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ORIGINAL ARTICLE

The Association between Motor Laterality and Cognitive Impairment in Parkinson's Disease

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Background and Purpose The relationship between the side of motor symptoms and cognitive impairment has rarely been reported in Parkinson's disease (PD). We aimed to estimate the influence of motor laterality on cognition in PD patients.

Methods We enrolled 67 patients with PD, and they were divided into two groups according to side of symptom onset or predominant motor symptom presentation (right and left). Right-sided PD (RPD, 40) and left-sided PD (LPD, 27) patients underwent a neuropsychological battery exploring memory, attention/working memory, frontal/executive, visuospatial, and language functions. Student's *t*-test and Chi-square test have been carried out to compare the clinical and neuropsychological data between two groups.

Results There were no significant differences in any neuropsychological test between the RPD and LPD groups, except for digit forward span test. RPD patients scored lower on the digit forward span test than LPD patients (5.43±9.49 vs. 6.15±1.38, p=0.045).

Conclusions RPD patients seem to experience more difficulties in attention and working memory than did LPD patients. The laterality of motor symptoms is not a major determinant for cognitive impairment in PD patients but, we should consider differences of cognitive deficits depending on the side of motor symptoms to treat patients with PD.

Key Words Parkinson's disease, cognitive impairment, motor asymmetry, laterality, working memory.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia, rigidity, resting tremor, and postural instability.[1] According to the supportive positive feature of PD according to UK brain bank criteria, the symptom of PD starts on one side of the body. In addition, even if the symptoms spread to the other side later, there is a persistent asymmetry affecting the side of onset and asymmetric tendencies are reported to be 47% to 85%.[2,3] There is no study explaining the precise pathophysiology of asymmetric occurrence. However, hypotheses such as an asymmetry of neuronal loss in both sides of the substantia nigra, one-sided weakness of the blood brain barrier of the midbrain, and an asymmetric neuroprotective effect caused by enhanced unilateral physical activity have been suggested as possible pathological theories.[4-7] Our previous study revealed a significant thinning of motor-related cortical areas in the contralateral hemisphere occurs to the symptomatic side only in left-sided PD (LPD) patients.[8] If different cortical thinning areas according to side of symptom dominance and asymmetric dopaminergic depletion are exist, there would presumably be differences in cortical functioning-including cognitive functioning-depending on which side is symptomatic. Our study aimed to investigate whether asymmetric motor laterality could predict specific measures of cognitive functioning.

METHODS

Patients

We recruited early PD patients with right-handed who visited Soonchunghyang University Hospital and Samsung Medical Center from March 2011 to December 2012. Inclusion criteria were: 1) the clinical diagnosis of PD was based on the UK Brain Bank Criteria;[1] 2) a Hoehn and Yahr (H&Y) stage of less than 2.5. Exclusion criteria were the presence of either: 1) secondary or atypical parkinsonism; 2) a serious medical condition such as an infection or malignancy; 3) present or past medication which might influence cognitive functioning within the past 6 months; or 4) severe cognitive impairment as judged by scores on clinical dementia rating (3, 4, 5). We enrolled 78 patients with early PD. Among these patients, Unified Parkinson's Disease Rating Scale (UPDRS) data was not present in the records of 4 patients. Additionally, 7 patients did not have lateralized PD symptoms. Finally, 67 patients were analyzed and divided into two groups in accordance with the side of symptom onset or motor laterality. These groups comprised 40 right-sided PD (RPD) patients and 27 LPD patients. The methods for obtaining information were approved by the Institutional Review Board of the Soonchunhyang University School of Medicine.

Measurements

The patients' motor functions and clinical stages were assessed by UPDRS part III and H&Y score. Motor laterality was defined as follows: 1) side of symptom onset, 2) opposite side of dominantly-decreased dopamine uptake in positron emission tomography using ^{18}F-fluorinated N-3-fluoropropyl-2-beta-carbonethoxy-3-beta-(4-iodophenyl) nortropane, and 3) a conjunctive point of high composite scores summing the individual motor items of UPDRS part III (rigidity, bradykinesia, and tremor). If no differences were found between right and left side scores, we defined the side of symptom onset as motor laterality. The status of overall cognitive functioning was measured using the Korean version of the Montreal Cognitive Assessment (K-MoCA) and the Seoul Neuropsychological Screening Battery (SNSB). The SNSB is composed of five cognitive domains: attention, memory, language, visuospatial function, and frontal/executive function.[9] The scoring of UPDRS part III, H&Y, and cognitive performance were conducted during the 'on' state of PD.

Statistical analysis

Statistical analyses were performed with SPSS 18.0 (IBM, Chicago, IL, USA), and the significance threshold was set at 0.05. The independent *t*-test was used to compare the means of variables and the chi-square test was used to compare the gender ratio.

RESULTS

Demographic and clinical features

The demographic characteristics of each group are described in Table 1. There were no significant differences in terms of age, gender, duration of education, duration of disease, UPDRS-III, and H&Y stage. General cognitive functioning was assessed by Korean version of the Mini-Mental State Examination and K-MoCA-neither of which showed differences between RPD and LPD.

Comparison of neuropsychological procedures between RPD and LPD

The neuropsychological data of each group are presented in Table 2. The digit forward score was lower in subjects with RPD than in those with LPD (5.43±9.49 vs. 6.15±1.38). There were no significant differences in the digit backward test, memory, language, visuospatial function and frontal/executive

Table 1. Demographic and clinical characteristics

Variable	RPD (*n*=40)	LPD (*n*=27)	*p* value
Age (years)	67.78±8.36	64.96±7.87	0.286
Sex (M:F, %)	15:25 (37.5:62.5)	13:14 (48.1:51.9)	0.386
Education (years)	10.53±4.86	9.53±4.83	0.410
Disease duration (years)	7.08±4.54	6.67±3.42	0.692
UPDRS-III	18.03±14.47	17.67±9.84	0.911
K-MMSE (total score)	26.68±3.39	27.27±2.81	0.460
K-MoCA (total score)	23.69±4.46	23.92±4.77	0.847
H&Y stage	2.00±0.43	1.79±0.69	0.299

Data are mean±standard deviation or *n* (%) values.
F: female, H&Y: Hoehn and Yahr Stage, K-MMSE: Korean version of the Mini-Mental State Examination, K-MoCA: Korean version of the Montreal Cognitive Assessment, LPD: left-sided Parkinson's disease, M: male, RPD: right-sided Parkinson's disease, UPDRS: Unified Parkinson's Disease Rating Scale.

function between these patient groups.

DISCUSSION

Motor symptoms such as bradykinesia, rigidity, and resting tremor usually have a tendency to develop unilaterally (in one side of the body) in patients with PD. Although the parkinsonism gradually becomes bilateral, the initial side commonly remains more affected than does the side involved later on in the progression of the disease–and this distinction is called laterality.[10] The each cerebral hemisphere has its own distinct functions. For instance, the left cerebral hemisphere is dominant in language ability, whereas the right cerebral hemisphere is dominant in visual and spatial ability.[11] Supposing that motor laterality reflects an asymmetric degeneration, the predominant involvement of one-sided hemisphere would affect related cognitive dysfunction according to the lateralized side.

The results of our study showed that only digit span forward was lower in RPD than LPD. Most previous studies revealed no significant differences between LPD and RPD group performance of the digit span test;[12,13] whereas two studies found results similar to ours.[14,15] The 'digit span forward' task has been suggested as being a task of working memory and simple verbal fluency.[16] In RPD, the left hemisphere would presumably be affected more than the right hemisphere would be, given that the cognitive battery weighted on language might be influenced. The digit span forward test was significant, but the *p*-value was close to 0.05. There were no significant differences in the demographic characteristics of each group. However, data including age, duration of disease, UPDRS-III, and H&Y stage were comparatively more likely to affect cognitive impairment in RPD. If the sample size increases, and if the above cofactors are corrected, the digit span forward might not be significant either.

There were a few studies reporting the association between motor laterality and cognitive profiles, and the results varied. Some studies revealed that side of onset does not influence cognition.[17,18] Cooper et al.[19] observed a significant association between RPD and verbal memory, visuospatial function, and verbal fluency; and LPD was not related to any composite cognitive domain. In previous studies, the sample size was too small to generalize from the results; and those studies did not

Table 2. Comparison of neuropsychological tests between the right and left groups

Neuropsychological tests	RPD (*n*=40)	LPD (*n*=27)	*p* value
Memory			
SVLT-immediate	0.06±1.11	-0.34±1.29	0.175
SVLT-delay	-0.26±1.11	-0.74±1.31	0.114
SVLT-recognition	0.08±0.70	0.16±0.90	0.686
Attention/working memory			
DF	5.43±9.49	6.15±1.38	0.045
DB	3.65±1.44	3.48±1.15	0.614
VT	0.90±0.30	0.92±0.26	0.720
Frontal/executive function			
TMT-A	33.80±21.13	32.50±23.92	0.817
TMT-B	60.37±39.79	68.29±59.87	0.533
COWAT-animal	-0.73±1.06	-0.95±0.81	0.365
COWAT-market	-0.36±1.11	-0.49±1.01	0.648
COWAT-ㄱ	-0.69±1.21	-0.29±1.13	0.199
COWAT-ㅇ	-0.46±1.08	-0.36±0.85	0.714
COWAT-ㅅ	-0.49±1.21	-0.48±0.93	0.967
Stroop-word	-0.22±2.57	0.25±1.19	0.382
Stroop-color	-0.89±3.16	-0.43±1.55	0.490
Visuospatial cognition			
CDT	2.63±0.63	2.85±0.46	0.092
Language			
SK-BNT	-0.18±1.46	0.26±1.58	0.262

Data are mean±standard deviation values.
CDT: Clock Drawing Test, COWAT: Controlled Oral Word Association Test, DB: digit backward, DF: digit forward, LPD: left-sided Parkinson's disease, RPD: right-sided Parkinson's disease, SK-BNT: short form of the Korean Boston Naming Test, SVLT: Seoul Verbal Learning Test, TMT: Trail-Making Test, VT: Vigilance Test.

explain the differences in cognitive functioning, depending on the side of hand dominance because the dominant hand was not set.[13] Furthermore, the patients who had severe cognitive impairment in late-stage PD were also included; and neither H&Y stage nor the severity of motor symptoms were considered.[19,20] In order to overcome these limitations, we compared the differences and characteristics of cognitive functioning according to motor laterality in early PD patients (H&Y stage ≤2.5) who were right-handed.

The pathophysiology of the relationship between motor laterality and cognition in PD patients has not been clearly defined. Several studies have claimed that decreased dopamine secretion caused by asymmetric neuronal degeneration in the substantia nigra is related to motor laterality. Neurodegenerative change of the substantia nigra controls the corpus striatum asymmetrically, and it influences circuits-including basal ganglia and the cerebral cortex–which are related to cognitive functions.[4,21] A previous study, which had shown that similar cognitive impairments had been caused by ventral pallidotomy and by prefrontal injury, support the aforementioned hypothesis.[22] Furthermore, relationship between working memory and the prefrontal lobe cortex was reported in a study using positron emission tomography and functional magnetic resonance imaging.[23,24] Additionally, an animal study found that working memory was found to be related to dopamine release into the prefrontal lobe and to the stimulation of the dopamine D1 receptor of the dorsolateral prefrontal lobe. These findings support the hypothesis that cognitive deficits are caused by an interruption of the circuit connecting the basal ganglia and the frontal cortex. Based on these findings, our result implied a greater influence on verbal fluency and working memory in RPD than in LPD.

This study had several limitations. Firstly, the sample size was relatively small, making the results of this study difficult to be generalized. Secondly, clinical data was collected retrospectively, and selection bias could exist. Thirdly, although medication such as an anticholinergic agent could influence cognitive functioning in patients, we did not check precise medications.

In conclusions, our study demonstrated that there were no differences in overall cognitive domains depending on the side of motor laterality. However, RPD patients had significantly lower scores in the digit span forward than did LPD patients. These data implied that patients with RPD had more impaired verbal fluency and working memory than did those with LPD. We need to consider motor function laterality as well as cognitive impairment in the treatment of PD patients. To confirm this, further studies are needed for exploring the possibility that directly-related factors may influence the cognitive functioning of PD patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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