ORIGINAL ARTICLE

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Nonmotor Symptoms and Cognitive Decline in *de novo* Parkinson's Disease

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ABSTRACT: ***Background:*** Cognitive impairments are common in Parkinson's disease (PD). Despite its clinical importance, the development of dementia is still difficult to predict. In this study, we investigated the possible associations between non-motor symptoms and the risk of developing dementia within a 2-year observation period in PD. ***Methods:*** A total of 80 patients with PD participated in this study. Nonmotor symptoms (the Nonmotor Symptoms Questionnaire), PD status (Unified Parkinson's Disease Rating Scale), depression (Geriatric d Depression Scale or Montgomery-Asberg Depression Scale), stereopsis and severity of nonmotor symptoms (Non-motor symptoms scale) were assessed. Global cognitive function (Mini-Mental State Examination) were evaluated at baseline and 2 years later. ***Results:*** Presence of depression, vivid dreaming, REM sleep behavior disorders, hyposmia, abnormal stereopsis, non-smoking and postural instability/ gait disturbance phenotype were associated with a significantly more rapid decline of Mini-Mental State Examination. Logistic regression analyses demonstrated that depression (odds ratio = 13.895), abnormal stereopsis (odds ratio = 10.729), vivid dreaming (odds ratio = 4.16), REM sleep behavior disorders (odds ratio = 5.353) and hyposmia (odds ratio = 4.911) were significant independent predictors of dementia risk within 2 years. Postural instability/ gait disturbance phenotype and age >62 years were also independent predictors of dementia risk (odd ratio = 38.333, odds ratio = 10.625). ***Conclusions:*** We suggest that depression, vivid dreaming, REM sleep behavior disorders, hyposmia and abnormal stereopsis are closely associated with cognitive decline, and that presence of these nonmotor symptoms predict the subsequent development of Parkinson's disease dementia.

RÉSUMÉ: Symptômes non moteurs et déclin cognitif dans la maladie de Parkinson de novo. ***Contexte:*** Le déficit cognitif est fréquent dans la maladie de Parkinson (MP). Malgré son importance clinique, l'apparition de la démence demeure difficile à prédire. Dans cette étude, nous avons examiné l'association possible entre les symptômes non moteurs et le risque de présenter une démence au cours d'une période d'observation de 2 ans chez des patients atteints de MP. ***Méthode:*** Quatre-vingt patients atteints de MP ont participé à cette étude. Les symptômes non moteurs (Nonmotor Symptoms Questionnaire), le stade d'évolution de la MP (Unified Parkinson's Disease Rating Scale), la stéréopsie et la sévérité des symptômes non moteurs (Non-motor symptoms scale) ont été évalués. La fonction cognitive globale (Mini-Mental State Examination) a été évaluée au début de l'étude et 2 ans plus tard. ***Résultats:*** La présence de dépression, de rêves intenses et troublants, de troubles du comportement du sommeil paradoxal, d'hyposmie, d'anomalies de la stéréopsie, le fait d'être non-fumeur et l'instabilité posturale/la démarche anormale étaient associés à un déclin significativement plus rapide du score au Mini-Mental. Les analyses de régression logistique ont montré que la dépression (rapport de cotes (RC) = 13,895), la stéréopsie anormale (RC = 10,729), les rêves intenses et troublants (RC = 4,16), les troubles du comportement du sommeil paradoxal (RC = 5,353) et l'hyposmie (RC = 4,911) prédisaient de façon indépendante le risque de démence au cours des 2 prochaines années. Une instabilité posturale/une démarche anormale et un âge supérieur à 62 ans prédisaient de façon indépendante le risque de démence (RC = 38,333, RC = 10,625). ***Conclusions:*** Nous proposons que la dépression, les rêves intenses et troublants, les perturbations du comportement du sommeil paradoxal, l'hyposmie et la stéréopsie anormale sont étroitement associés au déclin cognitif et que la présence de ces symptômes non moteurs prédit l'apparition subséquente de la démence dans la maladie de Parkinson.

Keywords: Nonmotor symptoms, hyposmia, depression, stereopsis, dementia, Parkinson's disease

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Dementia related to Parkinson's disease (PD) is associated with increased mortality,[1] reduced quality of life,[2] and increased caregiver distress[3] and is a major risk factor for nursing home placement.[4] A patient with PD is five to six times more likely to have dementia than an age-matched control without PD.[5] Increasing age is the most important risk factor for PD dementia (PDD), and it is more likely to occur in the postural instability and gait disturbance motor phenotype than in the tremor dominant phenotype of PD.[6] Among non-motor symptoms (NMS), psychosis including visual hallucinations has been associated with increased risk of PDD.[7] Cognitive dysfunction is related to neurocirculatory abnormalities, especially orthostatic hypotension and supine hypertension.[8] However, it is uncertain whether various NMS are risk factors for dementia in PD.

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Recently, we suggested that deficits of stereopsis are common in drug-naïve PD patients.[9] Our previous voxel-based morphometry study suggested that abnormal stereopsis implicated cortical visual dysfunction as part of the NMS in PD.[10] The involvement of extra-striate visual cortices is also associated with visual hallucinations, one of the high risk factors for dementia in PD.[11] These findings suggest that abnormal stereopsis, which is related to the visual association area, may be a predicting factor for dementia in PD.

In this present study, we studied the decline of Mini-Mental Status Examination (MMSE) scores over two years according to the presence of NMS including stereopsis. To define the possible associations between NMS and the risk of developing dementia, we investigated the risk factors for dementia conversion within a two-year observation period in PD.

METHODS

Standard protocol approvals, registrations, and patient consent

The study was approved by the Korea University Guro Hospital Institutional Review Board. All patients provided written informed consent.

Subjects

We recruited consecutively drug-naïve PD patients, meeting the United Kingdom Parkinson's Disease Society's criteria for idiopathic PD, from the Parkinson's Disease Center at Korea University Guro Hospital from November 2008 to August 2010.[12] To ascertain dopaminergic drug treatment response, we reviewed medical records of all included patients for two years. Exclusion criteria were as follows: (1) history of head trauma, stroke, exposure to anti-dopaminergic drugs, or central nervous system (CNS) infection; (2) abnormal thyroid function testing; (3) structural lesions or hydrocephalus on brain magnetic resonance imaging (MRI); (4) abnormal cognitive function (MMSE ≤ 24) and (4) red-flag signs suggesting Parkinson plus syndrome. We classified PD patients into either a dementia converting group or a dementia non-converting group.

Clinical assessment

Patients underwent a neurologic examination and a clinical assessment. Symptom history, level of education, comorbid diseases and medication history were assessed. The Hoehn and Yahr (H&Y) stage was determined,[13] and the degree of disease severity was quantified by the Unified Parkinson's Disease Rating Scale (UPDRS).[14] The Non-motor Symptoms Scale for Parkinson's disease (NMSS) was used to evaluate the presence and severity of NMS. Depression was rated with the Korean version of the Montgomery-Asberg Depression Scale (K-MADS)[15] or the Geriatric Depression Scale-15.[16] We assessed olfactory function using structural screening questionnaires including odor detection, discriminatuion and identification. Rapid eyeball movement (REM) sleep behavior disorders (RBD) was screened with RBD screening questionnaires.[17] The two-step test for stereopsis was performed. The first step involved tests for visual acuity and strabismus. Patients with strabismus, nystagmus, ocular motility disturbance, or poor visual acuity in either eye (<20/40 Snellen fraction) were excluded from the study. The second step involved the measurement of stereopsis. Stereopsis was assessed using Titmus stereotest plates (Stereo Optic Co., Inc., IL, USA). Normal stereopsis was defined as an arc <60 seconds in the Titmus fly test. Previous studies of adult stereoacuity reported that a reduction of the Titmus fly test score was observed in five of 60 normal subjects.[18] All tests were conducted at a distance of 40 cm, under an illumination of 200 lux. The motor phenotype was determined according to the UPDRS motor score, using the method prescribed by Jankovic et al.[19]

The general cognitive status of each subject was evaluated by means of the MMSE and the Clinical Dementia Rating (CDR) scale at baseline and two years later.[20] For analytic purposes, the total daily L-dopa equivalent dose (total LEDD, mg/day) after two years was calculated based on theoretical equivalence from the literature.[21] Dementia was diagnosed according to the *Movement Disorders Society* criteria of PD dementia, defined as impairment of $\geq$ two cognitive domains using neuropsychological tests associated with significant functional impairment from cognitive decline.[22] Detailed cognition was evaluated using the Seoul Neuropsychological Screening Battery,[23] which consists of an attention test (forward digit span, backward digit span and letter cancellation), a language and related function test (spontaneous speech, comprehension, repetition, naming measured by the Korean version of the Boston Naming test, reading, writing, finger naming, right-left orientation, body part identification, calculation and praxis), a visuospatial function test (drawing an interlocking pentagon and the Rey complex figure test), a verbal memory test (three word registration, three word recall, and the Seoul Verbal Learning Test which included immediate recall, delayed recall, and recognition), a non-verbal memory test (immediate recall, delayed recall and recognition of a Rey complex figure) and a frontal executive function test (motor impersistence, contrasting program, go-no-go test, fist-edge-palm, alternating hand movement, alternating square and triangle test, Luria loop, Controlled Oral Word Association Test: animal, supermarket and letter, Korean-color Word Stroop Test: word reading and color reading).

Statistical analysis

The data were expressed as mean $\pm$ standard deviation (SD) or as n (%). Simple bivariate analyses were performed to identify potential predictors of cognitive decline. Non-categorical clinical variables including age were dichotomized at the median. Between-group comparisons were made using the Student's t-test or one-way analysis of variance (ANOVA). In the second stage of analysis, variables significantly associated with cognitive decline in the bivariate analyses (P value of ≤ 0.05) were entered into a logistic regression analysis, using dementia conversion as the dependent variable. A backward stepwise method was used to remove non-significant predictors. All analyses were performed using Statistical Package for the Social Sciences (SPSS) 12.0 for Windows.

RESULTS

Baseline and clinical characteristics

A total of 80 patients were enrolled in the study. The mean (SD) interval of follow-up assessments from initial

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Table 1: Demographic and baseline clinical data in dementia-converter and non-converter

	All participants (N = 80)	Non-converters (N = 62)	Dementia-converters (N = 18)	*p*
Sex (male, %)	30, 37.5%	25, 40.3%	4, 22.2%	0.045*
Age (years)	68.1 ± 10.8 (62)	65.7 ± 11.4	73.8 ± 6.3	0.041*
Education (years)	5.9 ± 3.4 (5)	6.6 ± 3.1	3.2 ± 3.3	0.290
Disease duration (months)	29.8 ± 26.8 (26)	28.4 ± 20.1	31.3 ± 21.3	0.194
MMSE	27.9 ± 3.6 (28)	28.7 ± 1.8	24.0 ± 3.2	0.008*
H&Y stage	2.8 ± 1.3 (2)	2.2 ± 0.9	3.17 ± 0.7	0.838
UPDRS I	4.9 ± 2.8 (3)	3.58 ± 1.9	7.17 ± 2.4	0.508
UPDRS II	10.3 ± 5.4 (8)	10.6 ± 5.7	8.78 ± 4.8	0.217
UPDRS III	12.6 ± 7.7 (12)	11.0 ± 8.2	16.4 ± 6.3	0.025*
NMSS	21.1 ± 10.3 (19)	19.6 ± 9.9	22.2 ± 11.0	0.424

Data = mean ± SD (median), *Significant difference

assessment was 2.2 (0.4) years. The demographic and clinical characteristics are shown in Table 1. Dementia-converting group had significant low MMSE scores, older age and higher UPDRS motor scores at baseline.

MMSE decline over two years

The mean MMSE score (mean ± SD) at initial evaluation was 27.9 ± 3.6, and the mean decline of the MMSE score was 2.7 ± 2.6 in 2 years. The mean decline of the MMSE score over 2 years in the dementia converting group (6.6 ± 1.7) was significantly higher than that of non-converting group (1.4 ± 1.2) ($p < 0.001$). Among the non-motor symptoms, vivid dreaming ($p = 0.021$), RBD ($p = 0.003$), constipation ($p = 0.043$), hyposmia ($p = 0.002$), abnormal stereopsis ($p = 0.001$) and depression ($p = 0.002$) were associated with a more rapid rate of cognitive decline. Old age (≥62 years, **median age**, $p < 0.001$), female gender ($p = 0.048$), non-smoking ($p = 0.007$), postural instability/ gait disturbance (PIGD) phenotype ($p < 0.001$) and severe motor dysfunction (UPDRS III score >12, $p < 0.001$) were also associated with a more rapid rate of cognitive decline. Table 2 summarizes the bivariate analyses of clinical variables versus rate of cognitive decline over two years.

Risk factors of dementia conversion

Logistic regression analysis demonstrated that vivid dreaming, RBD, hyposmia, depression and abnormal stereopsis were significant independent predictors of dementia risk within two years. The total score of NMSS was not an independent predictor of dementia risk. Old age (age ≥62 years), PIGD phenotype and motor disability (UPDRS III score >12) were also significant independent predictors of dementia risk over two years. Table 3 summarizes the logistic regression results of the factors predicting dementia converting.

DISCUSSION

Dementia associated with PD is a common complication, affecting 80% of PD patients during the course of their illness.[24] In our present study, 22.5% (18/80) of enrolled patients met the criteria of PD dementia at 24 months. A PD cohort study in

Table 2: Bivariate comparisons of demographic and clinical variables versus rate of cognitive decline over two years (change in MMSE), using the Student's t-test or ANOVA

Variable	Changes of MMSE over 2 years, Mean ± SD	*p* value
Dementia conversion		
Non-converter (n = 62)	1.4 ± 1.2	<0.001*
Converter (n = 18)	6.6 ± 1.7	
Sex		
Male (n = 30)	2.0 ± 2.3	0.048*
Female (n = 50)	3.1 ± 2.7	
Age		
<62 years (n = 23)	1.2 ± 1.5	<0.001*
≥62 years (n = 57)	3.7 ± 2.7	
Smoking		
Yes (n = 19)	1.3 ± 1.4	0.007*
No (n = 61)	3.1 ± 2.7	
Alcohol		
Yes (n = 20)	2.0 ± 2.3	0.162
No (n = 60)	2.9 ± 2.6	
Vivid dream		
Presence (n = 38)	3.4 ± 2.7	0.021*
Absent (n = 42)	2.1 ± 2.4	
RBD		
Presence (n = 35)	3.7 ± 1.6	0.003*
Absent (n = 45)	2.0 ± 2.3	
Visual hallucination		
Presence (n = 8)	3.6 ± 2.6	
Absent (n = 72)	2.6 ± 2.6	0.287
Orthostatic dizziness		
Presence (n = 33)	2.5 ± 2.6	0.479
Absent (n = 47)	2.9 ± 2.6	

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Table 2. *(Continued)*

Variable	Changes of MMSE over 2 years, Mean ± SD	*p* value
Constipation		
Presence (n = 33)	3.4 ± 2.7	0.043*
Absent (n = 47)	2.2 ± 2.4	
Depression		
Presence (n = 35)	3.7 ± 2.9	0.002*
Absent (n = 45)	1.9 ± 2.1	
Hyposmia		
Presence (n = 33)	3.8 ± 2.7	0.002*
Absent (n = 47)	2.0 ± 2.3	
Abnormal stereopsis		
Presence (n = 35)	3.6 ± 2.7	0.001*
Absent (n = 45)	1.6 ± 1.9	
Motor phenotype		
PIGD (n = 26)	5.2 ± 2.6	<0.001*
Non-PIGD (n = 54)	1.5 ± 1.6	
LED, 2 year follow-up		
0-150 (n = 46)	2.1 ± 2.5	0.109
151-250 (n = 20)	3.2 ± 2.9	
251-500 (n = 7)	3.9 ± 1.8	
500 < (n = 7)	4.0 ± 2.6	
HY stage		
1-2	1.4 ± 1.4	<0.001*
3-5	4.5 ± 2.8	
UPDRS I		
≤3	1.7 ± 1.6	0.001*
>3	3.1 ± 2.8	
UPDRS II		
≤8	2.7 ± 2.4	0.666
>8	2.7 ± 2.7	
UPDRS III		
≤12	1.3 ± 1.5	<0.001*
>12	4.1 ± 2.7	
NMSS		
≤19	1.9 ± 2.3	0.215
>19	3.4 ± 2.7	

RBD = REM sleep behavior disorders; LED = levodopa equivalent dose; HY = Hoehn and Yahr; PIGD = postural instability and gait disturbance; UPDRS = Unified Parkinson's disease rating scale; NMSS = Non-motor symptoms scale; CI = confidence interval; B = regression coefficient; S.E = standard error; Wald. = Wald statistic; df = degree of freedom; Sig. = significance; Exp(B) = expected regression coefficient
*Significant difference

Cambridge reported that the overall proportion of patients with dementia at 3.5 years is 10%.[25] A systematic review of prevalence studies of dementia in PD determined the prevalence to be 31.5%.[26] Differences in study design, age and disease stage of subjects may account for these variations. The conversion rate to dementia of our study is relatively high. Our study was not a community based study but an hospital based study. Difference in study design may be considered as an explanation of high conversion rate.

Vivid dreaming, RBD, hyposmia, abnormal stereopsis and depression were significant NMS PD dementia predictors at 24 months in this study. These NMS are also associated with a more rapid rate of cognitive decline. Several cross-sectional and prospective studies show that RBD is associated with increased risk of dementia.[27,28] A recent three-year longitudinal study demonstrated that severe olfactory dysfunction is a prodromal symptom of PD dementia.[29] Although the diagnoses of RBD and hyposmia were not based on polysomnogram or the objective smell test, our questionnaire-based study also showed that RBD and hyposmia were the most significant risk factors for PD dementia. Recently, we reported that deficits of stereopsis are common in drug-naïve PD patients;[9] we also suggested that the neural correlate of stereopsis may lie in the non-dominant extra-striate visual cortex with voxel-based morphometric study and abnormal stereopsis implicated in cortical visual dysfunction as part of the NMS in PD.[10] Visuospatial and perceptual deficits are more frequently observed in PD dementia patients experiencing pathological changes in the visual association area.[30] These findings suggest that abnormal stereopsis, which is related to the visual association area, may be a predicting factor for dementia in PD. In this study, abnormal stereopsis was associated with increased risk of dementia. Although visual hallucinations are a well-known risk factor of PD dementia, we did not find a significant association between visual hallucinations and dementia conversion in our present study. Failure to detect a significant association is likely due to the subject characteristics in our study. The subjects of our study were drug-naïve patients, and the numbers of patients with visual hallucinations was small.

The most important risk factor for PD dementia among the demographic factors assessed is increasing age. In our present study, old age (≥62 years), PIGD phenotype and PD motor dysfunction, reflected by UPDRS III scores, are also PD dementia predictors.

This study of 80 cognitively normal *de novo* PD patients, observed prospectively for two years, resulted in an average annual decline of 1.3 points of the MMSE score. The average annual decline of the MMSE score in the dementia converting group was 3.28 points, which is significantly higher than that of the non-converting group (0.72 points). These results are similar to previous studies. Presence of depression, vivid dreaming, RBD, hyposmia, abnormal stereopsis, non-smoking and the PIGD phenotype were associated with a significantly more rapid decline of MMSE.

It must be acknowledged that there were several limitations to the current study. One limitation includes the dependence on subjective scale of NMS. The presence of olfactory dysfunction and RBD are dependent on subjective or caregiver recall. The second limitation is a short follow-up duration. A 2-year follow-up period is not adequate to assess advanced PD patients. Performing an extended follow-up study is therefore necessary.

With increased awareness of the non-motor risk factors for the development of dementia in PD, clinicians may be better able to

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Table 3: Logistic regression results to predict dementia conversion

							95% C.I. for EXP(B)	
	B	S.E	Wald	df	Sig.	Exp(B)	Lower	Upper
Age > 62	2.4	1.1	4.9	1	0.027*	10.6	1.3	86.1
Female	1.8	0.6	3.5	1	0.063	3.2	0.9	11.2
PIGD	3.6	0.8	22.6	1	<0.001*	38.3	8.5	172.4
Vivid dreaming	1.4	0.6	5.7	1	0.017*	4.2	1.3	13.4
RBD	1.7	0.6	7.7	1	0.005*	5.4	1.6	17.5
Visual hallucination	1.1	1.0	1.2	1	0.273	3.1	0.4	24.0
Orthostatic dizziness	−0.2	0.6	0.2	1	0.693	0.8	0.3	2.4
Constipation	0.6	0.6	1.3	1	0.251	1.9	0.6	5.6
Depression	1.6	0.6	6.9	1	0.008*	0.2	0.1	0.7
Hyposmia	1.6	0.6	6.9	1	0.008*	4.9	1.5	15.9
Abnormal stereopsis	2.6	0.8	10.7	1	0.001*	13.9	2.9	67.1
UPDRS I > 3	1.2	0.7	3.1	1	0.078	3.4	0.9	13.2
UPDRS II > 8	−0.4	0.6	0.6	1	0.417	0.6	0.2	1.9
UPDRS III > 12	2.2	0.7	10.4	1	0.001*	9.4	2.4	36.9
NMSS >19	0.6	0.5	1.2	1	0.277	1.8	0.6	5.5

PIGD = postural instability and gait disturbance; RBD = REM sleep behavior disorders; UPDRS = Unified Parkinson's disease rating scale; NMSS = Non-motor symptoms scale; CI = confidence interval; B = regression coefficient; S.E = standard error; Wald. = Wald statistic; df = degree of freedom; Sig. = significance; Exp(B) = expected regression.
*Significant difference

actively monitor cognitive dysfunction in their PD patients who present with the particular risk factors detailed in this study.

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