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파킨슨병 환자에서 보행동결과 인지기능의 연관성

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Freezing of Gait and Cognitive Functions in Patients with Parkinson's Disease

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Background: Freezing of gait (FOG) in Parkinson's disease (PD) is a unique motor symptom, representing the breakdown of essential components of gait. We aimed to study the correlation between FOG and cognitive functions, particularly focusing on frontal and parietal functions, in patients with PD. **Methods:** We prospectively studied 25 patients with PD, including 15 PD patients with freezing (PDF) and 10 PD patients without freezing (PDNF). Gait analysis was performed with 3-dimensional gait analysis system that includes six cameras. The frequency of freezing episodes per one cycle, total step numbers per one cycle, and total time of one gait cycle were evaluated. All patients were evaluated with K-MMSE, Montreal Cognitive Assessment-Korean (MoCA-K), and Rey Complex Figure Test (RCFT). **Results:** In PDF, there was significant improvement in total step number, total time, gait velocity, cadence, and stride length after using visual cue. For auditory cue, in PDF, there was significant improvement in total step number, total time, freezing number, and cadence. FOG in PD was associated with some aspects of frontal dysfunction. However, there was no significant correlation between gait features and other cognitive tests, including total scores of K-MMSE, MoCA-K, and RCFT, in both PDF and PDNF. **Conclusions:** FOG in PD was significantly improved by external cues. FOG in PD was associated with some aspects of frontal dysfunction, which warrants for further investigations in detail.

Key Words: *Freezing of gait, Parkinson's disease, Cognitive function, Gait analysis*

INTRODUCTION

Freezing of gait (FOG) is a unique and disabling gait disturbance that frequently occurs in association with Parkinson's disease (PD). FOG is defined as a sudden transient break, or motor block, in walking motion [1]. FOG is considered a distinct clinical feature in PD, independent of akinesia [2], and it is experienced by around half of patient with PD. FOG in PD is characterized by a difficulty in stepping forward, which appears either in the initiation of or during gait, with the inability to lift the foot from the floor and trembling of the legs. PD patients describe this phenomenon as having their feet "glued" or "magnetized" to the floor. In PD, it generally occurs as a relatively late manifestation and occurs during "off" or "on" state with the latter being unresponsive to dopaminergic therapy [2, 3]. The most common forms of freezing are seen with initiating gait and with turning. Freezing may also be caused by the presence of a visible obstacle in the path, a change in pattern of design on the floor, walking in narrow spaces or crowds, or when they are approaching their destination.

Although the pathogenic mechanism of FOG still remains unclear, the primary underlying dysfunction may be related to the inability to execute a programmed complex motor act

in response to an established plan of action [4]. It has been suggested that FOG results from frontal malfunction or a disconnection between the frontal lobe and basal ganglia (BG) [5, 6], and FOG has been significantly correlated with executive dysfunction [7]. Clinically, the occurrence of FOG can be seen as an attention problem and dysfunction of posterior parietal regions that are involved in the integration of proprioceptive sensory information. It appears that a frontal-BG-parietal network functions as a motor control system based on proprioceptive, visual, and attentional information. However, little is known about their clear role in the pathophysiology of FOG in PD.

It is a unique feature that FOG can be dramatically improved by external cues, such as visual, auditory, or verbal stimuli. In addition, FOG may be improved or aggravated by intrinsic and extrinsic situations.

In the present study, we studied the characteristics of FOG in PD patients and their association with cognitive function, especially focusing on the frontal and parietal domains.

MATERIALS AND METHODS

1. Patients

We prospectively studied 25 patients with PD who visited the Center for Parkinsonism and Other Movement Disorders at Asan Medical Center between December 2007 and May 2008. The diagnosis of PD was based on the diagnostic criteria of United Kingdom Parkinson's Disease Society Brain Bank [8]. Patients with history of encephalitis, oculomotor dysfunction, pyramidal tract signs, cognitive impairment (Korean-Mini Mental State Examination, K-MMSE <24) and cerebellar dysfunction were excluded. Those with symptoms suggestive of secondary parkinsonism, psychiatric disorders, or severe systemic illnesses were also excluded. The patients whose brain magnetic resonance imaging (MRI) showed a focal atrophy or any abnormal signal changes were excluded. All patients gave informed consent to participate in this study, which was approved by the Ethics Committee of our institute.

The presence of FOG was based on the history, FOG questionnaire [9], and Unified Parkinson's Disease Rating Scale (UPDRS) part II [10]. There were 15 PD patients with freezing (PDF) and 10 without freezing (PDNF). The freezing of gait questionnaire was used by translating the original version [9]. PD patients and their caregivers were directly interviewed. The parkinsonian motor features was evaluated using UPDRS part III and Hoehn & Yahr (H & Y) stage [11]. Axial subscore of UPDRS was defined as the sum of following UPDRS III items: speech, rising from chair, posture, postural instability, and gait [12]. Levodopa equivalent dose (LED) was calculated as follows; Levodopa equivalent dose=(standard levodopa dose × 1)+(slow release levodopa × 0.75)+(bromocriptine × 10)+(ropinirole × 20)+(pergolide × 100)+(pramipexole × 100), if entacapone was used, standard Levodopa dose+(slow release Levodopa × 0.75) [13].

2. Gait analysis

Gait analysis was performed with 3-dimensional gait analysis system that includes six cameras by two specialists in the department of rehabilitation. A research nurse was standing by the patient throughout the gait analysis in order to prevent the patient from falling. A neurologist and clinical specialist nurse measured the frequency of freezing episodes per one cycle, total step numbers per one cycle, and total time of one gait cycle. Video recording was done in all patients to evaluate other gait features. Before gait analysis, physical examination of the pelvis and legs was performed and retroreflective markers were attached to the areas of anterior superior iliac spines, lateral aspect of the thigh and shank, knee joint axis, lateral malleolus, heel, forefoot, and sacrum. Height and weight were also measured.

Patients were instructed to complete cycle of gait analysis three times. One gait cycle was defined as a to-and-fro walk between two points 7 meters apart. After baseline evaluation of gait features, visual and auditory cues were given. White stripes that were 50 centimeters high and 10 centimeters wide were used for visual cue (Fig. 1A). A metronome was used for the auditory cue (Fig. 1B). Visual and auditory cues were flexibly applied to each patient according to the baseline charac-

teristics of stride and cadence. We analyzed spatiotemporal and kinematic data of gait. Kinematic data was collected from sagittal, coronal, and transverse axes. The parameters were velocity, stride, and cadence with one limb and two limbs.

3. Cognitive tests

All patients were evaluated with K-MMSE [14], Montreal Cognitive Assessment-Korean (MoCA-K) [15], and Rey Complex Figure Test (RCFT) [16]. We defined "frontal score" in MoCA-K test as the sum of Trail Making B task (1 point), a clock-drawing task (3 points), digits forward and backward (1 point each), a sustained attention task (target detection using tapping, 1 point), verbal fluency task (1 point), and two-item verbal abstraction task (2 points). We used RCFT for the assessment of visuospatial function.

4. Statistical analysis

The Mann-Whitney U test was used to compare non-parametric continuous variables, such as age, height, weight, education level, K-MMSE score, MoCA-K score, H&Y stage, UPDRS score, RCFT score, levodopa dose, LED, axial subscore, score of gait questionnaire, and score of freezing questionnaire. Contingency tables were analyzed using the chi-square test. Spearman's correlation coefficient was used for comparison of the gait parameters (freezing and gait questionnaire scores, freezing number, total step time, total gait time, gait velocity, cadence, stride length) with cognitive test scores (K-MMSE, MoCA-K, frontal score of MoCA-K, RCFT). Wilcoxon signed rank test was used for the evaluation of differences between gait features with and without external cues.

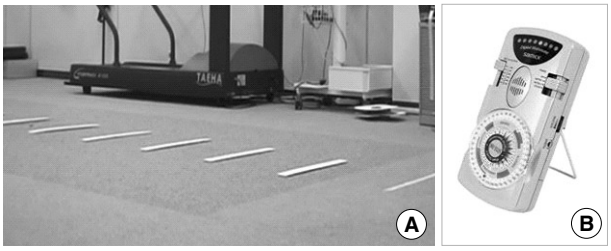

Fig. 1. Visual cue (A) and auditory cue with metronome (B) were used in gait analyses.

SPSS for Windows (version 12.0, SPSS Inc.) was used for all statistical analyses and p values <0.05 were regarded as statistically significant.

RESULTS

The demographic and clinical characteristics are summarized in Table 1. There were no significant differences in sex, height, weight, education, disease duration, and UPDRS III score between PDF and PDNF. The H&Y stage, UPDRS II score, axial subscore of UPDRS III were higher in PDF than in PDNF.

1. Gait analysis

The characteristics of gait features are described in Table 2. On gait analysis at baseline and with auditory cue, there were significant differences in total step number, total time, gait velocity, freezing number, and stride length between PDF and PDNF. On gait analysis with visual cue, only freezing number was different between the two groups. In PDF, there was

Table 1. Demographic data of Parkinson's disease patients with and without freezing

	PDF (n=15)	PDNF (n=10)	p value
Sex (M/F)	12/3	4/6	0.378
Age	69.13±8.09	63.20±7.59	0.037
Disease duration	7.57±3.41	5.00±4.10	0.083
H&Y stage	2.33±0.49	1.60±0.52	0.003
UPDRS II	12.64±4.41	6.20±3.85	0.005
UPDRS freezing	2.36±1.15	0.00±0.00	<0.001
UPDRS III	19.07±8.17	17.70±8.91	0.638
Axial score	4.57±2.03	1.40±0.97	<0.001
Education	10.00±5.42	10.20±3.79	0.668
K-MMSE	26.60±1.92	28.11±1.76	0.067
MoCA-K	22.27±3.56	22.70±3.74	0.696
Levodopa dose (mg)	946.67±281.87	470.00±255.17	<0.001
LED (mg)	1,093.80±294.52	526.40±277.03	<0.001
Gait questionnaire	29.93±3.34	3.70±3.34	<0.001
Freezing questionnaire	13.20±5.75	2.20±1.87	<0.001
Height (cm)	163.16±5.73	161.60±5.83	0.522
Weight (kg)	61.97±7.87	62.79±10.58	0.912

M/F, male/female; PDF, Parkinson's disease patients with freezing; PDNF, Parkinson's disease patients without freezing; UPDRS, Unified Parkinson's Disease Rating Scale; H & Y stage, Hoehn & Yahr stage; LED, Levodopa equivalent dose; K-MMSE, Korean-Mini Mental State Examination; MoCA-K, Montreal-cognitive assessment-Korean.

significant improvement in total step number, total time, gait velocity, cadence, and stride length before and after using visual cue (Fig. 2). For auditory cue, in PDF, there was significant improvement in total step number, total time, freezing number, and cadence (Fig. 2). In PDNF, total time, gait velocity, and cadence were significantly improved by visual cue and only cadence was improved by auditory cue.

Table 2. Summary of gait analyses in patients with Parkinson's disease

	PDF (n=15)	PDNF (n=10)	*p* value
Total step number (baseline)	71.58±58.71	26.60±1.96	<0.001
Total step number (visual cue)	29.81±4.73	26.70±1.42	0.132
Total step number (auditory cue)	56.25±41.01	25.10±2.96	0.001
Total time (baseline)	56.70±59.47	13.85±1.86	<0.001
Total time (visual cue)	23.04±16.07	15.40±2.27	0.063
Total time (auditory cue)	36.83±35.33	14.70±1.89	0.004
Gait velocity (baseline)	65.36±28.04	101.51±12.08	0.005
Gait velocity (visual cue)	82.38±23.04	93.93±11.92	0.114
Gait velocity (auditory cue)	66.87±26.75	99.61±11.57	0.003
Freezing number (baseline)	9.00±17.75	0.00±0.00	0.005
Freezing number (visual cue)	0.75±0.97	0.00±0.00	0.011
Freezing number (auditory cue)	3.92±11.42	0.00±0.00	0.024
Cadence (baseline)	122.45±31.20	112.06±7.88	0.454
Cadence (visual cue)	100.37±25.69	107.97±11.08	0.318
Cadence (auditory cue)	108.67±21.82	106.15±4.17	0.318
Stride length (baseline)	68.55±28.30	109.50±11.48	0.001
Stride length (visual cue)	97.93±14.09	104.75±8.69	0.305
Stride length (auditory cue)	76.35±30.55	111.58±11.45	0.003

PDF, PD patients with freezing; PDNF, PD patients without freezing.

2. Cognitive functions and their relationship with gait features

There was no significant difference in K-MMSE scores, MoCA-K total scores, frontal scores of MoCA-K, RCFT copy scores, RCFT immediate recall scores, and RCFT delayed recall scores between PDF and PDNF. There were no significant correlations between total scores of each cognitive test and gait parameters in PDF ($p>0.05$). In subgroup analysis for PDF, a significant negative correlation was shown between freezing number and the score of cube copying (Spearman's $\rho=-0.689$, $p<0.05$), clock drawing (Spearman's $\rho=-0.605$, $p<0.05$), naming (Spearman's $\rho=-0.630$, $p<0.05$), and repetition (Spearman's $\rho=-0.850$, $p<0.05$). A significant negative

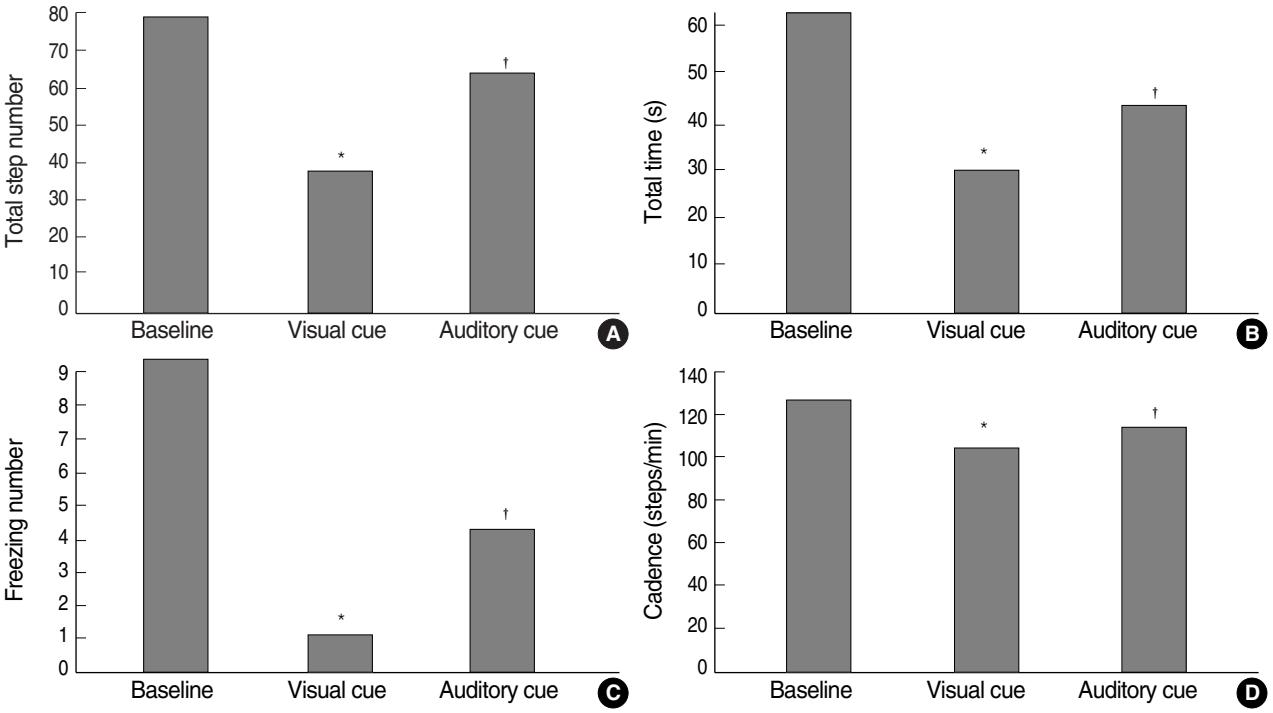

Fig. 2. Gait parameters under three conditions (baseline, visual cue, auditory cue) in patients with FOG (A) Total step number, (B) Total time, (C) Freezing number, (D) Cadence.
*, significant difference from baseline; †, significant difference from baseline.

Table 3. Correlation between gait parameters and cognitive tests in patients with freezing and without freezing

	Negative correlation	Positive correlation
PDF	Cube copying (total time, freezing number)	Cube copying (Cadence)
	Clock drawing (freezing number)	Immediate recall of verbal memory (stride length)
	Naming (freezing number)	Verbal fluency (cadence)
	Immediate recall of verbal memory (cadence)	
	Digit span (cadence)	
	Repetition (total time, total step number, freezing number)	
PDNF	MoCA-K score (total step number)	K-MMSE score
	Trail making test (stride length)	MoCA-K score
	Clock drawing (total time)	Clock drawing
	Immediate of verbal memory (gait and freezing questionnaire)	Immediate recall of verbal memory (stride length)
	Delayed recall of verbal memory (total time)	Delayed recall of verbal memory (gait velocity, cadence)
	Calculation (total step number)	Cued recall of verbal memory (total time)
	Immediate recall of RCFT (stride length)	

PDF, patients with freezing; PDNF, patients without freezing; MoCA-K, Montreal-cognitive assessment-Korean; RCFT, Rey Complex Figure Test; K-MMSE, Korean-mini mental state examination.

correlation was shown between total gait time and the score of cube copying (Spearman's ρ=-0.612, p<0.05), repetition (Spearman's ρ=-0.7686, p<0.05). A significant negative correlation was shown between cadence and the score of immediate recall of verbal memory (Spearman's ρ=-0.676, p<0.05), digit span (Spearman's ρ=-0.718, p<0.05). A significant positive correlation was shown between cadence and the score of cube copying (Spearman's ρ=0.526, p<0.05), and verbal fluency (Spearman's ρ=0.718, p<0.05) (Table 3). In PDNF, there were correlation between a few cognitive tests and gait features (Table 3). A significant positive correlation between cadence and K-MMSE score was demonstrated (Spearman's ρ=0.742, p<0.05). MoCA-K score was negatively correlated with total step number (Spearman's ρ=-0.658, p<0.05) and positively correlated with cadence and stride length (Spearman's ρ=0.640, Spearman's ρ=0.634, respectively with p< 0.05). Trail making test, clock drawing, immediate and delayed and cued recall of verbal memory, calculation, and immediate recall of RCFT was positively or negatively correlated with cadence, stride length, total time, questionnaire scores, total step number (Table 3).

DISCUSSION

In the present study, FOG in PD was associated with some aspects of frontal dysfunction. However, there was no other significant correlation between gait features and other cognitive tests, including total scores of K-MMSE, MoCA-K, and RCFT, in both PDF and PDNF. In accordance with previous studies [17, 18], essential gait features were improved by visual and auditory cues in PDF. These results support the evidence that FOG in PD may be associated with abnormal attention processing and executive dysfunction.

FOG in PD is a very difficult problem to manage pharmacologically [19] and the effects of subthalamic nucleus deep brain stimulation seem to be mainly limited to the off-period freezing [20]. In the present study, the levodopa dose and levodopa equivalent dose were higher in PDF than in PDNF. These results may be related to the clinical practice of maximal levodopa titration in PDF, although the therapeutic response had been poor. FOG may be particularly hazardous, given the close connection between FOG and falling [19]. The researches for elucidating the pathophysiology of FOG in PD have been complicated because FOG is a complex phenomenon with various motor control deficits at play [21, 22].

Cueing may be defined as applying temporal or spatial external stimuli associated with the initiation and ongoing facilitation of motor activity [23]. Whether beneficial effects of cueing relate to prompting a more appropriate movement timing and amplitude or through heightening attention for gait remains a contentious issue [24]. Interestingly, auditory cue was less beneficial for FOG in PDF than did visual cue. This may be related to differences in attentional demand between

modalities of two external cues [25]. Some patients in PDF showed inability to match their movements and gait steps closely to an external rhythm of auditory cue and hastening increased at higher pacing frequencies. In these cases, the auditory cue might play a role as environmental or emotional constraints. This may be similar to cognitive load, such as verbal fluency task or serial 7 calculation, that worsens FOG in PD. The most effective frequency of auditory cue with metronome was quite variable among patients with PD, suggesting the individual variation of abnormality of neural networks responsible to the development of FOG.

In the present study, a few sub-items showed a significant correlation with gait features in PDF. Sub-items were verbal fluency, digit span, cube copying, clock drawing, immediate recall of verbal memory, naming, and repetition (Table 3). In particular, freezing number showed negative correlations with scores of cube copying, clock drawing, naming, and repetition. Cadence was negatively correlated with digit span and was positively correlated with verbal fluency. In PDNF, cognitive tests which were correlated with gait features were Trail making test, clock drawing, immediate and delayed and cued recall of verbal memory, and calculation. Both PDF and PDNF showed low scores of items of MoCA-K and this might lead to low statistical power for detecting a true difference between the two groups by MoCA-K. In the present study, we could not observe the significant difference in the correlation analysis between gait parameters and cognitive tests in patients with PDF and PDNF. These results suggest the followings: First, comprehensive neuropsychological tests were not performed in the present study. Second, we did not use the appropriate test which we could judge the ability to switch cognitive programs. FOG may be related to an inability to properly switch motor programs and maybe this motor problem is a manifestation of impairment of the ability to initiate cognitive programs [26]. Third, frontal dysfunction is a common symptom in PD whether they have a freezing or not. The severity or timing of frontal dysfunction might be different between two groups, but in this study we could not find out the differences.

Our study has limitations. First, more specific tests for the evaluation of frontal and parietal functions were not performed because this study was designed to use MoCA-K and MMSE, considering the reported usefulness of both tests. If frontal assessment battery and apraxia test and finger naming tests are added, we can evaluate the frontal function and the left parietal function. Second, subjects of this study were beyond the early stage of PD. Therefore, many patients might have attention deficit and executive dysfunction that are frequently observed in PD patients, regardless of FOG. A larger longitudinal study with early staged PD patients is needed to solve this issue.

In summary, our study supports the evidence that FOG can be significantly improved by external cues. FOG in PD was associated with some aspects of frontal dysfunction, which warrants for further investigation in detail by well-designed prospective studies with detailed neuropsychiatric tests.

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