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Gait Patterns in Parkinson's Disease with or without Cognitive Impairment

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background and Purpose: Cognitive and gait disturbance are common symptoms in Parkinson's disease (PD). Although the relationship between cognitive impairment and gait dysfunction in PD has been suggested, specific gait patterns according to cognition are not fully demonstrated yet. Therefore, the aim of this study was to investigate gait patterns in PD patients with or without cognitive impairment.
Methods: We studied 86 patients at an average of 4.8 years after diagnosis of PD. Cognitive impairment was defined as scoring 1.5 standard deviation below age- and education-specific means on the Korean version of the Mini-Mental State Examination (K-MMSE). Three-dimensional gait analysis was conducted for all patients and quantified gait parameters of temporal-spatial data were used. Relationships among cognition, demographic characteristics, clinical features, and gait pattern were evaluated.
Results: Cognitive impairment was observed in 41 (47.7%) patients. Compared to patients without cognitive impairment, patients with cognitive impairment displayed reduced gait speed, step length, and stride length. Among K-MMSE subcategories, "registration," "attention/calculation," and "visuospatial function" were significantly associated with speed, step length, and stride length. However, age, disease duration, Hoehn-Yahr (HY) stage, or Unified Parkinson's Disease Rating Scale (UPDRS) motor score was not significantly related to any gait analysis parameter.
Conclusions: Our present study shows that cognitive impairment is associated with slow and short-stepped gait regardless of HY stage or UPDRS motor score, suggesting that cognitive impairment may serve as a surrogate marker of gait disturbance or fall in PD patients.

Keywords: Gait; Parkinson's Disease; Cognitive Impairment

INTRODUCTION

Parkinson's disease (PD) is mainly characterized as a degenerative disorder of the brain which destroy parts of the brain that control movement. Shuffling gait, impaired balance, and freezing of gait are main motor dysfunctions shown in patients with PD. Postural control and gait dysfunction may occur in early stages of PD. They are characterized by slowing of gait,

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reduced arm swing, shorter step length, postural instability, and loss of disassociated arm and trunk movements during gait.[1,2]

Many patients with PD trend to suffer the risk of falls due to occurrence of gait disturbance and freezing of gait. Prospective studies have reported that 70% of patients with PD have at least one fall in a year and 39% fall recurrently.[3] Consequences of falls include fractures and injury, fear of future falls, hospital admission, and increased caregiver burden. Median survival in patients with recurrent falls is 6 years.[3] Falls are correlated with multiple factors, including postural, gait, and cognitive dysfunctions.

Walking is a complex task in which cognitive resources continuously monitor bilateral coordination and dynamic postural control are both necessary for the walking process, including cognitive motor control.[4] In this context, a systematic review has revealed that there is as direct relationship between cognitive deficit severity and gait abnormalities in patients with dementia.[5] Cognitive impairment in PD typically consists of deficits in attention, executive, and visuospatial functions as well as memory resources.[6] Even in early PD, attention and executive function deficits are features of basal ganglia pathology and necessary to appropriately allocate cognitive resources for optimal performance of simultaneous tasks.[7,8] Since cognitive deficits are correlated with higher fall risk[9] and shorter survival time,[10] it is worth studying if cognitive deficits may be mirrored by gait performance to support clinical routine with quantitative data and early detect risk factors for falls.

In this study, we hypothesized that cognitive deficits might be associated with gait performance in patients with PD. The objective of this study was to find specific cognitive domain associated with gait parameters and investigate gait patterns in PD patients with or without cognitive impairment.

METHODS

Patients

This study retrospectively reviewed medical records of patients with PD who were admitted to our hospital between January 2014 and December 2016. Among 124 potential subjects, 86 patients who met the following inclusion criteria were enrolled. Inclusion criteria were as follows: patients who had a diagnosis of PD according to United Kingdom Parkinson's Disease Brain Bank criteria, the loss of dopaminergic neurons was confirmed on 18F-N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) scan, and those who could perform independent gait for at least 10 m for 3-dimensional (3D) motion analysis (3DMA). Exclusion criteria were as follows: patients with atypical parkinsonism, or those who had coexisting neurological and/or orthopedic disease that could influence gait function. The Institutional Review Board (IRB) at Veterans Health Service Medical Center approved procedures and protocols of this study (approval No. 2016-12-010). The requirement for informed consent was waived due to its retrospective nature.

Clinical and cognitive evaluations

Hoehn-Yahr (HY) staging and Unified Parkinson's Disease Rating Scale (UPDRS) motor domain were used as severity scales of motor symptom. These assessments were administered by a single neurologist immediately before 18F-FP-CIT PET scanning when antiparkinsonian agents had been ceased for at least 6 hours.

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Patient's cognition was assessed by the Korean version of the Mini-Mental State Examination (K-MMSE). Cognitive impairment was defined as K-MMSE scoring more than 1.5 standard deviations below each participant's corresponding age- and education-matched cohort.

Gait analysis

Gait analysis was conducted using an 8 infrared, 60-Hz camera motion analysis system (Motion Analysis Corp., Santa Rosa, CA, USA) and three force plates (sampling rate 1,200 Hz; Kistler Corp., Amherst, NY, USA). Reflective markers were placed on predefined anatomical landmarks of the pelvis, thigh, knee, shank, and foot.[11] Simultaneous recordings of spatiotemporal and lower extremity kinematics and kinetics (foot-floor contact patterns) were obtained as patients walked 6 m barefoot at their self-selected walking speed. Joint kinematics and external moments were calculated with Cortex program (Motion Analysis Corp.). This study used the following specific variables: spatiotemporal domain- cadence (steps/min), walking speed (cm/s), step width (cm), step length (cm), step time (sec), stride length (cm), and stride time (sec) (**Fig. 1**).

Statistical analysis

We analyzed the relationship between cognitive impairment and gait analysis parameters. We also compared demographics, UPDRS motor score, HY stage according to cognitive impairment status. Continuous or numerical variables are expressed as mean (standard deviation) and compared using Student's *t*-test. Categorical variables were analyzed by χ^2 test or Fisher's exact test. Spearman's and Pearson correlation tests were adopted to identify the relationship between K-MMSE and gait analysis parameters. All statistical analyses were performed with SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA). Statistical significance was considered at $p<0.05$.

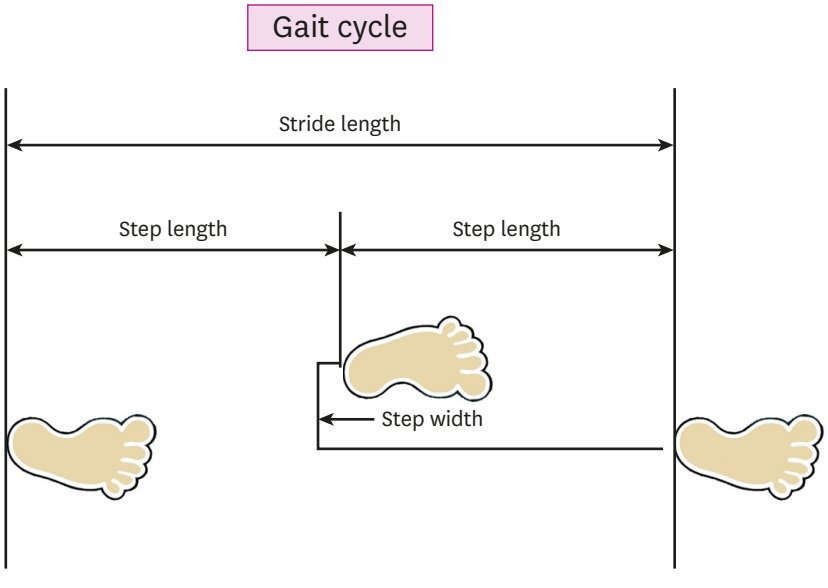

Fig. 1. Spatio-temporal gait parameters.

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RESULTS

Demographic and clinical features of PD patients with or without cognitive impairment

A total of 86 six patients with a mean age (standard deviation) of 70.8 (4.2) years were included in the study. All patients were males because this study was conducted on Vietnam veterans. Their mean education period was 11.0 (3.5) years. Their mean K-MMSE score was 23.6 (5.4). Compared with normative database for K-MMSE developed by Kang,[12] 47.7% of participants were classified as cognitively impaired. Forty-one patients were classified as PD with cognitive impairment while 45 patients were classified as PD without cognitive impairment. The 2 groups did not significantly differ in any demographics or clinical variables, including UPDRS motor score or HY stage (**Table 1**). However, the 2 groups differed significantly in K-MMSE score and all cognitive domains (**Table 2**).

Difference in gait parameters between PD patients with and without cognitive impairment

PD patients with cognitive impairment had shorter step length and stride length than those without cognitive impairment. Gait speed was slower in cognitive impairment group than that without cognitive impairment group, although the difference was not statistically significant between the 2 groups. However, there were no significant differences in cadence, step width, step time, or stride time between the 2 groups (**Table 3**).

Correlations between gait parameters and cognitive domains

Results of correlations between cognitive domain and gait parameters are shown in **Table 4**. Step length (Spearman's r=0.254) and stride length (r=0.239) were significantly associated with K-MMSE total score (p<0.001). Among cognitive domains, registration, attention/calculation, and visuospatial function were positively correlated with step length and stride length. In addition, visuospatial function was significantly associated with speed (r=0.289).

Table 1. Demographic and clinical features of PD CI+ or PD CI−

Characteristics	PD CI+ (n=41)	PD CI− (n=45)	p value
Age (yr)	71.28±4.39	70.36±4.00	0.432
Male	41 (100)	45 (100)	
Height (cm)	163.45±4.30	164.17±6.43	0.465
Education (yr)	11.10±3.34	10.93±3.56	0.925
Disease duration (yr)	4.95±2.71	4.75±2.44	0.684
HY stage	1.71±0.78	1.61±0.66	0.522
UPDRS motor score	18.85±8.52	18.12±7.94	0.469

Data are expressed as number (percent), mean±standard deviation.
PD: Parkinson's disease, PD CI+: PD patients with cognitive impairment, PD CI−: PD patients without cognitive impairment, HY stage: Hoehn-Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2. K-MMSE scores in PD CI+ or PD CI−

Characteristics	PD CI+ (n=41)	PD CI− (n=45)	p value
Total K-MMSE score	19.98±5.53	27.02±1.88	<0.001
Orientation	7.65±2.60	9.60±0.77	<0.001
Registration	2.73±0.64	2.95±0.22	0.028
Attention/calculation	1.53±1.30	3.95±1.13	<0.001
Recall	1.03±0.80	1.93±0.87	<0.001
Language	6.56±1.93	7.76±0.44	<0.001
Visuospatial	0.46±0.51	0.87±0.34	<0.001

K-MMSE: Korean version of the Mini-Mental State Examination, PD: Parkinson's disease, PD CI+: PD patients with cognitive impairment, PD CI−: PD patients without cognitive impairment.

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Table 3. Comparison of gait parameters between PD CI+ or PD CI−

Characteristics	PD CI+ (*n*=41)	PD CI− (*n*=45)	*p* value
Cadence (steps/min)	105.20±13.60	106.10±24.65	0.883
Speed (cm/s)	55.12±29.25	66.94±30.61	0.052
Step width (cm)	15.03±3.37	14.61±2.64	0.566
Step length (cm)	30.44±16.53	38.23±14.66	0.013
Step time (sec)	0.58±0.08	0.60±0.16	0.972
Stride length (cm)	62.78±30.90	74.24±28.04	0.029
Stride time (sec)	1.88±0.73	1.84±0.83	0.162

PD: Parkinson's disease, PD CI+: PD patients with cognitive impairment, PD CI−: PD patients without cognitive impairment.

Table 4. Correlations between gait parameters and cognitive domains

Characteristics	Cadence	Speed	Step width	Step length	Step time	Stride length	Stride time
Total K-MMSE score	−0.040	0.210	0.086	0.254*	0.029	0.239*	−0.058
Orientation	−0.098	0.091	0.058	0.100	0.088	0.118	0.090
Registration	−0.096	0.135	−0.014	0.218*	0.095	0.183	−0.012
Attention/calculation	−0.095	0.210	0.159	0.265*	0.083	0.252*	−0.096
Recall	0.038	0.064	0.053	0.050	−0.044	0.036	−0.015
Language	0.079	0.127	0.003	0.160	−0.079	0.109	−0.048
Visuospatial function	−0.018	0.289†	0.102	0.310†	0.011	0.326†	−0.087

K-MMSE: Korean version of the Mini-Mental State Examination.
*p<0.05; †p<0.01.

DISCUSSION

In the present study, we demonstrated that cognitive impairment in PD patients was associated with slow and short-stepped gait. Among specific cognitive domains, deficits in global cognitive function, registration, attention/calculation, and visuospatial function were associated with shorter step and stride length and slower gait speed. These results are in agreement with those of previous studies showing that executive functions, attention, visuospatial abilities, and memory are associated with gait impairment in PD.[4,8,13-15] This study has some advantages over previous ones by using 3DMA system, considering various clinical variables, and using K-MMSE in routine practice to reflect real clinical situation.

It has long been recognized that postural instability/gait disturbance (PIGD) phenotype is associated with cognitive impairment in PD. Compared to those with tremor-dominant phenotype, patients with PIGD-dominant phenotype have greater impairment on measures of global cognition,[16] higher frequency of PD-mild cognitive impairment (MCI),[17] and increased risk for developing dementia.[18] However, the relationship between specific cognitive domains and PIGD symptoms is not well characterized. Various associations between PIGD symptoms and visuospatial function[19] or language[17] have been reported. Associations between specific cognitive domains and PIGD symptoms could implicate distinct neural pathways underlying cognitive dysfunction and PIGD symptoms in PD. Moreover, PIGD symptoms respond poorly to dopaminergic treatment. This may reflect the involvement of neurotransmitters systems other than dopamine.[20,21] Several studies have assessed effect of levodopa on locomotion components of PD with relatively inconsistent results, suggesting that several factors might play a role in PD.[22,23]

Postural control requires integration of various systems, including visual, somatosensory, and vestibular systems. It is also essential to adapt to continuous environmental changes.[24] However, postural control may be disrupted by concurrent cognitive performance or another motor task.[25] Dysfunction in specific gait variables has been associated with an increased risk of cognitive decline and Alzheimer's disease.[26] Furthermore, in a large

community-based cohort, gait dysfunctions are found to be frequent in older adults diagnosed with MCI.[27]

In a study on PD patients, those with PD-MCI in different domains have been reported to display higher postural instability and gait disorder subscale scores than cognitively normal patients.[27] Cognitive impairment often manifests initially as executive dysfunction. It affects both integration of sensory information and motor planning required for maintaining balance, especially in dynamic activities such as walking.[28] Previous studies have pointed out that both attention and executive functions play crucial role in gait control of PD patients.[28] Freezing of gait is also associated with executive dysfunction and worse progression of cognitive impairment in PD patients. Attention deficits can lead to major changes in gait variability and stability.[29] When PD patients accomplish a predetermined combined gait task, they are more likely to reduce walking speed and stride length and exhibit more freezing episodes compared to performing single tasks. Single tasks are controlled by the basal ganglia that are affected in PD. Dual tasks activate the frontal brain area and require voluntary and conscious control.[30]

Recently, it has been reported that visuospatial dysfunction is more related to gait disturbance than attention and executive function. Some studies have evaluated the effect of space perception on gait in PD patients and shown that visuospatial ability is more greatly affected in PD patients with freezing of gait than that in those without freezing of gait.[31,32] PIGD are associated with visuospatial functions in newly diagnosed PD patients.[19] Therefore, when assessing gait and balance impairments, physicians should also evaluate cognitive state including executive and visuospatial functions. Detection of cognitive and gait disturbances in PD patients may improve their quality of life and reduce their risk of falls by earlier intervention and adequate therapeutic strategies.

To compensate for the reduced gait stability, patients with PD need additional attentional cognitive resource.[33] Different strategies have been trialed to reduce fall risk in PD. Although consensus-based recommendations to reduce fall risk were published in 2014, they had a small evidence base.[34] It has been shown that acetylcholinesterase inhibitor treatment with donepezil can reduce fall frequency in a cross-over trial of 23 patients,[35] supporting the potential role of acetylcholinesterase inhibitors in decreasing falls in PD. In a recent phase 2 trial, rivastigmine improved gait stability. It might reduce the frequency of falls.[36] However, there was no improvement in cognitive or executive function. Therefore, the benefit of acetylcholinesterase inhibitor on falls might not be mediated via improved cognition, specifically improved attention to compensate for impaired gait resulting from striatal dopaminergic loss or via a direct effect on gait.[37] Future trials are needed to determine how falls are related to cholinergic and attention function. In our study, we did not investigate difference in gait pattern according to acetylcholinesterase inhibitor administration. We only evaluated gait pattern according to the presence or absence of cognitive decline. Further study is needed to evaluate the difference in gait pattern according to the administration of acetylcholinesterase inhibitor in patients with cognitive impairment.

Our study has several limitations. First, we used K-MMSE to assess cognitive function. Because K-MMSE has limitations in evaluating frontal lobe and right hemisphere functions, Montreal Cognitive Assessment (MoCA) is a widely used in clinical routine. It is an internationally accepted scale to evaluate the cognitive status of PD.[38] Therefore, it is necessary to conduct follow-up studies in detail by MoCA or detailed neuropsychiatric test.

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However, our study findings have significant clinical implications because we can predict gait with K-MMSE that can be easily implemented in routine clinical practice. Second, because of its retrospective design, we could not identify drug on and off states. Although gait analysis was performed at least 6 hours after drug discontinuation, it could be biased by individual and pharmacological factors. Finally, patients with relatively low HY stages were included in this study because they were patients with low risk of falls due to safety concerns. Therefore, we could not evaluate the cognitive domain to predict fall. Further studies are needed to elucidate relationship between fall and cognitive domains.

In conclusion, our data demonstrate that PD patients have cognitive impairment documented by K-MMSE with slow and shot stepped gait. This suggests that cognitive decline may serve as a good surrogate marker of gait disturbance or fall in PD patients.

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