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Original Research Article

NON MOTOR SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE – AN OBSERVATIONAL STUDY

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Abstract

Background: In multiple studies around the globe, non-motor symptoms (NMS) have been identified as a source of immense disability in patients with Parkinson's disease (PD). The study was aimed to assess the Non Motor Symptoms in patients with Parkinson's Disease and its impact on Quality of Life. **Materials and Methods:** Observational, Cross sectional Study, single center, one point in time evaluation study in a tertiary care hospital in Parkinson's Disease patients fulfilling the criteria of the UK-PDSBB. Epidemiology, medication, and the incidence of non-motor symptoms will be statistically analysed. **Result:** In total, 40 PD subjects, including 24 males (60%) and 16 females (40%). The mean age of all patients was 55.93 ± 9.29, mean UPDRS III score was 36.08 15.20, Mean duration of PD symptoms was 4.6 ± 2.84 years. 12 (30%) patients were in stage 1, 6 (15%) were in stage 1.5, 2(5%) were in stage 2, 3 (8%) were in stage 2.5, 12 (30%) were in stage 3 and 5(13%) were in stage 4. The mean total NMSS score was 20.55 (SD: 17.285). Higher scores were noted in the Miscellaneous sleep/fatigue, mood/cognition, gastrointestinal and urinary domains. There was a significant correlation between NMSS and disease duration and H&Y staging, PDQ-39 SI, disease duration, PDQ-39 SI. The PDQ-39 SI score strongly correlated with that of NMSS. When evaluating the correlation between PDQ-39 SI and the different NMSS dimensions, significant correlations from low to high were observed in urinary, gastrointestinal, miscellaneous, mood and sleep/fatigue. 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, NMSS, and UPDRS III on Hr-QoL. **Conclusion:** The whole model explained 75% of the variance of the PDQ-39. NMSS explained more of the variability in Hr-QoL than UPDRS III (57.8% vs. 17.2% respectively). NMS has strong, independent association with lower Hr-QoL, as evaluated by the PDQ-39.

INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative disorder with disturbance of the central dopaminergic system. About 1.5% of the worldwide population aged older than 60 years are affected by PD. PD is characterized by both motor symptoms such as bradykinesia, resting tremor, and rigidity, as well as non-motor symptoms. Non motor symptoms of PD, such as dementia, sleep, urinary, and autonomic dysfunction are not responsive to L-dopa. Non motor symptoms include 30 items distributed in nine different domains: Cardiovascular, Sleep/fatigue, Mood/cognition, Perceptual problems/hallucinations, Attention/memory, Gastrointestinal tract, Urinary, Sexual function and Miscellaneous. Non motor symptoms may precede motor symptoms but are present throughout the disease course.[1,2]

Two studies by Sullivan et al. and Shulman et al. have shown that non motor symptoms occurred with a prevalence ranging from 21% at the initial diagnosis of PD to 88% after 7 years of onset. Since non motor symptoms may precede motor symptoms, the correct identification of non-motor symptoms will help identify PD in the very early stages when the motor signs are not obvious. Non motor symptoms of PD are not responsive to L-dopa. These non-L-dopa

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responsive symptoms are the major cause of morbidity, mortality and institutionalization in patients with PD. Several clinical determinants of Health-Related Quality of Life (Hr-QOL) in PD have been evaluated. Although motor symptoms are important predictors of Hr-QoL scores in PD, NMS also contributet to reduced Hr-QOL in PD.[3,4]

Non-motor symptoms, in particular depression, but also cognitive impairment, fatigue, sexual dysfunction, sweating dysfunction (hypo/hyperhidrosis), sleep quality, excessive daytime somnolence, bladder and bowel problems, and weight loss also contribute to reduced Hr-QOL in PD. As improving the Hr-QoL is the major task in the management of patients with PD, the primary purpose of this study was to assess NMS in Parkinson's Disease patients and to investigate the association between NMS and HrQoL in patients with PD along with influence of disease duration, severity and MS on NMS, and Hr- QoL.

MATERIALS AND METHODS

Observational, Cross sectional Study, single center, one point in time evaluation study.

The study will be done at Krishna institute of medical Sciences, Secunderabad, which is a tertiary care hospital from July 2017 to 14 June 2019.

Sample Size: sample size was calculated for prevalence of 1.8%

Reference for Prevalence: Surathi P et al,[5] Research in Parkinson's Disease in India: A Review. Ann. Indian Acad. Neurol. 2016.

Sample size Calculations: Sample Size for Frequency in a Population.

Population size (for finite population correction factor or fpc) (N):1000000

Hypothesized % frequency of outcome factor in the population (p): 1.8%+/-5

Confidence limits as % of 100(absolute +/- %) (d):5%

Design effect (for cluster surveys-DEFF): 1

Sample size n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) +p*(1-p)] =28

Sample Size: 28 at 95% CI (Prevalence of 1.8%).

Inclusion Criteria

Parkinson's Disease patients fulfilling the criteria of the UK-PDSBB.[6]

Exclusion Criteria

Parkinson plus disease, Secondary Parkinsonism, Cognitive dysfunction, PD patients with disability due to neurological disorders other than PD, such as cerebrovascular disease or sequelae or psychosis; 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 anaemia, or any other acute or chronic debilitating or life-threatening disease/state); Informed consents will be obtained from all participants in this study. We recruit PD patients consecutively from the Department of Neurology, KIMS Hospital, Secunderabad, Telangana State, from July 2017 to 14 June 2019. Patients will be diagnosed with PD according to UK Parkinson's Disease Society Brain Bank criteria. Patients are then staged according to Hoehn-Yahr (H-Y) staging. Motor symptoms will be assessed by the unified Parkinson's disease Rating Scale (UPDRS) III. Non motor symptoms in the pts will be assessed by NMS Questionnaire and NMS Scale. Health-related quality of life will be assessed by Parkinson's Disease Questionnaire PDQ-39.

Epidemiology, medication, and the incidence of non-motor symptoms will be statistically analyzed. Impact of disease duration, severity of disease, motor symptoms and non-motor symptoms on Health related of quality of life will be assessed. Ethical approval was obtained from the Institutional Review Board of the hospital after submission of the study proposal and design.

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, NMSS, and PDQ-39 were calculated by summing single items. The strength of the association for correlation coefficients was interpreted as follows: <= 0.19, negligible; 0.20 to 0.39, weak; 0.40 to 0.59, moderate; 0.60 to 0.79, strong; and > 0.80, very strong. 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 PDQ39 SI. Stepwise multiple linear regression analysis 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.

RESULTS

In total, 40 PD subjects, including 24 males (60%) and 16 females (40%), were enrolled in this cross-sectional study. The mean age of all patients was 55.93 ± 9.29 in the study population, the minimum age was 34 years, and maximum age was 72 in the study population.

Among the study population, 24 (60%) patients were male and remaining 16 (40%) patients were female.

The mean UPDRS III score was 36.08 15.20 in the study population, the minimum score was 8 and maximum was 71. Mean duration of PD symptoms was 4.6 ± 2.84 years in the study population, the minimum duration was 1 year, and maximum duration was 12 in the study population. Among the study population, 12 (30%) patients were in stage 1, 6 (15%) were in stage 1.5, 2(5%) were in stage 2, 3 (8%) were in stage 2.5, 12 (30%) were in stage 3 and 5(13%) were in stage 4. [Table 1]

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The mean total NMSS score was 20.55 (SD: 17.285), with the maximum score being 80 and the minimum score being 1. Higher scores were noted in the Miscellaneous sleep/fatigue, mood/cognition, gastrointestinal and urinary domains. Prevalence of NMS according to domains: cardiovascular problems (12 %); sleep/fatigue (29%); mood (16); perceptual problems (3); attention/memory (6); gastrointestinal (23); urinary (23); sexual function (1); and miscellaneous (32). The most common symptom reported in the study population was unexplained pains in 68%, followed by urinary frequency in 45% patients and constipation in 40% patients. [Table 2]

There was a significant correlation between NMSS and disease duration (rS = 0.358, P = 0.023) and H&Y staging (rS = 0.502, P = 0.001). Notably, NMSS also correlated with the UPDRS III score (rS = 0.622, P = <0.001). 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 we measured by the UPDRS III (rS = 0.487/0.614/0.685, P = 0.001/<0.001/< 0. 001). The PDQ-39 SI score strongly correlated with that of NMSS (rS = 0.782, P < 0.001). [Table 3]

Table 1: Descriptive analysis of variables

Variables	Minimum	Maximum	Mean	Std. Deviation
UPDRS SCORE OFF	8	71	36.08	15.200
Duration of PD	1	12	4.60	2.845
Modified HOEHN AND YAHR Staging	1.0	4.0	2.213	1.0675

Table 2: Descriptive analysis NMS

	Minimum	Maximum	Mean	Std. Deviation
NMSS SCALE	1	80	20.65	17.165
Cardiovascular	0	7	1.72	2.689
Sleep/fatigue	0	29	4.48	6.598
Mood/cognition	0	18	2.47	4.484
Perceptual problems	0	9	.37	1.564
Attention/memory	0	6	.40	1.194
Gastrointestinal	0	18	3.10	4.601
Urinary	0	19	3.13	4.450
Sexual function	0	1	.03	.158
Miscellaneous	0	20	4.95	4.940
Valid N (listwise)				

Table 3: Correlations Between Demographics and Clinical Variables, NMSS and PDQ-39 SI, and NMSS Domains and PDQ-39 SI.

	Age	Duration yrs	Updrs score off	Modified hoehn and YAHR staging	NMSS scale	PDQ 39
Age	1.000	-.116	-.240	-.155	-.216	-.246
	.	.475	.136	.340	.181	.125
Duration yrs	-.116	1.000	.400*	.419**	.358*	.487**
	.475	.	.011	.007	.023	.001
Updrs score off	-.240	.400*	1.000	.572**	.622**	.685**
	.136	.011	.	.000	.000	.000
Modified hoehn and yahr staging	-.155	.419**	.572**	1.000	.502**	.614**
	.340	.007	.000	.	.001	.000
NMSS scale	-.216	.358*	.622**	.502**	1.000	.782**
	.181	.023	.000	.001	.	.000
PDQ 39	-.246	.487**	.685**	.614**	.782**	1.000
	.125	.001	.000	.000	.000	.

Table 4: Spearman's rank correlation coefficient (rs) and P value between NMSS domains and PDQ-39 SI

		Cardiovascular	Sleep/fatigue	Mood/cognition	Perceptual problems	Attention/memory	Gastrointestinal	Urinary	Sexual function	Miscellaneous	PDQ 39
Cardiovascular	rS	1	.236	.285	.220	-.109	.317*	.185	-.104	.310	.351*
	p		.143	.074	.172	.505	.046	.253	.523	.052	.026
Sleep/fatigue	rS	.236	1	.576**	.104	-.080	.032	.057	-.085	.595**	.563**
	p	.143		.000	.523	.623	.844	.725	.600	.000	.000
Mood/cognition	rS	.285	.576**	1	.387*	-.084	.032	.018	-.090	.512**	.722**
	p	.074	.000		.014	.605	.842	.915	.583	.001	.000
Perceptual problems	rS	.220	.104	.387*	1	.165	-.166	-.011	-.039	.092	.395*
	p	.172	.523	.014		.310	.307	.948	.812	.572	.012
Attention/memory	rS	-.109	-.080	-.084	.165	1	-.003	.097	-.054	-.270	-.183

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	p	.505	.623	.605	.310		.986	.554	.739	.092	.257
Gastrointestinal	rS	.317*	.032	.032	-.166	-.003	1	.348*	.102	-.074	.370*
	p	.046	.844	.842	.307	.986		.028	.530	.649	.019
Urinary	rS	.185	.057	.018	-.011	.097	.348*	1	-.041	.038	.301
	p	.253	.725	.915	.948	.554	.028		.802	.818	.059
Sexual function	rS	-.104	-.085	-.090	-.039	-.054	.102	-.041	1	-.162	.146
	p	.523	.600	.583	.812	.739	.530	.802		.316	.367
Miscellaneous	rS	.310	.595**	.512**	.092	-.270	-.074	.038	-.162	1	.470**
	p	.052	.000	.001	.572	.092	.649	.818	.316		.002
PDQ 39	rS	.351*	.563**	.722**	.395*	-.183	.370*	.301	.146	.470**	1
	p	.026	.000	.000	.012	.257	.019	.059	.367	.002	

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

Table 5: Multiple linear regression analysis with Hr-QoL as the dependent variable

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	.437	8.942		.049	.961
	Age	-.096	.135	-.063	-.709	.483
	Duration yrs	.934	.497	.182	1.880	.069
	Updrs score off	.164	.121	.175	1.354	.185
	Modified hoehn and yahr staging	1.771	1.436	.133	1.233	.226
	NMSS SCALE	.466	.091	.568	5.100	.000

a. Dependent Variable: PDQ 39

When evaluating the correlation between PDQ-39 SI and the different NMSS dimensions, significant correlations from low to high were observed in urinary (P = 0.011), gastrointestinal (P = 0.011) miscellaneous (P = 0.007), mood (P < 0.001) and sleep/fatigue (P = <0.001) (rS = 0.318– 0.613). For the remaining four dimensions, no significant correlations. [Table 4]

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, NMSS, and UPDRS III on Hr-QoL. 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 75% of the variance of the PDQ-39 SI. NMSS explained more of the variability in Hr-QoL than UPDRS III (57.8% vs. 17.2% respectively). NMS has strong, independent association with lower Hr-QoL, as evaluated by the PDQ-39. [Table 5]

DISCUSSION

Many clinical studies and observations have suggested that NMS such as sleep disorders, Gastrointestinal, cognitive disorders, Psychiatric disorders, Urinary and Sexual disorders are frequent in PD.[7,8] The NMS depends on the disease severity and duration, so management of these symptoms become increasingly important as the life expectancy of the population increases. However, research has only recently focused on the effect of NMS on quality of life, institutionalization rates, health economics and mortality rates in PD. The NMS complex is frequently unrecognized and/or neglected by healthcare professionals, as reported by Shulman and colleagues.[9]

Physicians concentrate more on the motor manifestations, this may be due to lack of awareness of NMS in PD, and even there is a possibility that these symptoms may not be declared by patients to the healthcare professionals. An international survey showed that up to 65.2% of NMS in PD might remain undeclared to health care professionals because patients are either too embarrassed to reveal them or are unaware that the symptoms are linked to PD. Due to this unawareness of NMS coupled with the absence of a single composite tool for the assessment and documentation of NMS has resulted in an incomplete and ineffective therapy for PD, resulting in patient distress, disease burden and impaired quality of life. Even Neurologists commonly fail to identify the major NMS, such as depression, sleep disturbances, anxiety and fatigue, in more than half of their patients.[10]

In a study using the NMS Questionnaire (NMSQ), PD patients reported nine to 12 different NMS in their clinic visits, many of which had not been discussed with the doctor before being flagged by the NMSQ. In addition, a clinician administered scale, the NMS scale, that allows easy identification of the NMS by the physician has also been introduced. This scale not only identifies the NMS more exhaustively but also rates them on scores for severity and frequency thus providing a composite and accurate scoring for them. The introduction of this tool has been validated by studies across populations. NMS are also highly prevalent in PD patients across all stages and the duration of the disease. Compared with age matched controls, some patients of PD reported more than 10 NMS symptoms each, respectively.[11,12]

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This study also showed that the number of symptoms correlates with disease duration and severity. As compared with control patients, PD patients had significantly higher scores than controls for complaints of dribbling, impaired taste/smell, impaired swallowing, constipation, urinary urgency, weight loss, forgetfulness, sadness, impaired concentration, hallucinations, anxiety, sexual dysfunction, falling, daytime sleepiness, vivid dreams and sweating.

Another large, multicentre study comprising 545 patients using the NMSQ data in the UK, USA, Germany, Israel, Japan and Italy, reported that the mean total NMS (NMSQ‑T) was 10.3 ± 5.4 (SD), with nocturia (61.9%) being reported as the most frequent symptom while incontinence of faeces was the least prevalent (8.21%).[12] Only eight (1.6%) patients in this study declared that they had no NMS at all. In our study all patients have NMS with unexplained pains(68%) being reported as most frequent symptom followed by urinary symptoms(45%), constipation(40%), while bowel incontinence was least prevalent(3%).There were no significant differences in NMS scores by gender, with the exception that depression/anxiety, sexual dysfunction, and cardiovascular and miscellaneous NMS were more prevalent in women.[12]

The NMS scale (NMSS), that rates the symptoms in terms of frequency and severity, has also been validated in two major international studies in over 600 patients. The NMSS was introduced in a landmark study involving 242 patients across centers in the UK, Italy, Germany, USA and Japan by Chaudhuri et al.[13] The mean NMSS score reported was 56.5 ± 40.7.Maximum scores were recorded for the sleep, mood and perceptual disorders, attention/memory, and urinary and sexual function domains.

The first report from India is by Krishnan et al.8, which compared 174 patients and 128 normal controls to assess the prevalence of NMS has reported a high frequency of NMS in all nine domains in patients with PD compared with controls. Li et al.[11] studied 82 Chinese patients with PD and found that the prevalence of NMS being 100%, and the NMSS significantly correlated with disease duration which is similar to our study .Wang et al,[14] have also reported similar findings from China in addition to validating the Chinese version of the NMSS.

A multicenter survey, the PRIAMO study, using a semi structured interview in 1072 consecutive patients with PD from Italian centers to assess the prevalence of NMS found that 98.6% of the patients with PD reported the presence of NMS. The most common symptoms were fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urgency and nocturia (35%), drooling of saliva and difficulties in maintaining concentration (31%). The mean number of NMS per patient was 7.8 (range, 0–32). In our study all patients have NMS with unexplained pains(68%) being reported as most frequent symptom followed by urinary symptoms(45%), constipation(40%), while bowel incontinence was least prevalent(3%).

Our study population comprised 40 patients with a mean age of 55.93. The mean NMS score was 20.55, with males scoring 24.96 and females scoring 22.8. The difference between the genders was not significant. These results were consistent with those of Song et al.[15] Chaudhari et al,[16] reported mean NMS score of 56.5, which might be due to the more advanced stage disease as brought out by higher Hoehn and Yahr stages among the cases in that study. Previous studies have reported NMS in 90% or more patients irrespective of the disease stage. All patients in our study complained that NMS were distressing either in terms of frequency or severity. The most common symptoms were miscellaneous (80%), sleep/fatigue(73%), Gastrointestinal (58%), urinary (58%) and mood/cognition(40%); the other Indian study has reported disturbances in sleep/fatigue in 89%, mood/cognition in 88% and miscellaneous NMS in 80% of these patients. These results are very similar to those obtained by the international, multicenter study by Chaudhari et al.[15,16]

Almost all previous studies reported disturbances in the sleep, miscellaneous, urinary, gasrointestinal and sexual domains.16 However there are minor differences in the frequency of various domains involved; the PRIAMO study, for example, reports fatigue, anxiety and insomnia as the most common symptoms, followed by urinary complaints and difficulties in concentration.[17]

Our study does not report olfaction as being as common as seen in some other reports. Thus, there are minor differences among the various studies regarding the relative frequency of the symptoms. Krishnan et al.8 report insomnia/fatigue as being the most common symptom followed by mood and cognitive disturbances as well as the miscellaneous, urinary and memory domains. This is in contrast to our findings of the predominance of the miscellaneous, followed by the urinary domain, constipation, sleep and mood/cognition domains in that order. Olfaction and sexual dysfunction are less prevalent in our study. The cultural behaviour is probably responsible for the underreporting of sexual dysfunction. The sample size and differences in sample characteristics may also be responsible for this difference. Thus grossly, the pattern of NMS in Indian subjects seems to be similar to that of the PD population surveyed elsewhere.

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 our study ($rS = 0.502$, $P < 0.001$) which is consistent with study of Chaudhuri et al,[16] which showed a significant association between the NMSS and H&Y ($rS = 0.330$, $P = <0.001$;). Highly significant correlations were also observed between motor dysfunctions and NMS burden, between motor dysfunctions and Hr-QoL, and between disease severity and Hr-QoL. This

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result suggested that both disease severity and motor dysfunctions may influence NMS and Hr-QoL.

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. Standardized coefficient b scores were 0.656 and 0.185 for NMSS and UPDRS III, respectively. Although both of them presented significant associations with HrQoL, NMS appeared to be more closely correlated with Hr-QoL based on this data as its standardized coefficient b score was higher than that of the UPDRS III, demonstrating that NMS play a crucial role in HrQoL. In addition, the R2 change for NMSS and UPDRS III were 57.8% and 17.2%, respectively. This further demonstrated that compared with UPDRS III, the NMSS appeared to have a greater impact on HrQoL. 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. Recently, increasing attention has been paid to the impact of NMS on the HrQoL of PD patients. One study by Grosset et al,[18] 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. Our data presented here strongly suggests that it is imperative to correctly diagnose and manage NMS in PD to improve the HrQoL of patients.

CONCLUSION

Our current data demonstrate that NMS are very common in PD patients. NMS have independent but close relationships with age, disease duration, severity, and Hr-QoL. Hr-QoL is determined by the complex interaction of the MS and NMS of the disease in PD patients. NMS (especially miscellaneous, urinary, gastrointestinal, sleep/fatigue and mood) 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. The overall evaluation of PD symptoms should include MS and NMS, focusing beyond the conventional MS. It is imperative to correctly diagnose and manage NMS in PD to improve the HrQoL of patients. Further studies are needed to investigate how to improve the Hr-QoL of PD patients and relieve their NMS.

Limitations of this study:

- Only a small number of PD patients (40 patients recruited) and the disease duration was relatively short (4.68 years) in this study;
- The low mean score of the UPDRS III scale (mean = 36);
- Mainly PD patients in early stages of disease were enrolled, as indicated by the low median stage of the H&Y scale.
- For NMS questionnaire, we only chose PD subjects with sufficient cognitive ability, significantly narrowing the population in this study.
- In addition, different stages of PD patients in both UPDRS III and H&Y score should be included to compensate for current shortcomings.

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