RESEARCH ARTICLE

Health-Related Quality of Life in Early Parkinson's Disease: The Impact of Nonmotor Symptoms

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ABSTRACT: Nonmotor symptoms (NMS) are common in patients with established Parkinson's disease (PD) and have a major impact upon quality of life. We investigated the significance of NMS in relation to health-related quality of life (HRQoL) in patients with newly diagnosed PD. Patients and healthy controls were recruited as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's Disease Study. Prevalence of NMS was determined with the Non-Motor Symptom Questionnaire. HRQoL was recorded with the 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39). Further assessments included measures of motor disability, depression, sleep, and cognition. One hundred and fifty-eight patients with newly diagnosed PD and 99 controls participated in this cross-sectional study. Patients reported greater numbers of NMS than controls (mean 8.3 ± 4.3 versus 2.8 ± 2.5 symptoms; $P < 0.001$). Patients reported lowest HRQoL in the domains assessing bodily discomfort, mobility, and activities of daily living. Motor and nonmotor symptoms impacted negatively upon HRQoL scores. Patients with the postural instability and gait difficulty motor subtype reported worse HRQoL, compared with those with tremor-dominant disease. Depression ($P < 0.001$), incomplete bowel emptying ($P < 0.001$), anxiety ($P < 0.001$), impaired concentration ($P < 0.001$), memory complaints ($P < 0.001$), and insomnia ($P = 0.001$) had the greatest negative impact upon HRQoL. NMS are common in patients with early PD and represent a significant cause of poorer health-related quality of life. Cognitive, neuropsychiatric, and sleep disturbances are particularly associated with reduced well-being. Screening and management of these symptoms should be prioritized at the time of diagnosis. © 2013 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; non-motor symptoms; quality of life; anxiety; depression

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People with Parkinson's disease (PD) experience a diverse range of nonmotor symptoms (NMS), which, in addition to motor disability, result in significantly reduced health-related quality of life (HRQoL).[1-4] NMS manifest as cognitive, neuropsychiatric, autonomic, and sensory disturbances, which frequently worsen with disease progression. In the advanced stages of disease, NMS are major determinants of loss of independence, caregiver strain, and nursing home placement.[5] Some NMS respond to dopaminergic therapy[6,7]; however, many are likely to have a nondopaminergic pathophysiological substrate involving Lewy body pathology in cholinergic, serotonergic, noradrenergic, and other neurotransmitter systems. Because of their heterogeneous and often nonspecific nature,

NMS are frequently under-recognized by patients and clinicians,[8] thereby representing a missed opportunity to improve health status in patients through disease education strategies and appropriate interventions.

The recently described Parkinson At Risk Syndrome highlights the frequency with which constipation, hyposmia, rapid eye movement (REM) sleep behavior disorder (RBD), and depression precede the recognition of the classical motor manifestations of PD.[9] Furthermore, in a large study of patients with pathologically proven PD, O'Sullivan et al. reported that NMS were the initial presenting feature in 21% patients, and that in these patients, diagnostic delay and misdiagnosis were common.[10] Although reported as frequent and mild,[11] the impact of NMS upon HRQoL in early PD has not been fully evaluated. We prospectively recruited a large group of patients with newly diagnosed PD and determined the impact of NMS and motor symptoms upon HRQoL.

Patients and Methods

Patients

Patients were recruited as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's Disease (ICICLE-PD) Study.[12] ICICLE-PD is a prospective, longitudinal study of patients with newly diagnosed PD designed to evaluate the significance of cognitive, neuropsychiatric, and quality-of-life measures in patients with early PD. We sought to identify and assess every new case of PD in Newcastle-upon-Tyne and Gateshead from June 1, 2009 to December 31st, 2011. Seventy primary care practices (35 practices in Newcastle and 35 in Gateshead) were requested to refer all patients with parkinsonism. We also requested colleagues in secondary care to refer all patients with parkinsonism. This group included neurologists (n = 20), geriatricians (n = 15), and PD nurse specialists (n = 5). All patients were diagnosed by a physician specializing in movement disorders and fulfilled the UK Brain Bank Criteria for idiopathic PD.[13] Exclusion criteria comprised the following: patients with parkinsonism who were diagnosed before onset of the study; insufficient working knowledge of English (defined as being unable to perform the assessments and questionnaires in the opinion of the assessor); patients with significant memory impairment or dementia at presentation (defined as Mini-Mental State Examination [MMSE] score <24, or fulfilling Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for dementia.[14] Further exclusion criteria included the following: drug-induced parkinsonism secondary to dopamine receptor blocking agents at the onset of symptoms; vascular parkinsonism; and atypical parkinsonian disorders, including progressive supranuclear palsy, MSA, or corticobasal degeneration, according to accepted diagnostic criteria.[15]

Controls

Healthy control subjects were recruited from the North East of England through local advertising, word of mouth, and community groups. Carers, spouses, and relatives of patients with PD were not used as controls to limit bias, because we requested carer involvement in the assessment process of those with PD. Furthermore, we reasoned that a high burden of NMS in the participant (e.g., depression) may be likely to bias the response of the carer. Controls underwent a similar assessment schedule to patients, with the exception of PD-specific scales.

Clinical Assessments

All subjects underwent medical assessment, which included the following: interview with a physician specializing in movement disorders; symptom history; level of education; comorbid disease; medication use; social support; and ability to perform activities of daily living (ADLs). All patients were evaluated in the "on" state. Motor disability and disease severity were rated with the *Movement* Disorders Society revised UPDRS (MDS-UPDRS) part III[16] and H & Y staging,[17] respectively. Motor subtype was determined by the method described by Jankovic et al. and based on the revised MDS-UPDRS,[18,19] whereby patients are categorized into tremor dominant, postural instability with gait difficulty (PIGD), or indeterminate subtypes based on a ratio between the mean tremor score versus the mean PIGD score.

Assessment of NMS

The 30-item Non-Motor Symptoms Questionnaire (NMSQuest) was used as the primary screening instrument for NMS.[20] The NMSQuest explores gastrointestinal (GI), urinary, neuropsychiatric, sexual, cardiovascular, and sleep disturbances, with answers recorded as "present" or "absent." Global cognitive function was assessed using the MMSE[21] and Montreal Cognitive Assessment (MoCA).[22] Depression was rated with the Geriatric Depression Scale-15 (GDS-15).[23] The Pittsburgh Sleep Quality Index (PSQI) was used to rate nocturnal sleep disturbance; a score of >5 indicated significant nocturnal sleep disturbance and poor sleep quality.[24] Daytime somnolence was measured by the Epworth Sleepiness Scale (ESS), where a score of ≥ 10 was considered significant.[25]

Self-reported HRQoL was measured by the Parkinson's Disease Quality of Life Questionnaire (PDQ-39).[26] The PDQ-39 has excellent internal consistency and test-retest validity, and, furthermore, it is sensitive to change over time, making it suitable for use in

longitudinal studies. It has been validated for use in PD and has been widely adopted.[27] Comprised of 39 items, it assesses HRQoL across eight domains encompassing mobility (10 items), ADLs (six items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items), and bodily discomfort (three items). Responses are recorded on a scale ranging from 0 (never) to 4 (always). The score from each subscale is transformed into a 0 to 100 score by summing the raw score from each item, dividing by the maximum possible raw score, and multiplying by 100. A composite summary index score (PDQ-SI) of the eight domains provides an overall measure of the impact of illness on functioning and well-being that reduces the role of chance, which may occur when exploring individual PDQ-39 domains. This is calculated using the mean of each domain score: Higher scores indicate poorer perceived health.

Statistical Analysis

Statistical analyses were performed with SPSS software (Version 19.0; SPSS, Inc., Chicago, IL). Data were examined for normality of distribution with visual histograms and Kolmogorov-Smirnov's test. Normally distributed continuous data were analyzed using Student's *t* test. Data that did not have a normal distribution were analyzed with Mann-Whitney's U test. Pearson's chi-squared tests were used to analyze categorical data, except where the count was less than 5, in which case Fisher's exact test was used. Spearman's rank-correlation coefficients were calculated to examine the bivariate association between demographic and clinical variables. Pearson's correlation coefficient was used for partial correlations, controlling for various factors. The relationship between motor and nonmotor symptoms and HRQoL was further examined through multiple regression analyses. A P value of <0.05 was deemed to be significant. Bonferroni's correction was used to correct for multiple testing.

Ethical Approval

The study was approved by the Newcastle and North Tyneside Research Ethics Committee. All patients provided written informed consent.

Results

One hundred and fifty-eight patients fulfilled the criteria for incident PD and were recruited into the study. Mean age of PD patients was 66.5 ± 10.3 years and 104 (65.8%) were male. Ninety-nine controls were recruited and these were similar in age (67.9 ± 8.2 years; $P = 0.220$) and gender (54% male; $P = 0.071$). Demographic, clinical, and social data are listed in Table 1. Patients with PD did not differ significantly from controls with regard to mean age, gender, or years of education. Consistent with the short disease duration (6.3 ± 5.9 months), 127 (80%) of those with PD were graded H & Y stage 1 or 2. Only twenty (12.7%) patients with PD were not receiving antiparkinsonian medication.

TABLE 1. Demographic, clinical, and social characteristics for patients with PD and healthy controls

Characteristic	PD N = 158	Control N = 99	*P* Value
Male, n (%)	104 (65.8)	54 (54.5)	0.071
Age, mean (SD)	66.5 (10.3)	67.9 (8.2)	0.220
Years of education, mean (SD)	12.8 (3.9)	13.1 (3.4)	0.265
Marital status, n (%)			
Single	14 (8.9)	8 (8.1)	0.828
Married/partner	115 (72.8)	69 (69.7)	0.593
Widow	20 (12.7)	16 (16.2)	0.431
Separated/divorced	9 (5.7)	6 (6.1)	0.903
Independent with ADLs, n (%)	133 (84.2)	99 (100)	<0.001
Disease duration, months (SD)	6.3 (5.9)	-	-
H & Y stage, n (%)			
1	35 (22.2)	-	-
2	92 (58.2)	-	-
3	30 (19.0)	-	-
4	1 (0.6)	-	-
PD treatment			
Drug naïve, n (%)	20 (12.7)	-	-
Levodopa, n (%)	47 (29.7	-	-
Dopamine agonist, n (%)	58 (36.7)	-	-
MAOB inhibitor, n (%)	73 (46.2)	-	-
Levodopa dose equivalent, mean (SD)	176.6 (146.7)	-	-

Abbreviations: SD, standard deviation; MAOB, monoamine oxidase type B.

Mean scores and descriptive statistics of rating scales in PD and control groups are shown in Table 2. NMS were more frequent in patients with PD than controls (mean number of NMS 8.3 ± 4.3 symptoms per patient, compared to mean 2.8 ± 2.5; $P < 0.001$). Total scores for the NMSQuest domains are shown in Table 2. The most commonly experienced NMS were hypersalivation and dribbling (55.1%), urinary urgency (45.6%), hyposmia (43.7%), anxiety (42.4%), and constipation (42.4%); all were significantly more common in those with PD than in controls. Complaints of forgetfulness and poor memory were also common among patients in the PD group (53.8%), but were also reported by many in the control group (40.8%), and the difference was not significant. Patients with PD had small, but significant, reductions in MMSE and MoCA scores, compared to controls, and had more depressive symptoms as rated by the GDS-15. Twenty patients with PD had a diagnosis of depression preceding study participation and were receiving treatment with antidepressant medication (mean GDS-15 score: 5.15 ± 3.24). Twenty-three patients had a GDS-15 score of ≥ 6, 15 of whom were not previously diagnosed with depression or being treated with antidepressant medication. There were no

TABLE 2. Cognitive, depression, sleep, NMS, and Quality of Life Scores

	PD N = 158	Control N = 99	Range	*P* Value
MMSE, mean (SD)	28.6 (1.4)	29 (1.2)	0-30	0.003
MoCA, mean (SD)[a]	25.1 (3.6)	26.8 (2.6)	0-30	0.001
GDS-15, mean (SD)	2.9 (2.6)	1 (1.5)	0-15	<0.001
PSQI, mean (SD)	6.3 (3.9)	5.4 (3.5)	0-21	0.056
ESS, mean (SD)	6.2 (4.5)	5.4 (4)	0-24	0.160
MDS-UPDRS part III, mean (SD)	27.1 (12)	-	0-132	-
NMSQuest total score, mean SD	8.3 (4.3)	2.8 (2.5)	0-30	<0.001
GI	2.1 (1.3)	0.5 (0.8)	0-7	<0.001
Urinary	0.7 (0.7)	0.4 (0.6)	0-2	<0.001
Attention, apathy, and memory	1.1 (0.9)	0.5 (0.6)	0-3	<0.001
Hallucinations and delusions	0.2 (0.4)	0	0-2	<0.001
Depression and anxiety	0.8 (0.8)	0.2 (0.5)	0-2	<0.001
Sexual function	0.4 (0.6)	0.2 (0.5)	0-2	0.004
Cardiovascular	0.6 (0.6)	0.2 (0.4)	0-2	<0.001
Sleep	1.5 (1.3)	0.6 (0.8)	0-5	<0.001
Miscellaneous	1 (1)	0.4 (0.7)	0-5	<0.001
PDQ-SI, mean (SD)	18.1 (13.2)	-	0-100	-
Mobility	23.6 (24.8)	-	0-100	-
ADLs	21.2 (20)	-	0-100	-
Emotional well-being	20 (18.5)	-	0-100	-
Stigma	15 (21.3)	-	0-100	-
Social support	3.7 (12.1)	-	0-100	-
Cognition	21 (19.1)	-	0-100	-
Communication	11.2 (14.4)	-	0-100	-
Bodily discomfort	29.1 (22.5)	-	0-100	-

[a]Completed in 143 of 158 subjects.
Abbreviation: SD, standard deviation.

significant differences between patients and controls with regard to nocturnal sleep disturbance or excessive daytime somnolence. One-hundred and four patients (65.8%) were classified as having the PIGD motor subtype. There was no significant difference in age between those patients with the PIGD subtype (67.5 ± 9.3 years) and those who were tremor dominant (66.6 ± 11.1 years; $P = 0.254$). Patients classified with the PIGD subtype reported a significantly greater number of total NMS per patient (mean, 9.3 ± 4.2), compared with those with indeterminate (mean, 7.5 ± 4.7) or tremor-dominant subtypes (mean, 6.3 ± 3.6; $P < 0.001$). Although the PIGD group had higher total MDS-UPDRS part III scores, the difference between the PIGD and tremor-dominant patients was not significant ($P = 0.085$). Two patients were excluded from motor subtype analysis because of comorbid disease (polio = 1; rheumatoid arthritis = 1). Following Bonferroni's correction, only hypersalivation and dribbling remained significantly more common in those with the PIGD subtype (66.7%) than in those with tremor-dominant disease (33.3%; $P < 0.001$).

The mean composite PDQ-SI score was 18.3 ± 13.2; domains with the highest scores were bodily discomfort (29.1 ± 22.5), mobility (23.6 ± 24.8), and ADLs (21.2 ± 20.0).

TABLE 3. Relationship between specific NMS and PDQ-SI in patients with early PD

NMS	N (%)	Z Score	*P* Value[e]
Hypersalivation	87 (55.1)	−1.738	0.082
Dysphagia	32 (20.3)	−2.638	0.008
Nausea	14 (8.9)	−2.372	0.018
Constipation	67 (42.4)	−2.924	0.003
Bowel incontinence	9 (5.7)	−1.00	0.318
Sensation of incomplete bowel emptying	50 (31.6)	−5.049	<0.001
Urinary urgency	72 (45.6)	−1.230	0.219
Nocturia	40 (25.3)	−2.914	0.004
Forgetfulness and memory	85 (53.8)	−3.735	<0.001
Loss of interest and apathy	42 (26.6)	−2.925	0.003
Impaired concentration	46 (29.1)	−4.637	<0.001
Lower limb swelling	28 (17.7)	−2.524	0.012
Pain (unexplained)	59 (37.3)	−0.1326	0.185
Delusions	1 (0.6)	−0.655	0.628
Low mood	58 (36.7)	−4.379	<0.001
Depression (GDS >6)[a]	23 (14.6)	−5.191	<0.001
Anxiety	67 (42.4)	−4.961	<0.001
Impaired sex drive and libido	28 (17.7)	−2.418	0.016
Sexual dysfunction	33 (20.9)	−0.427	0.669
Dizziness (orthostatic)	51 (32.3)	−2.852	0.004
Falls	36 (22.8)	−2.367	0.018
Excessive daytime somnolence (ESS >10)[c]	40 (25.3)	−2.816	0.005
Insomnia	28 (17.7)	−3.180	0.001
Dream re-enactment behavior	55 (34.8)	−1.059	0.290
Vivid dreams	48 (30.4)	−2.431	0.015
Poor sleep[b]	74 (46.8)	−2.958	0.002
Restless legs	43 (27.2)	−2.407	0.016
Hallucinations (visual)	34 (21.5)	−1.887	0.059
Diplopia	16 (10.1)	−2.597	0.009
Hyperhydrosis	15 (9.5)	−2.693	0.007
Hyposmia	70 (44.3)	−1.082	0.279
Cognitive impairment[d]	63 (39.9)	−1.683	0.092
Weight change	36 (22.8)	−1.492	0.136

Symptoms were screened by NMSQuest, unless otherwise stated. Relationships were examined using Mann-Whitney's test.
[a]GDS-15 ≥6;
[b]PSQI >5;
[c]ESS ≥10;
[d]MoCA ≤25.
[e]Following Bonferroni's adjustment, significant *P* value = 0.002.

The relationship between NMS and HRQoL (PDQ-SI) is shown in Table 3. There was a significant correlation between the total number of NMS reported and PDQ-SI (Spearman's rho = 0.606; $P < 0.001$; Fig. 1). Depression ($P < 0.001$), anxiety ($P < 0.001$), impaired concentration ($P < 0.001$), memory complaints ($P < 0.001$), and sleep disturbance ($P = 0.002$) were all associated with reduced quality of life. After controlling for the effects of motor disease severity, as rated by the MDS-UPDRS, higher GDS-15 (Pearson's r = 0.611; $P < 0.001$; Fig. 2), PSQI (Pearson's r = 0.438; $P < 0.001$), and ESS scores (Pearson's r = 0.373; $P = 0.001$) were all associated with worse PDQ-SI scores, whereas MMSE (Pearson's r = −0.075; $P = 0.376$) and MoCA (Pearson's r = −0.066; $P = 0.439$) scores were not; older age was associated

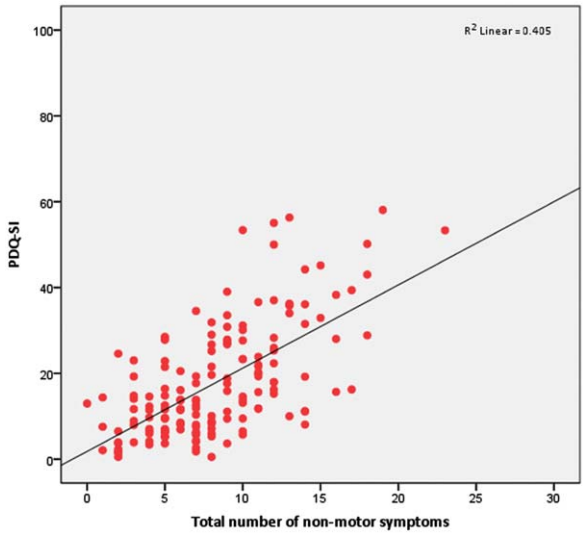

FIG. 1. Scatter plot of correlation between total number of NMS and PDQ-SI.

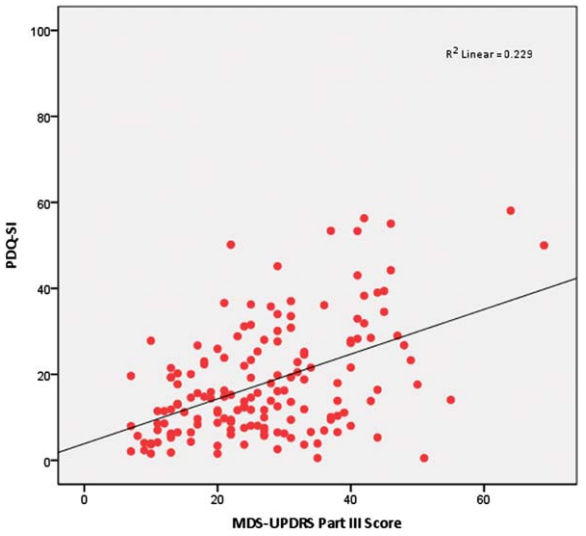

FIG. 3. Scatter plot of correlation between increasing motor disability and PDQ-SI.

with a lower PDQ- SI score (Pearson's r = −0.219; $P = 0.006$). To understand NMS as determinants of HRQoL, a step-wise multiple linear regression model was used with PDQ-SI as the output variable and NMS as explanatory variables. NMSQuest items of "low mood," "daytime sleepiness," and "insomnia" were replaced in this model because these symptoms are more accurately rated with the GDS-15, ESS, and PSQI, respectively. In this model, NMS with the greatest negative impact on HRQoL were depression (standardized β = 0.307; $P < 0.001$), impaired concentration (standardized β = 0.204; $P < 0.001$), RBD (standardized β = 0.160; $P = 0.009$), anxiety (standardized β = 0.156; $P < 0.001$), sensation of incomplete bowel emptying (standardized β = 0.153; $P = 0.014$), hyperhydrosis (standardized β = 0.151; $P = 0.014$), leg swelling (standardized β = 0.143; $P = 0.017$), diplopia (standardized β = 0.122; $P = 0.040$), and forgetfulness (standardized β = 0.121; $P = 0.048$). In combination, these symptoms had a high predictive value of reduced HRQoL (R = 0.521; $R^2 = 0.491$).

Higher PDQ-SI scores were positively correlated with greater motor disability, as rated by total MDS-UPDRS part III score (Spearman's rho = 0.424; $P < 0.001$; Fig. 3) and H & Y stage (Spearman's rho = 0.278; $P < 0.001$). Higher PDQ-SI scores also correlated with bradykinesia (Spearman's rho = 0.356; $P < 0.001$) and rigidity (Spearman's rho = 0.271; $P = 0.001$). Patients with the PIGD subtype reported greater reductions in HRQoL in terms of functional mobility ($P < 0.001$), ADLs ($P = 0.036$), bodily discomfort ($P = 0.004$), and emotional well-being ($P = 0.006$), whereas there was no association between the tremor-dominant subtype and any of the PDQ-39 domains.

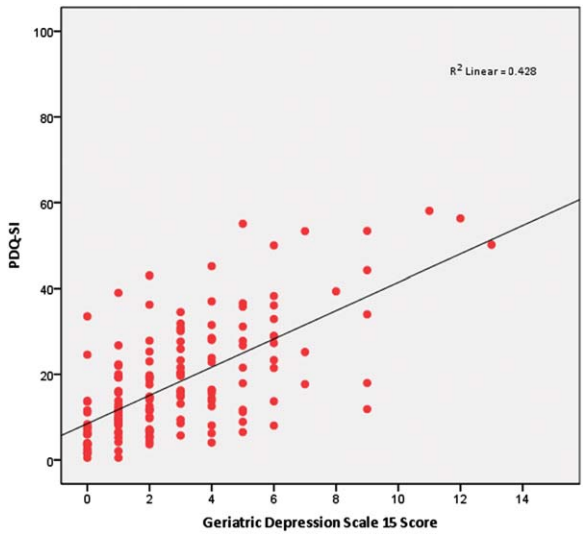

FIG. 2. Scatter plot of correlation between GDS-15 and PDQ-SI.

Discussion

This study demonstrates that NMS are common in patients with newly diagnosed PD and have a significant negative impact upon self-reported HRQoL. The patients in this study each experienced a mean of eight NMS, a finding consistent with 8 to 12 NMS per patient reported in other large international studies of prevalent PD cases.[1,4,7,11,20] In patients with more advanced PD, determinants of HRQoL include depression and other neuropsychiatric symptoms, such as anxiety, forgetfulness, impaired concentration, and apathy.[1,28,29] Although lower MMSE and MoCA scores in our PD patients were not associated with

reduced HRQoL in the PDQ-SI, self-reported impaired concentration and forgetfulness did impact negatively upon HRQoL. This may indicate a lack of sensitivity of the MMSE and MoCA for detecting functionally significant cognitive impairment in early PD, or reflect a lack of specificity in the NMS stem question. Another explanation may be the effect of undiagnosed depressive symptomatology, which is known to impact upon self-reporting of subjective memory disturbance; 15 patients with a GDS-15 score $\geq$6 were not previously known to be depressed. It is of note that forgetfulness and memory problems were also commonly reported by control subjects, and therefore these subjective findings should be interpreted with caution.

Prospective longitudinal studies report hyposmia,[30] constipation,[31] and RBD[32] to be common, even before onset of motor symptoms, and have been postulated as representing the earliest stages of the disease process with degeneration of brain stem and peripheral nuclei occurring before significant substantia nigra degeneration (i.e., corresponding to Braak stages 1 and 2).[33] Depression and anxiety have been identified by case-control and retrospective studies as being present in up to one quarter of patients not only in the early stages of PD, but in the years preceding diagnosis.[34,35] The presence of these symptoms at high frequency in our incident cohort is therefore unsurprising and may be regarded as evidence of disease progression, because subjects evolve from premotor to mixed-motor and nonmotor manifestations of underlying α-synuclein pathology.

Patients with the PIGD motor subtype experienced a greater number of NMS than those with tremor-dominant disease (9.3 vs. 6.3 symptoms) and reported worse HRQoL in functional mobility, ADLs, bodily discomfort, and emotional well-being. PIGD patients were of a similar age, and so this observation may reflect more widespread or diverse pathological and/or neurochemical involvement in these subjects at a relatively early stage. For example, involvement of brainstem noradrenergic and cholinergic systems could account for the greater NMS burden in PIGD subjects. This would be consistent with other studies that indicate the PIGD subtype and the presence of levodopa nonresponsive motor symptoms, in association with neuropsychiatric features, may represent a more aggressive form of PD, particularly with regard to the development of cognitive impairment and dementia.[36-38]

The pathophysiological mechanisms for NMS are heterogeneous and, in some cases, unknown, although it is unlikely that nigrostriatal dopaminergic loss alone is the instrumental factor. In PD, cholinergic loss is associated with cognitive decline,[39] RBD,[40] and depression.[41] The frequency of many NMS is subject to variability, depending on motor state, being more common, although not necessarily more severe, in the "off" state and worsening HRQoL independent of motor state.[42]

Strengths of this study include a prospective design, large number of patients recruited, and the inclusion of a control group. The use of screening and assessment instruments validated for the assessment of NMS, nocturnal sleep disturbance, excessive daytime sleepiness, and depression strengthened our clinical assessment, helped mitigate some inherent weaknesses of the NMSQuest, and, most important, enhances the comparability of our findings with the work of others.[3,4,27,43-45]

Weaknesses of this study include the potential for recall bias with the NMSQuest, ESS, and PSQI. Although we recruited from a range of outpatient settings, including movement disorder, neurology, and medicine, for the elderly clinics, we cannot exclude the possibility of recruitment bias with younger, fitter, and more motivated patients consenting to participate, resulting in an underestimation of the true burden of NMS in relation to disease, particularly in those patients with comorbidities. Because we recruited from outpatient clinics, only 20 (12.7 %) of our patients were drug naïve. This reflects current clinical practice in many centers, with a tendency to prescribe antiparkinsonian medication earlier in the disease because of potential improvements in disease outcome and HRQoL.[44,46] Because most of the patients (87.3%) reported in this study were assessed after the introduction of antiparkinsonian medication, we are unable to ascertain the effects of such therapies on frequency and severity of NMS in these patients. Additionally, there may be a confounding effect of medications, such as pramipexole (n = 18), which may have antidepressant and somnolent effects.[47] We did not formally assess fatigue, another common symptom in PD. A further weakness is that we did not use specific scales to assess the severity of each NMS, and although, for many, these exist, in designing this study, we wished to avoid "scale fatigue" in our participants, which could have impacted upon long-term study participation.

Our results emphasize the importance of screening for NMS not only in the more advanced stages of PD, but at time of diagnosis. Proposals for a comprehensive grading scheme of PD severity, which combines both motor and nonmotor assessments, have recently been published; such an approach could enhance the clinician's ability to address the features of PD more holistically, which impact upon quality of life and disability.[48] Screening for depression may be particularly important; this symptom is consistently associated with an adverse impact on functional status and HRQoL across all disease stages and, despite the absence of robust, clinical trial data in patients with PD, may respond to pharmacological or nonpharmacological interventions.[49] Some

symptoms, such as restless legs, anhedonia, and constipation, may respond directly to dopaminergic therapy.[6] Conversely, hallucinations and impulse control disorders may be precipitated by dopaminergic medication. Other symptoms require a more targeted approach; for example, botulinum toxin injections are efficacious in the management of excessive salivation and drooling. Treatment of some NMS may worsen motor or cognitive features. For example, anticholinergic medications are associated with a faster rate of cognitive decline in PD[50] and yet are commonly prescribed for urinary urgency.

Improved awareness and understanding of the relationship between NMS, disability, and HRQoL will encourage a multidisciplinary approach to patient care and facilitate the provision of more comprehensive education for patients and caregivers. Furthermore, such information will better inform the basis of drug discovery programs for both motor and nonmotor symptoms. ■

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References

1. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24:1641-1649.
2. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR, Group NV. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 2011;26:399-406.
3. Li H, Zhang M, Chen L, et al. Nonmotor symptoms are independently associated with impaired health-related quality of life in Chinese patients with Parkinson's disease. Mov Disord 2010;25:2740-2746.
4. Crosiers D, Pickut B, Theuns J, et al. Non-motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire. Am J Neurodegener Dis 2012;1:160-167.
5. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 2000;48:938-942.
6. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009;8:464-474.
7. Erro R, Picillo M, Vitale C, et al. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry 2013;84:14-17.
8. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. Mov Disord 2010;25:704-709.
9. Stern MB, Siderowf A. Parkinson's at risk syndrome: can Parkinson's disease be predicted? Mov Disord 2010;25(Suppl 1):S89-S93.
10. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord 2008;23:101-106.
11. Müller B, Larsen JP, Wentzel-Larsen T, Skeie GO, Tysnes OB; Parkwest Study Group. Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov Disord 2011;26:65-72.
12. Khoo TK, Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. Neurology 2013;80:276-281.
13. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (IV-TR). 4th ed. (Text Revised). Washington DC: American Psychiatric Publishing, 2000.
15. Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. Mov Disord 2003;18:467-486.
16. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-2170.
17. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-442.
18. Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990;40:1529-1534.
19. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Tilley BC. Postural instability and gait difficulty scores from the MDS-UPDRS. Mov Disord 2011;26:358.
20. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 2006;21:916-923.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
22. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
23. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983; 17:37-49.
24. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.
25. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
26. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26:353-357.
27. Martinez-Martin P, Jeukens-Visser M, Lyons KE, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. Mov Disord 2011;26:2371-2380.
28. Leroi I, Ahearn DJ, Andrews M, McDonald KR, Byrne EJ, Burns A. Behavioural disorders, disability and quality of life in Parkinson's disease. Age Ageing 2011;40:614-621.
29. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am Geriatr Soc 2004;52:784-788.
30. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 2008;63:167-173.
31. Abbott RD, Petrovitch H, White LR, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 2001;57:456-462.
32. Iranzo A, Molinuevo JL, Santamaria J, et al. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 2006;5:572-577.
33. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121-134.
34. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000;15:669-677.
35. Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord 2003;18:414-418.

36. Burn DJ, Landau S, Hindle JV, et al. Parkinson's disease motor subtypes and mood. Mov Disord 2012;27:379-386.

37. Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2006;77:585-589.

38. Velseboer DC, Broeders M, Post B, et al. Prognostic factors of motor impairment, disability, and quality of life in newly diagnosed PD. Neurology 2013;80:627-633.

39. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 2003;60:1745-1748.

40. Kotagal V, Albin RL, Muller ML, et al. Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. Ann Neurol 2012;71: 560-568.

41. Bohnen NI, Kaufer DI, Hendrickson R, Constantine GM, Mathis CA, Moore RY. Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia. J Neurol Neurosurg Psychiatry 2007;78: 641-643.

42. Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology 2013;80:800-809.

43. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord 2007;22:1077-1092.

44. Grosset D, Taurah L, Burn DJ, et al. A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis. J Neurol Neurosurg Psychiatry 2007;78:465-469.

45. Asimakopoulos P, Caslake R, Harris CE, Gordon JC, Taylor KS, Counsell C. Changes in quality of life in people with Parkinson's disease left untreated at diagnosis. J Neurol Neurosurg Psychiatry 2008;79:716-718.

46. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009; 361:1268-1278.

47. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:573-580.

48. Ray Chaudhuri K, Rojo JM, Schapira AH, et al. A proposal for a comprehensive grading of Parkinson's disease severity combining motor and non-motor assessments: meeting an unmet need. PLoS One 2013;8:e57221.

49. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26(Suppl 3):S42-S80.

50. Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. J Neurol Neurosurg Psychiatry 2010;81: 160-165.