The spectrum of nonmotor symptoms in early Parkinson disease

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ABSTRACT

Objective: Nonmotor symptoms (NMS) are common in patients with established Parkinson disease (PD) but their frequency in early PD has not been extensively studied. Our aim was to determine the frequency of NMS in a cohort of patients with newly diagnosed PD.

Methods: A total of 159 patients with early PD and 99 healthy controls participated in this study. NMS were screened for using the Nonmotor Symptom Questionnaire. Other assessments included measures of motor disability (Movement Disorders Society–revised Unified Parkinson's Disease Rating Scale [MDS-UPDRS]), disease severity (Hoehn & Yahr staging), depression (Geriatric Depression Scale), and global cognitive function (Mini-Mental State Examination and Montreal Cognitive Assessment).

Results: The PD group reported a significantly greater number of NMS compared with controls (8.4 [4.3] vs 2.8 [2.6]). In the PD group, the most commonly experienced NMS were excessive saliva, forgetfulness, urinary urgency, hyposmia, and constipation. Patients with higher MDS-UPDRS III scores and those with the postural instability gait subtype experienced a greater number of NMS.

Conclusion: NMS are common in early PD and reflect the multisystem nature of the disorder. Even in the earliest stages of PD, NMS may be detrimental to patients' functional status and sense of well-being. *Neurology*® 2013;80:276–281

GLOSSARY

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **MDS-UPDRS** = Movement Disorders Society–revised Unified Parkinson's Disease Rating Scale; **MMSE** = Mini-Mental State Examination; **MoCA** = Montreal Cognitive Assessment; **NMS** = nonmotor symptoms; **NMSQuest** = Nonmotor Symptom Questionnaire; **PD** = Parkinson disease; **PIGD** = postural instability gait difficulty; **RBD** = REM sleep behavior disorder.

Patients with established Parkinson disease (PD) experience a diverse range of nonmotor symptoms (NMS).[1,2] Many of these have a dopaminergic basis but others do not, reflecting the multisystem nature of the disorder. With disease progression it is these NMS, rather than motor disability, that become important determinants of patients' quality of life.[3–5] NMS are often amenable to therapy; however, many symptoms go unreported and unrecognized by both patients and clinicians.[6] In a large retrospective review of the presenting complaints of patients with PD, 21% initially presented with nonmotor features. Furthermore, those presenting with NMS were more likely to experience a delay in diagnosis and a higher rate of misdiagnosis.[7]

There is a growing literature reporting the frequency of depression, sleep disturbance, anxiety, apathy, and cognitive impairments in early PD[8–10]; however, the prevalence and severity of autonomic and sensory disturbances in early disease is less well-described and has only been reported by 1 group to date in a large drug-naïve incident cohort.[11] Furthermore, when considering motor subtypes of PD, patients with the so-called postural instability gait difficulty (PIGD) subtype have been reported to experience depression more frequently and develop more rapid cognitive decline, compared with non-PIGD subtypes.[12,13]

Because of the broad range of NMS, studies have employed a variety of screening tools and questionnaires to capture the frequency and severity of these symptoms. A significant advance has been the

Podcast

From the Institute for Ageing and Health (T.K.K., A.J.Y., G.W.D., J.T.O., D.J. Burn) and Industrial Statistics Research Unit (S.C.), Newcastle University, Newcastle upon Tyne; Imperial College (D.J. Brooks), MRC Clinical Sciences Centre, London; and Cambridge Centre for Brain Repair (R.A.B.), Cambridge University, Cambridge, UK.

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development and validation of a PD-specific screening questionnaire, the Nonmotor Symptom Questionnaire (NMSQuest), a 30-item questionnaire with screening questions for neuropsychiatric, sleep, genitourinary, gastrointestinal, sensory, and cognitive disturbances.[14,15] It has been applied to cohorts with established PD in large international studies, but has not been used to date in patients with early or newly diagnosed PD.

To define the range and frequency of NMS in patients with early PD, we recruited a cohort of incident patients and healthy controls. We hypothesized that people with early PD would experience a greater number of NMS and that those with the PIGD motor subtype would experience more cognitive, neuropsychiatric, and autonomic problems.

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the Newcastle and North Tyneside Research Ethics Committee and performed according to the Declaration of Helsinki. All patients provided written informed consent.

Case ascertainment and diagnostic procedures. We sought to identify every new case of PD in Newcastle-upon-Tyne and Gateshead from June 1, 2009, to December 31, 2011. A 3-month run-in period was included prior to the official record of incident cases while a 3-month run-out period ensured all referrals had been received. The catchment area was located within Newcastle and Gateshead areas, as defined by the local Primary Care Trust. A total of 70 primary care practices (35 practices in Newcastle and 35 practices in Gateshead) were identified and encouraged to refer patients with suspected parkinsonism. We also informed colleagues in secondary care and invited them to refer all patients with suspected parkinsonism to our study. This group included neurologists (n = 20), geriatricians (n = 15), and PD nurse specialists (n = 5). These patients were recruited as part of the Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation-Parkinson's Disease (ICICLE-PD) study. All patients were diagnosed by a neurologist specializing in movement disorders and fulfilled the UK Brain Bank Criteria for idiopathic PD.[16] Exclusion criteria comprised the following: parkinsonism diagnosed prior to the 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), and significant memory impairment or dementia at presentation (defined as Mini-Mental State Examination [MMSE] score <24 or fulfilling *DSM-IV* criteria for dementia[17]). Further exclusion criteria included the following parkinsonian disorders: drug-induced parkinsonism secondary to exposure to dopamine receptor blocking agents at the onset of symptoms; vascular parkinsonism; and atypical forms of parkinsonism such as progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration, according to accepted diagnostic criteria.[18]

Controls. Age-matched healthy control subjects were recruited from northeast England and underwent a similar assessment schedule as patients. Participants were recruited though local advertising and community sources to ensure they were representative of the local population. Spouses, relatives, and carers of participants with PD were not permitted to act as controls.

Clinical assessment and characterization. All patients with newly diagnosed PD who agreed to participate underwent medical assessment by a physician which included symptom history, level of education, comorbid disease, and medication use. Disease severity was rated by Hoehn & Yahr stage[19] and motor disability was assessed with the Movement Disorders Society–revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts II and III.[20] Motor phenotype was determined according to the MDS-UPDRS revision[21] of the method described by Jankovic et al.[22] Global cognitive function was assessed using the MMSE[23] and Montreal Cognitive Assessment (MoCA).[24] Depression was rated with the Geriatric Depression Scale–15.[25]

Assessment of NMS. The NMSQuest was used as the primary screen for NMS.[14] The screening questions were coded using a

Table 1 Characteristics of patients with early PD and control groups[a]

	PD (n = 159)	Controls (n = 99)	*p* Value
Male, n (%)	105 (66.0)	54 (54.5)	0.065[b]
Age, y, mean (SD)	66.6 (10.3)	67.9 (8.2)	0.451
Median disease duration, mo	4.4	NA	NA
MDS-UPDRS part III subscore, mean (SD)	27.3 (12.1)	NA	NA
Hoehn & Yahr stage, n (%)		NA	NA
1	35 (22)		
2	92 (57.8)		
3	31 (19.5)		
4	1 (0.6)		
5	0		
Antiparkinsonian medication, n (%)		NA	NA
Drug-naïve	20 (12.6)		
Levodopa	48 (30.2)		
Dopamine agonist	58 (36.5)		
MAOB inhibitor	73 (45.9)		
Levodopa dose equivalent, mg, mean (SD)	177.4 (146.6)		
MMSE	28.6 (1.4)	29.0 (1.2)	0.003
MoCA[c]	25.1 (3.6)	26.8 (2.6)	0.001
GDS-15[d]	2.9 (2.7)	1.0 (1.6)	<0.001

Abbreviations: GDS-15 = Geriatric Depression Scale-15; MAOB = monoamine oxidase; MDS-UPDRS = Movement Disorders Society–revised Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NA = not applicable; PD = Parkinson disease.

[a] All comparisons between patients with PD and healthy controls were performed using the Wilcoxon rank sum test, unless indicated otherwise ([b]; χ^2 test).

[b] χ^2 test.

[c] MoCA completed in 144 patients with PD and 94 control subjects.

[d] GDS-15 completed in 97/99 subjects.

Table 2 Frequency of nonmotor symptoms in patients with PD and controls[a]

	PD	Control	p Value
Total no. (%) of NMS	8.4 (4.3)	2.8 (2.6)	<0.001[b]
Gastrointestinal tract, n (%)			
Sialorrhea	89 (56.0)	6 (6.1)	<0.001[b]
Dysphagia	32 (20.1)	3 (3.0)	<0.001[b]
Nausea	15 (9.4)	4 (4.0)	0.142
Constipation	67 (42.1)	7 (7.1)	<0.001[b]
Bowel incontinence	9 (5.7)	5 (5.1)	1.000
Incomplete bowel emptying	51 (32.1)	12 (12.1)	<0.001[b]
Hyposmia	71 (44.7)	10 (10.1)	<0.001[b]
Weight change (unexplained)	36 (22.6)	19 (19.2)	0.536
Urinary tract, n (%)			
Urinary urgency	74 (46.5)	19 (19.2)	<0.001[b]
Nocturia	42 (26.4)	17 (17.2)	0.095
Sexual function, n (%)			
Sexual dysfunction	33 (20.8)	10 (10.1)	0.026
Impaired libido	28 (17.6)	7 (7.1)	0.016
Cardiovascular, n (%)			
Orthostatic symptoms	53 (33.3)	11 (11.1)	<0.001[b]
Falls	37 (23.3)	4 (4.0)	<0.001[b]
Lower limb swelling	29 (18.2)	11 (11.2)	0.157
Neuropsychiatric and cognitive, n (%)			
Forgetfulness/memory	88 (55.3)	41 (41.4)	0.040
Impaired concentration	47 (29.6)	2 (2.0)	<0.001[b]
Anxiety	68 (42.8)	10 (10.1)	<0.001[b]
Low mood	59 (37.1)	10 (10.1)	<0.001[b]
Loss of interest/apathy	44 (27.7)	3 (3.0)	<0.001[b]
Delusions	1 (1.0)	0 (0.0)	1.000
Visual hallucinations	35 (22.0)	0 (0.0)	<0.001[b]
Sleep, n (%)			
Daytime somnolence	59 (37.1)	18 (18.2)	0.001[b]
Insomnia	28 (17.6)	13 (13.1)	0.385
Dream re-enactment	55 (34.6)	8 (8.1)	<0.001[b]
Vivid dream imagery	48 (30.2)	5 (5.1)	<0.001[b]
Restless legs	44 (27.7)	11 (11.1)	0.002[b]
Pain (unexplained), n (%)	60 (37.7)	3 (3.0)	<0.001[b]
Miscellaneous, n (%)			
Diplopia	16 (10.1)	3 (3.0)	0.048
Hyperhydrosis	16 (10.1)	6 (6.1)	0.360

Abbreviations: NMS = nonmotor symptoms; PD = Parkinson disease.
[a] All statistical tests performed with Pearson χ^2 unless frequency less than 3, when Fisher exact test was used.
[b] Following Bonferroni correction for 30 multiple tests, $p < 0.002$ was considered a significant difference in frequency of NMS between patients with PD and controls.

binary approach of present or absent. The presence of a positive symptom was examined in further detail in relation to PD, to determine the nature and temporal association with diagnosis.

Statistics. Statistical analyses were performed with SPSS 19.0/PASW (SPSS, Chicago, IL). Continuous and count data were compared using the Wilcoxon rank sum test, and categorical data with χ^2 tests. A p value of <0.05 was deemed to be significant for all univariate analysis. Bonferroni adjustment was performed to correct for multiple testing, yielding a $p = 0.002$ level of significance. Spearman rank correlation coefficient was used to assess the association between demographic and clinical variables.

RESULTS A total of 466 potential participants were referred to the study; of these, 173 had a diagnosis of idiopathic PD. A total of 159 patients with early PD were identified and consented to participate. There was no difference in sex between patients who participated in the study and those who declined (male: female ratio; study participants = 1.4:1, study decliners = 1.1:1) (χ^2, $p = 0.482$); however, those who declined were significantly older (mean age 75.5 [8.6] vs 67.4 [9.9] years, $p < 0.001$). Ninety-nine age-matched control subjects were recruited. The demographic and clinical characteristics of the patient and control groups are shown in table 1.

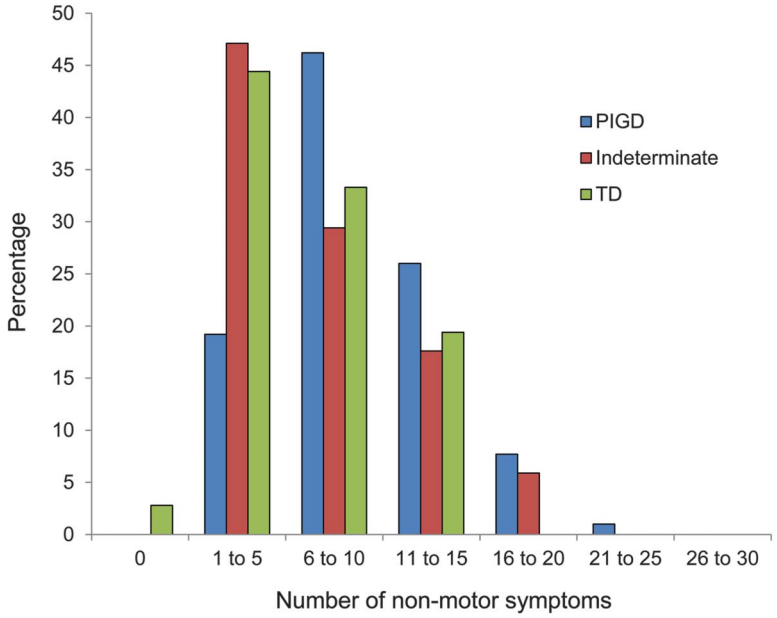
Patients with PD experienced a significantly greater number of total NMS (mean 8.4 [4.3]) than the control subjects (mean 2.8 [2.5]) ($p < 0.001$). Table 2 shows the frequency of NMS in the patient and control groups. The most commonly experienced NMS in the PD group were excessive saliva and dribbling, urinary urgency, hyposmia, anxiety, and constipation; these were all significantly more common in the patients with PD than in the controls. Complaints of forgetfulness and poor memory were also common among the PD group (55.3%) but, notably, were also reported by 41.4% of the control group.

Patients with higher total MDS-UPDRS part III scores experienced greater numbers of NMS (Spearman $\rho = 0.335$, $p < 0.001$). There was no significant difference in total number of NMS with age (Spearman $\rho = -0.067$, $p = 0.401$) or sex ($p = 0.325$).

A total of 104 patients (66.2%) were classified as having the PIGD subtype; these patients experienced a significantly greater number of total NMS (mean 9.3 [4.2]) compared to those with indeterminate (mean 7.5 [4.7]) or tremor-dominant subtypes (mean 6.3 [3.6]) ($p < 0.001$) (figure). Although the PIGD group had higher total MDS-UPDRS part III scores, the difference between the PIGD and tremor-dominant groups was not significant ($p = 0.085$). Following Bonferroni correction, only sialorrhea remained significantly more common in those with the PIGD phenotype (66.7%) than in those with tremor-dominant disease (33.3%, $p = 0.001$).

DISCUSSION We have shown that NMS are common in early PD and occur more frequently than in age-matched controls. Patients with early PD report a higher total number of NMS, the most common being

Figure Motor subtypes and distribution of Nonmotor Symptom Questionnaire



Total number of nonmotor symptoms by motor phenotype. PIGD = postural instability gait difficulty; TD = tremor-dominant.

excessive saliva, forgetfulness, urinary urgency, hyposmia, and anxiety. The high frequency of excess saliva and drooling supports the finding by Muller et al.[11] who, using the MDS-UPDRS, also found this to be the most common NMS in their large incident, untreated PD cohort. Drooling is more commonly associated with established and advanced disease.[1,2,14] Lewy bodies within the submandibular gland are reported in patients with PD and dementia with Lewy bodies[26,27] and also in incidental Lewy body disease.[26] This, together with so-called Lewy body dysphagia,[28] suggests a possible early pathophysiologic basis for this symptom.

Symptoms of urinary urgency were common in our PD group. These findings are similar to other studies which have screened for NMS in early and later stage disease.[11,14,29] Although urinary symptoms are a frequent complaint in community-dwelling older people,[30] there was a clear excess in our cohort of patients with PD compared with age-matched controls.

Over half of our patients with PD complained of forgetfulness or memory problems, although this was also a frequent complaint in our control group. This could raise questions regarding the specificity of the NMSQuest in this regard, although the proportion of patients with PD reporting this symptom is comparable to other studies that used more detailed cognitive assessments.[31,32] The mean MMSE score in our patients with PD was 29, and the MoCA 25, indicating that, objectively, these patients were cognitively well-preserved.

We were surprised by the frequency of visual hallucinations in our cohort, which was higher than might be expected in newly diagnosed patients. This may reflect misinterpretation on the respondent's behalf or a lack of specificity of the question. Alternatively, fragmentary visual phenomena, such as sensations of passage or presence, in particular, may be more common than previously recognized in early PD.[33]

Early sleep disturbance occurred in one-third of our patients and was more common than in controls. The occurrence of REM sleep behavior disorder (RBD) has been associated with the subsequent development of neurodegenerative disease characterized by deposition of α-synuclein.[34] Moreover, the development of RBD in PD has recently been associated with the development of PD dementia.[35] Unlike the studies of Postuma et al.[36] and, more recently, Romenets et al.,[37] neither RBD nor most NMS were more frequent in patients with the PIGD subtype. This disparity may reflect differences between motor subtype and RBD at different disease stages and the fact that our subjects were at an early disease stage.

Further understanding the evolution of these NMS will come through research into premotor PD, which should clarify the temporal evolution of these symptoms in relation to the motor features. Better delineation of these symptoms could also be beneficial to focus possible disease-modifying therapies at the very earliest disease stages.

The main strengths of this study are that we have recruited a large cohort of patients with newly diagnosed PD and age-matched controls. In keeping with current clinical practice, many patients were taking antiparkinsonian medication, most commonly rasagiline, making our findings ecologically relevant to clinicians. The inclusion of an age-matched control group facilitated better definition of disease-specific features and we believe that by not recruiting spouses and carers of patients with PD we reduced the risk of bias. Other strengths include the use of validated instruments for the assessment of motor symptoms and NMS. A comprehensive medical history helped to address potentially confounding factors with regards to the relevance of NMS in relation to PD.

This study has several limitations. Not all patients with newly diagnosed PD agreed to take part; those who declined were older and reasons included functionally limiting comorbidities, social reasons, having to provide care for another relative, and lack of interest. It is possible that the patients who declined to participate would have reported an even higher burden of NMS. Other limitations include the dependence on subjective recall of NMS, which is open to reporter bias and dependent on cognitive aspects, though subjects with significant cognitive impairments and dementia were excluded, and many histories were taken in the presence of a carer, who corroborated findings.

The wide range of NMS experienced by patients with PD underscores the multisystem nature of PD from disease onset and could implicate dysfunction of other neurotransmitters such as serotonin, noradrenaline, and acetylcholine. These systems could represent future therapeutic targets. With awareness of the frequency of these symptoms in early PD, clinicians may be better placed to actively seek and manage these problems effectively in their patients.

AUTHOR CONTRIBUTIONS

Dr. Tien K. Khoo is a study investigator. He was involved with the study design and coordination of the study. He was also involved with participant recruitment, clinical assessment, data collection, and data analysis, and wrote and revised the manuscript. Dr. Alison J. Yarnall was involved with study coordination, participant recruitment, clinical assessment, data collection, and review of the manuscript. Dr. Gordon W. Duncan was involved with study coordination, participant recruitment, clinical assessment, data collection, and manuscript revision. Dr. Shirley Coleman was involved with the statistical design and analysis of the study. Professor O'Brien is a principal investigator and coapplicant for the funding grant. He was involved in the study supervision and reviewed and approved the final manuscript. Professor Roger A. Barker is a principal investigator and coapplicant for the main funding grant (Parkinson's UK). He was also involved with the study design. Professor David J. Brooks is a principal investigator and coapplicant for the main funding grant (Parkinson's UK). He was also involved with the study design and reviewed the manuscript. Professor David J. Burn is the chief investigator and main applicant for the funding grant (Parkinson's UK). He was involved with the study design and also supervised the study as well as reviewed the manuscript.

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DISCLOSURE

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