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Original Article

Can levodopa prevent cognitive decline in patients with Parkinson's disease?

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Abstract: Cognitive impairment in Parkinson's disease (PD) will become more important since the number of elderly patients with PD is increasing. We prospectively studied non-demented patients with PD over the course of 3 years to identify factors associated with PD that contribute to a decline in cognitive function. From among 100 consecutive patients, we registered 79 patients with PD. A total of 55 patients completed the study during 3 years and were divided to two groups: patients with a decline in cognitive function and those without a decline in cognitive function after 3 years. Seventeen independent variables were evaluated with the use of logistic regression models. The increase in the daily levodopa dose was related to a decline in cognitive function on univariate logistic regression analysis (OR = 0.279, P = 0.024, 95% CI = 0.092-0.848). Other variables were not related to a decline in cognitive function. The increase in the daily dose of levodopa was greater in patients without a decline in cognitive function than those with a decline in cognitive function; on the other hand, the cognitive function unchanged. Our results suggest that the treatment with levodopa might prevent a decline in cognitive function in PD.

Keywords: Parkinson, levodopa, cognition, dementia, dopamine

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized not only by motor symptoms, but also by non-motor symptoms. In particular, cognitive impairment will become more important since the number of elderly patients with PD is increasing. The development of dementia is associated with increased disability, hospitalization [1], and ultimately higher mortality [2]. We prospectively studied non-demented patients with PD over the course of 3 years to identify factors associated with PD that contribute to a decline in cognitive function. This study evaluated unique independent variables, such as the progression of disease stage, motor complications, depression, sleep quality over the course of 3 years, and the use of increased doses of dopaminergic medications, as well as variables associated with PD at study entry. Our results suggest that levodopa might prevent a decline in cognitive function.

Material and methods

Participants and initial assessments

We initially screened 100 consecutive patients who fulfilled the UK Parkinson's Disease Society Brain Bank criteria [3]. In accordance with our recently reported methods [4, 5], we first had the patients complete diary questionnaires for 4 weeks to find patients who had hallucinations and exclude patients who had dementia or higher brain dysfunction that would preclude following our instructions. The clinical diary included a total of 10 questions [4, 5] and inquired about hallucinations. The patients wrote their responses to the questions after awakening in the morning. If a patient had drunk alcohol the previous night, we did not use their responses for that night. Patients who were given quetiapine, clozapine, rivastigmine, donepezil, galanthamine, or yokukansan were excluded. Patients who had received deep brain stimulation surgery or had a previous diagnosis of schizophrenia were also excluded. The severity of PD was graded according to the scores on the Unified Parkinson's Disease Rating Scale (UPDRS) [6]. Cognitive function was assessed with the Mini-Mental Status Examination (MMSE). The Zung Self-Rating Depression Scale (SDS) was used to evaluate depression [7]. SDS is widely used as a self-administered psychological test, and higher scores indicate severer depression. Several studies have used the SDS to evaluate depression in PD [8]. The

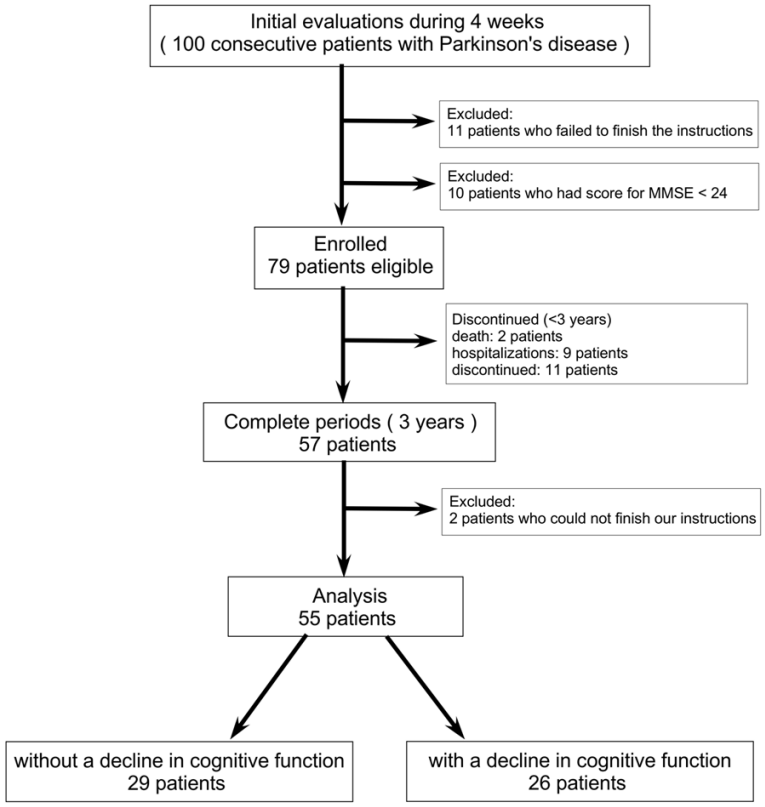

Figure 1. Selection procedure for patients included in analysis. From among the 100 patients, we excluded 11 patients who did not complete the required initial examinations during the first 4 weeks and 10 patients who had an MMSE score of < 24. We registered 79 patients and could finally follow up 57 patients for 3 years. In addition, we excluded two patients who could not continue our examinations after 3 years. The remaining 55 patients were included in data analysis.

Parkinson's Disease Sleep Scale (PDSS) [9] has also been used. The daily dose of antiparkinsonian agents was converted into the equivalent dose of levodopa as follows: (regular levodopa dose × 1) + (levodopa controlled-release dose × 0.75) + (entacapone or stalevo × 0.33) + (pramipexole dose × 100) + (ropinirole dose × 20) + (rotigotine dose × 30) + (pergolide dose and cabergoline dose × 67.0) + (bromocriptine dose × 10) + (selegiline dose × 10) + (amantadine dose × 1) at study entry [10, 11]. From among the 100 screened patients, we excluded 11 patients who did not complete the required initial evaluations during the first 4 weeks and 10 patients who had an MMSE score of < 24.

Follow-up assessments

From among the 100 patients, we registered 79 patients with PD (**Figure 1**). In accordance with our previously described methods [4, 5], these patients visited one examiner (H.K.) once every 1 to 3 months for 3 years. During the 3 years of follow-up, we excluded patients who showed evidence of epilepsy, stroke, or transient ischemic attacks, patients who were admitted to the hospital because of physical problems such as cardiac failure or pulmonary infection, and patients who had undergone surgical intervention. In addition, we excluded two patients who could not continue our examinations after 3 years. The study was discontinued in 22 patients (death in 2 patients and hospitalization due to physical problems in 9). A total of 24 patients were excluded, and the remaining 55 patients were included in data analysis.

Statistical analysis

The 55 patients were divided to two groups: patients with a decline in cognitive function (n = 29) and those without a decline in cognitive function (n = 26) after 3 years. A decline in cognitive function was defined as a decrease in the MMSE score after 3 years. Variables with a normal distribution are presented as the means ± standard deviation (SD), and variables that were not normally distributed were transformed to natural logarithms or categorical quartile groups. Differences in variables between patients with and those without a decline in cognitive function were evaluated by the Mann-Whitney test. A total of 17 variables were evaluated (**Table 1**). The variables were categorized as follows: (1) age, (2) gender (male = 1), (3) log-transformed disease duration, (4) total levodopa equivalent dose at study entry, (5) daily levodopa dose at study entry, (6) increase in total levodopa equivalent dose (absent = 0, present = 1), (7) increase in daily levodopa dose (absent = 0, present = 1), (8) Hoehn-Yahr stage at study entry, (9) development of Hoehn-Yahr stage

Table 1. Basic characteristics of patients with and without a decline in cognitive function

Variables	Total n = 55	Without cognitive impairments n = 29	With cognitive impairments n = 26	p
Age*, mean	69.4, 7.9	68.7, 9.4	70.2, 5.9	0.729
Male, n	24, 43	12, 41	12, 46	0.724
Disease duration*, average (months)	55.8, 40	55.7, 37	55.9, 43	
Log-transformed, mean	3.70, 0.88	3.74, 0.83	3.65, 0.94	0.555
Total levodopa equivalent dose*, average (mg/day)	325.1, 335.5	319.7, 209.2	331.3, 333.3	
IQR	335.5 (250, 400)	335.5 (200, 367)	333.3 (250, 450)	0.59
Total levodopa equivalent dose 3 years later, average (mg/day)	605.9, 570.0	610.5, 613.3	600.9, 480.0	0.613
Increase in total levodopa equivalent dose, n	50, 90	27, 93	23, 88	0.554
Daily levodopa dose*, mean (mg/day)	212.7, 147.2	201.7, 132.6	225.0, 163.8	0.461
Daily levodopa dose 3 years later, mean (mg/day)	296.3, 155.7	313.7, 176.2	276.9, 129.7	0.649
Increase in dairy levodopa dose, n	28, 50	19, 65	9, 34	0.023**
Hoehn-Yahr stage*, mean	2.8, 0.5	2.7, 0.5	2.8, 0.6	0.314
Hoehn-Yahr stage 3 years later, mean	3.4, 0.8	3.3, 0.9	3.4, 0.8	0.843
Development of Hoehn-Yahr stage, n	24, 43	13, 44	11, 42	0.852
UPDRS part III*, mean	24.3, 11.2	21.8, 9.8	27.1, 12.1	0.048**
Increased score on UPDRS part IV*, n	29, 52	14, 48	15, 57	0.489
Increased score on UPDRS part IV 3 years later, n	26, 47	12, 41	14, 53	0.36
MMSE*, average	27.9, 28.2	27.8, 28.2	28.0, 28.2	0.803
MMSE 3 years later, average	27.3, 28.0	28.5, 28.8	25.9, 26.5	P < 0.001
SDS score*, mean	44.2, 8.2	43.7, 7.2	44.8, 9.4	0.679
SDS score 3 years later, mean	44.4, 8.2	44.3, 8.1	44.6, 8.5	0.953
Increased SDS score 3 years later, n	29, 52	17, 58	12, 46	0.36
Sum score of PDSS*, average	430.2, 405.0	393.9, 395.0	470.6, 454.0	
Log-transformed, mean	5.87, 0.66	5.78, 0.67	5.96, 0.63	0.345
Sum score of PDSS 3 years later, average	549.9, 477	571.5, 555	525.9, 403.5	0.191
Increased total PDSS score 3 years later, n	43, 78	23, 79	20, 76	0.927
History of hallucinations*, n	6, 10	4, 13	2, 7	0.473

UPDRS: Unified Parkinson's Disease Rating Scale, PDSS: Parkinson's Disease Sleep Scale, SDS: Zung Self-Rating Depression Scale, MMSE: Mini-Mental Status Examination *at study entry, **P < 0.05, data are reported as mean (SD), median (IQR: interquartile range), number (%) or average (median).

(absent = 0, present = 1), (10) UPDRS part III score, (11) motor complications at study entry (absent = 0, present [defined as an increased score on UPDRS part IV] = 1), (12) motor complications 3 years later (absent = 0, present [defined as an increased score on UPDRS part IV] = 1), (13) SDS score at study entry, (14) increased SDS score 3 years later (absent = 0, present = 1), (15) log-transformed sum score of items on PDSS at study entry (which were rated from the direction of good to bad sleep), (16) increased total PDSS score 3 years later (absent = 0, present = 1), and (17) history of hallucinations (absent = 0, present = 1). We assessed variables related to the decline in cognitive function on univariate logistic regression analysis. Correlations of each variable were also evaluated by Spearman's rank correlation test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. *P* values of less than 0.05 were considered to indicate statistical significance. SPSS software for Macintosh (Version 18, IBM SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

As shown in **Figure 2**, the increase in the daily dose of levodopa was greater in patients without a decline in cognitive function than those with a decline in cognitive function; on the other hand, the cognitive function was unchanged in patients without cognitive impairment (**Table 1**). The increase in the daily levodopa dose was related to the decline in cognitive function on univariate logistic regression analysis (OR = 0.279, P = 0.024, 95% CI = 0.092-0.848) (**Table 2**). Other variables, including the total levodopa equivalent dose at study entry, the daily levodopa dose at study entry, and the increase in the total levodopa equivalent dose, were not related to the decline in cognitive function. There were no significant interactions among the study variables.

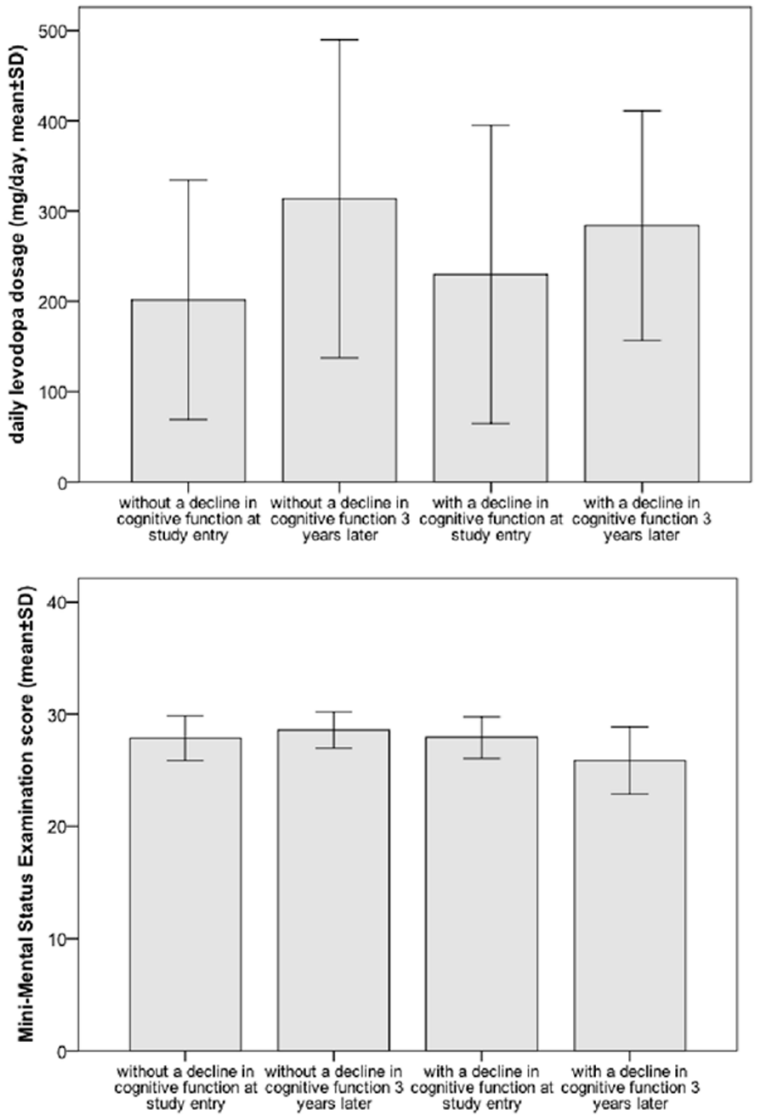

Figure 2. Daily levodopa dosage or Mini-Mental Status Examination (MMSE) between patients with a decline in cognitive function and those without a decline in cognitive function after 3 years. In patients with a decline in cognitive function at the study entry, the score for MMSE was decreased. On the other hand, the cognitive function unchanged in patients without a decline in cognitive function at the study entry. The increase in the daily dose of levodopa was greater in patients without a decline in cognitive function than those with a decline in cognitive function.

Discussion

The present study suggests that levodopa might prevent a decline in cognitive function in non-demented patients with PD. This finding is consistent with the results of previous studies providing evidence that levodopa has a positive effect on cognitive impairment [12-16]. Levodopa improved the neuropsychiatric scores for verbal attention and memory deterioration in patients with PD who had or did not have dementia [12]. Learning performance was improved in association with learning-related activation responses in the occipital association cortex on PET imaging in non-demented patients with PD [13]. Levodopa ameliorates cognitive deficits in PD with blood flow changes in the right dorsolateral prefrontal cortex [14]. Chronic dopaminergic replacement therapy with levodopa is associated with significant cognitive improvements in learning and long-term verbal and visual memory, visuospatial abilities, and frontal-lobe functioning [15]. Continuous duodenal infusion of levodopa improved the marked cognitive impairment and increased the MMSE score by three or six points in two patients with PD [16].

Resting-state imaging studies of cerebral function have shown a decrease in resting-state brain connectivity in PD. The default-mode network and frontoparietal networks are thought to be relevant for cognition [17], and disrupted connectivity of the default-mode network was evident in patients with PD who had dementia [18], or reduced connectivity of the frontoparietal networks was associated with mild cognitive impairment [19]. Early disruption of functional connectivity of the default-mode network appeared in patients with PD prior to clinical evidence of cognitive impairment [20]. Recent studies have shown that levodopa improved the deficient connectivity of the sensorimotor network [21] or basal ganglia network [22] in patients with PD. As for cognition, a resting metabolic imaging study showed that levodopa improved verbal learning performance in non-demented patients with PD who

Table 2. Crude Odd's ratio for patients with Parkinson's disease who had a decline in cognitive function

Variables	Odds ratio (95% CI)	P
Age*, mean	1.026 (0.957 to 1.100)	0.473
Male, n	0.824 (0.283 to 2.396)	0.722
Log-transformed disease duration*	0.882 (0.480 to 1.622)	0.687
Total levodopa equivalent dose*	1.211 (0.648 to 2.264)	0.548
Daily levodopa dose*	1.001 (0.997 to 1.005)	0.556
Increase in total levodopa equivalent dose	0.568 (0.087 to 3.698)	0.554
Increase in daily levodopa dose	0.279 (0.092 to 0.848)	0.024**
Hoehn-Yahr stage*	1.475 (0.572 to 3.800)	0.421
Development of Hoehn-Yahr stage	0.903 (0.310 to 2.626)	0.851
UPDRS part III*	1.047 (0.993 to 1.103)	0.088
Increased score on UPDRS part IV*	1.461 (0.503 to 4.241)	0.486
Increased score on UPDRS part IV 3 years later	1.653 (0.568 to 4.809)	0.356
SDS score*	1.016 (0.952 to 1.084)	0.637
Increased SDS score 3 years later	0.605 (0.208 to 1.760)	0.356
Log-transformed sum score of PDSS*	1.532 (0.666 to 3.525)	0.315
Increased total PDSS score 3 years later	1.061 (0.305 to 3.692)	0.926
History of hallucinations*	1.920 (0.321 to 11.470)	0.474

UPDRS: new revised Unified Parkinson's Disease Rating Scale, PDSS: Parkinson's Disease Sleep Scale, SDS: Zung Self-Rating Depression Scale, *at study entry, **P < 0.05.

had baseline elevations in resting PD-related cognitive pattern activity. Moreover, the degree of modulation of resting PD-related cognitive pattern activity paralleled cognitive changes associated with levodopa [23]. Levodopa might modulate the connectivity of these networks and compensate for the decline in cognition influenced by factors such as cortical Lewy body pathology or prolonged off-periods.

The present study had several important limitations. First, cognitive impairment was evaluated by using the MMSE. The Montreal cognitive assessment (MoCA) was reported to be a more sensitive tool than the MMSE for identifying early cognitive impairment in PD [24]. Use of the MoCA might lead to the detection of increased numbers of patients with cognitive impairment. Depression is closely related to cognition, and the present study evaluated depression by means of the SDS. The Hamilton depression score has been frequently used as a tool for evaluating depression [25]. Other limitations in the present study were the small number of subjects at the 3-year follow-up and the lack of repeated examinations using MMSE, SDS, PDSS, or UPDRS at regular intervals between study entry and 3 years later. Regularly performing such examinations might lead to a better understanding of the association between levodopa and cognition.

A positive effect of levodopa on cognition is not always evident in patients with various severities of PD. However, our results suggest that treatment with levodopa can prevent a decline in cognitive function in PD.

Disclosure of conflict of interest

None.

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