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Recuperation of slow walking in *de novo* Parkinson's disease is more closely associated with increased cadence, rather than with expanded stride length

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ABSTRACT

Introduction: Gait characteristics in the early stages of Parkinson's disease (PD) have been less investigated so far. Moreover, the levodopa effect on gait in early PD remains to be further elucidated. We prospectively designed the study to examine gait dynamics and effect of dopaminergic treatment in patients with de novo PD.
Methods: Spatiotemporal parameters were measured in healthy controls and drug naïve patients with PD, using computerized analysis with GAITRite system during usual gait. In PD group, motor symptoms and gait parameters were examined in both drug naive and levodopa 100 mg trial conditions.
Results: Twenty four de novo PD patients and 27 healthy controls (matched for age, sex, and height) were selected for the study. Compared with the controls, patients with de novo PD showed the decrease in stride length, in both Med-OFF and Med-ON conditions. Notably, drug naïve patients with PD demonstrated slow walking velocity, whereas those with levodopa administration exhibited the increase of cadence by shortening stride time, which resulted in the improvement of gait speed. In addition, the stride length (gait hypokinesia) correlated with postural instability and gait difficulty subscore, but not with tremor, rigidity, bradykinesia, or total motor score.
Conclusion: As a compensatory mechanism of slow walking, we found that the increment in cadence (frequency) is more important than the increment in stride length (amplitude) in gait dynamics in de novo PD. Additionally, the results may indicate that gait hypokinesia in PD could be regarded as one of axial symptoms.

1. Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder affecting various nervous systems including the striatonigral dopaminergic circuit. Clinically, early stages of the disease are characterized by asymmetric parkinsonism in limbs on one side of the body followed by parkinsonism in contralateral limbs. In contrast with limb motor symptoms, gait abnormalities and postural instability develop in the relatively late stages of PD. Consecutively, a majority of gait studies have focused on advanced stages of the disorder. The characteristic features of gait dynamics in patients with PD consist of slow speed, short step, narrow base, and increased gait variability [1]. As PD progresses, freezing of gait could also occur [2]. Freezing of gait and gait variability have been shown to be related to falls in patients with advanced PD [3,4].

Gait characteristics in the early stages of PD remain relatively little known. One study reported patients with early PD showed no alteration in gait parameters under usual walking condition [5]. In contrast, others reported that even patients with de novo PD could present with significant alterations of most spatiotemporal gait parameters including speed, stride length, swing time, and cadence under usual gait conditions [6,7]. Gait changes in de novo PD have not yielded a uniform consensus yet, therefore a detailed analysis of drug naïve PD patients needs to be conducted. Moreover, to our knowledge, the precise effect of levodopa on gait dynamics in de novo PD patients remains uncertain.

The present study therefore aimed to (1) characterize gait patterns in patients with de novo PD, (2) investigate compensatory mechanisms seen in gait dynamics during levodopa administration and identify levodopa-responsive gait parameters, and (3) uncover the correlation between motor symptoms and gait hypokinesia. We hypothesized that certain gait parameters in de novo PD would be responsive to levodopa and associated with limb motor symptoms. However, intriguingly, the results did not fully support our hypothesis, although gait impairment in de novo PD was improved by levodopa administration.

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2. Methods

2.1. Subjects

This study utilized a prospective design and was approved by the Institutional Review Board of the Korea University Guro Hospital. Patients with de novo PD and healthy participants were selected at a Parkinson's disease center in Korea University Guro Hospital between August 2014 and February 2015. Written informed consent was obtained from all participants. Clinical PD diagnosis was made according to the criteria outlined in Diagnostic Criteria for PD by Gelb DJ et al. [8]. The inclusion criteria for PD participants were as follows: 1) newly diagnosed and drug naïve PD, 2) disease duration less than 5 years and 3) elders between 50 and 75 years. Healthy volunteers were selected in accordance with both age and sex. Anyone exhibiting gait difficulty associated with musculoskeletal problems, previous stroke or headache trauma, coexisting vestibulopathy, or significantly impaired cognition was excluded from the study. In addition, after performing the gait study, patients with clinically poor levodopa responsiveness or motor symptom improvement less than 20% [9] were also excluded from the analysis to rule out the possibility of atypical parkinsonism.

Initially, thirty patients with de novo PD and 30 healthy volunteers participated in the study after providing informed consent. However, 6 of 30 PD patients were excluded: two patients with de novo PD due to disease duration > 5 years, 3 due to unclear diagnosis, and 1 due to unclear or poor levodopa responsiveness. Meanwhile, 3 of 30 healthy controls were excluded: one subject due to vestibular problems and 2 due to musculoskeletal problems. Finally, gait data from 24 patients with PD and 27 controls were analyzed. Using the protocol proposed by Jankovic et al. [10], PD subjects were classified into tremor dominant (TD), postural instability and gait difficulty (PIGD), and intermediate subtypes. Briefly, subjects were classified into TD when the ratio of mean tremor score/mean PIGD score was ≥1.5, into PIGD when the ratio was ≤1 and those between 1.0 and 1.5 were classified into the intermediate group. When analyzing gait data in post-hoc studies, the subtypes were divided into two groups; TD vs. non-TD groups (intermediate and PIGD subtypes).

2.2. Clinical assessments including gait analysis

The Korean version of the Montreal Cognitive Assessment (MoCA-K), height, and weight were evaluated in all participants. All participants performed the Timed Up and Go (TUG) test (walking 3 m). Before gait analysis for patients with PD, all subjects were assessed by one neurologist (K-Y.K) in accordance with the United Parkinson's Disease Rating Scale (UPDRS) Part II and Part III at baseline. In addition, before the Med-ON phase gait analysis, the same investigator (K-Y.K) re-evaluated each patient with the UPDRS Part III. PD participants were also assessed with the TUG test for the Med-ON phase.

To assess spatial and temporal parameters of gait dynamics, the GAITRite system (CIR System Inc, USA) with a 4.6-m-long walkway mat was used. Participants were asked to walk in three conditions randomly (i.e., forward gait at usual speed, backward gait, and serial seven gait) to minimize learning behavior in the experimental setting. Each gait condition consisted of walking 10 times and/or calculating average data of spatiotemporal parameters. In the current study, we analyzed gait parameters only for forward gait to investigate the primary goal. Subjects started to walk two steps before walking the mat and stopped two steps after walking the mat to minimize the acceleration/deceleration effects of initiation/termination in usual gait. PD patients underwent additional gait analysis in three different conditions randomly 1 h after taking carbidopa/levodopa at a concentration of 25/100 mg successively as the "Med-ON" phase. We analyzed only usual forward gait data averaged from ten walks, as described previously.

Basic gait parameters are listed as follows; velocity (cm/s), cadence (steps/min), stride time (s), stride length (cm), swing phase (%), double support time (s), and step width (cm). Each parameter was calculated on the basis of the left foot; since we focused on stride-to-stride gait dynamics rather than step-to-step characteristics with respect to the gait cycle, and accordingly, the site of the standard foot would not significantly influence the main outcomes. The coefficient of variation (CV) for each gait parameter was calculated as 100 × standard deviation/mean. In addition, we assessed gait asymmetry index; gait asymmetry was defined as 100 ÷ ln (SSWT/LSWT) (SSWT = short swing time; LSWT = long swing time) and gait CV asymmetry was 100/ln (SSWCV/LSWCV) (SSWCV = short swing time CV; LSWCV = long swing time CV) [11].

2.3. Statistical analyses

The Student's *t*-test was used to compare control and PD groups, and the paired *t*-test was applied to compare Med OFF and ON phases in the PD group. Analysis of variance (ANOVA) was used to compare three groups. Correlation analyses using Spearman's rho were conducted for stride length and motor scores in the PD group. A P value < 0.05 was defined as statistically significant. Statistical analyses were performed using SPSS version 20.0 (Chicago, IL).

3. Results

3.1. Participant demographic and clinical characteristics

Clinical demographics and characteristics of participants are summarized in Table 1. PD subjects and healthy volunteers were similar in regards to baseline characteristics. 14 (58.3%) out of 24 patients with de novo PD were classified into the TD subtype, 2 (8.3%) into the intermediate subtype, and 8 (33.3%) into the PIGD subtype.

3.2. Gait features of de novo PD: drug naïve state and levodopa effects

Spatiotemporal gait parameters for healthy controls and patients with de novo PD in both the Med-OFF/ON phases are displayed in Table 2 and Fig. 1. Compared to controls, patients with de novo PD in

Table 1
Demographic and clinical characteristics in patients with de novo Parkinson's disease and healthy subjects.

	De novo PD (n = 24)	Healthy controls (n = 27)	P-value
Male, n (%)	15 (62.5)	16 (59.3)	0.813
Age (years)	63.9 ± 6.3	61.4 ± 6.7	0.168
Height (cm)	163.04 ± 7.85	164.00 ± 8.04	0.669
Weight (kg)	61.1 ± 8.9	61.2 ± 9.2	0.975
Body mass index	22.91 ± 2.37	22.64 ± 2.15	0.663
Education of years	10.5 ± 4.9	10.5 ± 5.0	0.966
MoCA-K	25.0 ± 2.8	24.7 ± 4.6	0.785
Fear of fall questionnaire	4.54 ± 4.18	1.67 ± 1.62	0.002
Disease duration (years)	1.13 ± 1.45		
UPDRS Part 2	5.46 ± 4.11		
UPDRS Part 3, drug naïve	17.13 ± 6.40		
UPDRS Part 3, levodopa trial	11.08 ± 4.94		
Hoehn & Yahr stage	1.88 ± 0.40		
PD subtypes, n			
TD	14 (58.3%)		
Intermediate	2 (8.3%)		
PIGD	8 (33.3%)		

Data are represented as mean ± S.D.
MoCA-K, Korean version of Montreal Cognitive Assessment; PD, Parkinson's disease; UPDRS, United Parkinson' disease rating scale; TD, tremor-dominant; PIGD, postural instability and gait difficulty.