI

There was a significant correlation between NMSS and disease duration (r_S = 0.276, P = 0.012; Table 2) and H&Y staging (r_S = 0.230, P = 0.038; Table 2). Notably, NMSS also correlated with the UPDRS III score (r_S = 0.350, P = 0.001; Table 2). Significant correlations were also observed between PDQ-39 SI and the disease duration, PDQ-39 SI and disease severity that was measured by the H&Y scale, and PDQ-39 SI and MS that were measured by the UPDRS III (r_S = 0.258/0.340/0.453, P = 0.019/0.002/<0.001, respectively; Table 2). The PDQ-39 SI score strongly correlated with that of NMSS (r_S = 0.673, P < 0.

TABLE 2. *Spearman's rank correlation coefficient (r_s) and P values between demographic and clinical variables, and for NMSS and PDQ-39 SI*

	NMSS		PDQ-39 SI	
Variable	Coefficient of correlation	*P*	Coefficient of correlation	*P*
Age	−0.148	0.186	−0.007	0.947
Disease duration	0.276	0.012[a]	0.258	0.019[a]
H&Y	0.230	0.038[a]	0.340	0.002[b]
UPDRS III	0.350	0.001[b]	0.453	<0.001[c]
MMSE	−0.083	0.460	−0.169	0.130

r_S, Spearman's rank correlation coefficient; H&Y, the modified Hoehn and Yahr staging scale; UPDRS III, the Unified Parkinson's Disease Rating Scale part III; MMSE, Mini-Mental State Examination; NMSS, Nonmotor Symptoms Scale for Parkinson's disease; PDQ-39 SI, the 39-item Parkinson's Disease Questionnaire. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

001; Table 3). Specifically, when evaluating the correlation between PDQ-39 SI and the different NMSS dimensions, significant correlations from low to high were observed in urinary ($P = 0.025$), miscellaneous ($P = 0.003$), sleep/fatigue ($P = 0.002$), gastrointestinal ($P < 0.001$), and mood ($P < 0.001$) ($r_S = 0.248$–0.690). For the remaining four dimensions, no significant correlations were found (Table 3).

NMSS, UPDRS III, and Hr-QoL

A stepwise multiple linear regression analysis with Hr-QoL as the dependent variable was used to evaluate the independent effects of the potential factors including age, disease duration, H&Y staging, MMSE, NMSS, and UPDRS III on Hr-QoL. H&Y scores were treated as ranked data. Our study indicated that after NMS (NMSS) and MS (UPDRS III) were included in the model, no other variable met the $P < 0.05$ entry criteria. The final model explained that NMS (NMSS) and MS (UPDRS III) were the variables with the most crucial effects on the overall Hr-QoL, as measured by PDQ-39 SI. The whole model explained 53.6% of the variance of the PDQ-39 SI (Table 4). NMSS explained more of the variability in Hr-QoL than UPDRS III (47.8% vs. 5.87% respectively). NMS has strong, independent association with lower Hr-QoL, as evaluated by the PDQ-39.

TABLE 3. *Spearman's rank correlation coefficient (r_s) and P value between NMSS domains and PDQ-39 SI*

NMSS domains	r_s	*P*
Cardiovascular	0.109	0.329
Sleep/fatigue	0.340	0.002
Mood	0.690	<0.001
Perceptual problems	0.212	0.056
Attention/memory	0.202	0.069
Gastrointestinal	0.384	<0.001
Urinary	0.248	0.025
Sexual function	0.006	0.959
Miscellaneous	0.323	0.003
NMSS total	0.673	<0.001

r_S, Spearman's rank correlation coefficient; NMSS, Nonmotor Symptoms Scale for Parkinson's disease; PDQ-39 SI, the 39-item Parkinson's Disease Questionnaire.

DISCUSSION

Over the past few years, NMS in PD patients have received significant attention during the diagnosis, therapy, and evaluation of Hr-QoL of this disease. One international investigation by the Global Parkinson's Disease Survey Steering Committee[31] indicated that factors from NMS rather than MS contributed more to the variability in Hr-QoL of PD patients. Although NMS greatly influence the Hr-QoL of PD patients, more than 50% of existing NMS are missed in clinical practice,[32,33] and this situation is even worse on the mainland of China. As a developing country, the economic and social surroundings are different from those of developed countries; therefore, medical facilities or skills, particularly in the countryside, are not up to date. Neurologists or other practitioners on mainland China sometimes underestimate the importance of NMS on Hr-QoL and lack comprehensive and valid

TABLE 4. *Stepwise multiple linear regression analysis with Hr-QoL as the dependent variable*[a]

Variables	*B*	SE	Standardized coefficient β	*t*	*P*	R^2 change	R^2
Total							0.536
Constant	9.192	3.762		2.444	0.017		
NMSS	0.185	0.025	0.604	7.392	<0.001	0.478	
UPDRS III	0.539	0.172	0.255	3.128	0.002	0.058	

[a]Independent variables considered in Stepwise multiple linear regression modeling include: age, disease duration, H&Y (ranked data), MMSE, NMSS, and UPDRS III. Those variables with $P > 0.05$ were removed.

B, unstandardized coefficients; SE, standard error of *B*; R^2 change, the changed value of R^2 when the variables entered the equation; NMSS, Nonmotor Symptoms Scale for Parkinson's disease; UPDRS III, the Unified Parkinson's Disease Rating Scale part III; H&Y, the modified Hoehn and Yahr staging scale; MMSE, Mini-Mental State Examination.

specific tools to identify and evaluate NMS. Therefore, it is imperative that the effects of NMS on Hr-QoL be explored and the domains with significant impact on Hr-QoL be identified. This study aimed to investigate the impact of NMS on Hr-QoL in PD patients by systematically collecting information about demographic, motor, and nonmotor clinical syndromes in Chinese subjects with PD. To the best of our knowledge, this is the first report evaluating the association between nonmotor effects with Hr-QoL in Chinese patients with PD using both unified and integrated scales (NMSS and PDQ-39, respectively).

In this study, we found that NMS were very common in Chinese patients with PD, with a prevalence of the whole spectrum of NMS being 100%, and the NMSS (mean = 133.2, Table 1) was higher than that of a previous report (mean = 89.9).[34] Two reasons probably led to the discrepancy of NMSS between Chinese and Western subjects with PD. First, there were different social surroundings and medical environments between Chinese and Western populations. As a developing country, some Chinese patients with PD lacked sufficient healthcare and medical insurance, preventing them from visiting neurologists until the NMS became worse. Second, some general practitioners, especially in the countryside, were unable to efficiently recognize the NMS of PD; thus, PD patients only went to a neurologist when the symptoms worsened. The results of this study further indicated that Chinese doctors should increase their recognition capabilities of NMS in PD. To further specify the association of the individual domains of the NMSS with the PDQ-39 SI, using the Spearman's rank correlation coefficient analysis, we identified that some dimensions of NMS such as sleep/fatigue and mood significantly correlated with the PDQ-39 SI (Table 3). Although our results (Table 3) indicated the percent variation, they only explained the r_S separately and did not take into account the contributions of the other domains. These data further demonstrated that NMS had a profound impact on Hr-QoL and some NMS including sleep/fatigue may lead to poorer Hr-QoL in PD patients. These five domains mentioned in Table 3 would be the important targets for medical interventions for NMS, even in the early stages of PD, and should be further investigated in terms of clinical practice and Hr-QoL assessment. The result is consistent with several other studies showing that NMS are very common in PD and some NMS are major predictors of poor Hr-QoL in PD patients.[20,35,36]

To explore the association of disease duration, H&Y, and UPDRS III with the NMSS and PDQ-39 SI, Spearman's rank correlation coefficients were determined. A significant correlation between the NMSS and H&Y scores was reported in a previous study ($r_S = 0.33$, $P < 0.001$)[18] and showed a significant association between the NMSS and H&Y ($r_S = 0.230$, $P = 0.038$; Table 2), consistent with our study. Highly significant correlations (Table 2) were also observed between motor dysfunctions and NMS burden, between motor dysfunctions and Hr-QoL, and between disease severity and Hr-QoL. This result suggested that both disease severity and motor dysfunctions may influence NMS and Hr-QoL, and NMS may have multiple effects on the motor complications in PD. Interestingly, negative correlations that were not statistically significant ($r_S = -0.083$, $P = 0.460$) were found between the MMSE and NMSS scores, and between the MMSE and PDQ-39 SI ($r_S = -0.169$, $P = 0.130$). This result was similar to one study by Wang et al.[20] The reasons for the finding may be due to the facts that the Chinese subjects with PD in this study belonged had early stages of PD (H&Y stages I–II), and they showed only minor impairment in cognition or dementia (the mean MMSE score was 27.0 ± 2.2).

In our study, a stepwise multiple linear regression analysis was used to evaluate and compare the impact of NMS and MS on Hr-QoL in this study (Table 4). Standardized coefficient β scores were 0.604 and 0.255 for NMSS and UPDRS III, respectively. Although both of them presented significant associations with Hr-QoL, NMS appeared to be more closely correlated with Hr-QoL based on this data as its standardized coefficient β score was higher than that of the UPDRS III, demonstrating that NMS play a crucial role in Hr-QoL. In addition, the R^2 change for NMSS and UPDRS III were 47.8% and 5.87%, respectively. This further demonstrated that compared with UPDRS III, the NMSS appeared to have a greater impact on Hr-QoL. Our results are in agreement with Chaudhuri et al.'s study showing that the ability of the NMSS to predict Hr-QoL appeared to be more robust than that of the current UPDRS III.[19] Recently, increasing attention has been paid to the impact of NMS on the Hr-QoL of PD patients.[19,32,37] One study by Grosset et al. showed deterioration in Hr-QoL (measured by the PDQ-39) when MS and NMS were left untreated, further demonstrating that the overall evaluation of PD symptoms should include MS and NMS and focusing beyond the conventional MS.[38] Our data presented here strongly suggests that it is imperative to correctly diagnose and manage NMS in PD to improve the Hr-QoL of patients.

Several limitations of this study should be noted: (1) only a small number of PD patients (82 patients were

recruited) and the disease duration was relatively short (5.1 years) in this study; (2) the low mean score of the UPDRS III scale (mean = 16.9); (3) mainly PD patients in early stages of disease were enrolled, as indicated by the low median stage of the H&Y scale and the relatively high MMSE score (27.0); (4) to validate and complete the questionnaire, we only chose PD subjects with sufficient cognitive ability, significantly narrowing the population in this study. Therefore, larger studies need to be done, expanding the authors' work to a broader population. In addition, different stages of PD patients in both UPDRS III and H&Y score should be included to compensate for current shortcomings.

In conclusion, our current data demonstrate that NMS are very common in PD patients and have independent but close relationships with disease duration, severity, and Hr-QoL. Although the effects of PD on patients' Hr-QoL is determined by the complex interaction of the MS and NMS of the disease, NMS (especially sleep/fatigue, mood, gastrointestinal, urinary, and miscellaneous symptoms) appear to play an important role in the manifestation of Hr-QoL. The association between NMS and poor Hr-QoL should be very important to neurologists and clinical practitioners. Further studies are needed to investigate how to improve the Hr-QoL of PD patients and relieve their NMS.

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