

Gait Disturbance Associated with Cholinergic Dysfunction in Early Parkinson's Disease

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Abstract

Objective: The pathophysiology of gait disturbance in early Parkinson's disease (PD) is not fully understood, but cholinergic dysfunction may be associated with gait disturbance. Central cholinergic activity is closely related with olfaction in PD and it can be estimated with short-latency afferent inhibition (SAI). We hypothesize that cholinergic dysfunction, especially olfactory dysfunction, could be associated with gait disturbance in early PD.

Methods: A total of 57 early PD patients were enrolled. Olfaction was examined using the Korean version of the Sniffin' stick (KVSS) test. The PD patients were grouped as anosmia, hyposmia and normosmia according to the KVSS score. The gait parameters examined during 10 m of gait. SAI was measured by conditioning motor-evoked potentials, elicited by single transcranial magnetic stimulation (TMS) of the motor cortex, with electrical stimuli delivered to the contralateral median nerve at intervals ranging from N20 to N20+4 ms.

Results: The SAI response (N20 to N20+4 ms) and integrated SAI were less inhibited in PD for the anosmia and hyposmia groups than for the normosmia group (for all values, $p < 0.01$). In the PD anosmia group, the walking time was longer and more steps were taken during the 10 m gait than in the PD hyposmia and normosmia groups ($p = 0.01$, $p < 0.01$). In addition, gait speed was slower and stride length was shorter in the PD anosmia group than in the other groups ($p = 0.01$, $p < 0.01$). The TDI score was an independent factor that showed a correlation ($R^2 = 0.261$, 0.257) with gait speed in PD patients. A reduced TDI score was an independent determinant of reduced gait speed, explaining 25% of the variability even after correction of various factors related to cholinergic dysfunction.

Conclusion: Central cholinergic system influences cognition, gait, and olfaction in the early stage of PD.

Keywords: Parkinson's disease, Gait disturbance, Olfaction, Short latency afferent inhibition (SAI)

Introduction

Parkinson's disease (PD) is often referred to as Parkinson's complex because its pathology involves various central and peripheral nervous systems, and various motor and non-motor symptoms have been shown [1]. It is well known that motor symptoms of PD are caused by dopaminergic neuronal loss in substantia nigra pars compacta (SNpc); on the other hand, non-motor symptoms of PD are more complex and impair various neurotransmitters such as serotonin, acetylcholine and norepinephrine [2]. As the disease progresses, gait disturbance and falling are the most disabling symptoms; however, it is infrequently observed in the early stage and de novo PD patients [3]. Therefore, it is not clear that dopaminergic cell loss in the SNpc involves gait disturbance as a whole in accordance with PD stage. Dopaminergic treatment improves the motor symptoms of PD, but axial symptoms such as gait disturbance do not respond well [4]. Recent studies proposed that the non-dopaminergic pathway, especially the cholinergic pathway, is an important contributor to gait disturbance in PD [5-7], although the influence and role of cholinergic dysfunction in gait is not yet fully known.

Olfactory dysfunction is a common non-motor symptom that is involved in the initial stage of PD [8], but its pathophysiology is unclear. It is considered that neuronal degeneration with deposition of α -synuclein within the olfactory bulb and nucleus might be affected [9]. Recently, olfaction has been associated well with central cholinergic function and it could be estimated via short-latency afferent inhibition (SAI) [10]. SAI is a neurophysiological tool that evaluates sensory motor cortex excitability by time-locked coupling of peripheral nerve and motor cortex stimulation [11]. SAI is used as a central cholinergic marker in PD patients with various symptoms such as cognitive

impairment, visual hallucination, rapid eye movement (REM), sleep behavior disorder (RBD), olfaction and gait disturbance [7,10,12-14]. Rochester et al reported that central cholinergic dysfunction is closely associated with gait disturbance in early PD patients [7]. In addition, gait disturbance and postural instability have been associated with cholinergic degeneration in a PET study among faller, non-faller and controls [15]. In this study, we hypothesized that cholinergic dysfunction might be associated with gait dysfunction in early PD patients and analyzed the hierarchical central cholinergic activity quantitatively using an olfactory test and SAI.

Patients and Methods

Patients and clinical assessment

We enrolled 62 PD patients, who visited the movement disorder clinic at Chungnam National University Hospital from October, 2015 to May, 2017. All of the participants were diagnosed as probable PD by the United Kingdom Parkinson's Disease Society Brain Bank criteria. Among them, 5 participants who did not agree to the informed consent or withdrew consent were excluded. We also excluded patients who

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were diagnosed with atypical or secondary Parkinsonism. The study was approved by the local ethical committee and informed consent was obtained for all of the participants. This study was designed as a cross-sectional prospective study.

The inclusion criteria were 1) subjects who did not have significant cognitive impairment that interfered with activity of daily living (ADL) and 2) early PD patients below Hoehn and Yahr (H&Y) stage 3. The exclusion criteria were those who 1) had a history of nasolabial problems such as chronic sinusitis, allergic rhinitis, and nasal trauma and also had an obstructive lesion by otorhinolaryngologic examination with flexible fiberoptic laryngoscope, 2) observed bilateral resting hand tremor, and 3) used medications such as acetylcholinesterase inhibitors, benzodiazepine, anticholinergics and gabapentin. Basic demographic data, including gender, onset age, disease duration, type of Parkinsonism were recorded. All of the PD patients performed the Korean version of the Sniffin' stick (KVSS) test. The disease severity was evaluated using the United Parkinson's Disease Rating Scale (UPDRS) part III and H&Y stage. Cognitive function and depression were evaluated with the Korean version of the Mini-Mental Status Examination (K-MMSE), Korean version of Montreal Cognitive Assessment (K-MoCA), and Beck depression inventory (BDI).

Gait parameters

Gait assessment was performed at medication "on" state (after 1 h of dopaminergic medication) and average time (s) and number of steps taken during a 10 m walk were assessed three consecutive times in all participants. We analyzed items including walking time, number of steps, gait speed, stride length, and stride time during the 10 m walk in the same place without any obstacles. We excluded patients who had gait issues resulting from musculoskeletal or joint problems and those who showed freezing of gait.

Olfactory function assessment

The Korean version of the Sniffin' stick (KVSS)-II test was used to measure olfactory function. The KVSS test is a modified version of the Sniffin' stick test, and it is validated and frequently used in South Korea [16]. KVSS-II consists of three subgroup tests, including the odor threshold test, odor discriminatory test and odor identification test. For odor presentation, pens similar to Sniffin' sticks were used. The pen was filled with liquid odorants and the cap was removed by the examiner for 3 s and the tip of pen was placed 2 cm in front of the nostrils. The odor identification test consists of 16 items. Subjects select one of four odor items in an unknown state. From item to item, the test interval was 30 s. The sum of the 16 items was calculated as the odor identification score (ranging from 0 to 16). We divided the three PD groups as normosmia (above 27.25), hyposmia (20.25~27) and anosmia (below 20) by the KVSS score [16].

Short latency afferent inhibition

SAI was analyzed to quantify central cholinergic function. The protocol of SAI is based on previously reported methods [17]. Conventional transcranial magnetic stimulation (TMS) parameters were assessed using a Magstim magnetic stimulator (Magstim Company, Dyfed, UK). Initially, we obtained a control motor-evoked potential (MEP) without peripheral nerve stimulation. Next, conditioned MEP was investigated by conditioned stimuli delivered to the median nerve preceding cortical TMS with various inter-stimulus intervals (ISIs). ISIs was determined relative to the N20 latency obtained by somatosensory-evoked potential (SEP). Five hundred sweep signals were averaged to determine the latency of N20. Five inter-stimulus intervals were used

to evaluate SAI (N20, N20+1 ms, N20+2 ms, N20+3 ms, and N20+4 ms) and ten cortical stimuli with median nerve stimuli at the wrist were performed at each ISI. The peak-to-peak conditioned MEPs were averaged at each interval and regarded as test MEPs. Test MEPs were expressed as the percentage of control MEPs and conditioned response at five ISIs were also averaged to obtain the grand mean. The mean inhibition percentage of test MEP amplitude to control MEP was regarded as SAI. All subjects were subjected to visual-audio feedback with EMG monitoring to maintain maximal relaxation, and optimal dopaminergic medication was maintained to obtain complete relaxation. Recordings were performed on the non-symptomatic arm or the arm on the side where no tremors are observed by surface EMG.

Statistics

All data were analyzed with a statistical software program (SPSS 22.0, Chicago, IL, USA). Categorical variables (demographic data, electrophysiologic data, and gait parameters in three subgroup of PD) were compared using the Mann-Whitney U test, and Kruskal-Wallis test. Pairwise comparison was used for post hoc analysis. Pearson product correlation coefficients were calculated to analyze the association between gait speed and factors related to cholinergic dysfunction. All data are expressed as means and standard deviations unless otherwise noted.

Results

A total of 62 patients were selected initially, among them, 57 patients agreed to informed consent and participated. PD patients were grouped using KVSS as anosmia (n=16), hyposmia (n=19), or normosmia (n=22). Comparison of baseline clinical and demographic profiles including onset age, disease duration, severity (UPDRS-III, H&Y stage) and type of PD, education and K-MoCA showed no significant differences (Table 1). There were more female than male patients enrolled in all groups. BDI was higher in the anosmia than in the normosmia group (p=0.01). The K-MMSE score was significantly lower in the anosmia PD group compared with those of in the other groups (p=0.02). Olfactory function using the KVSS test showed a hierarchical level among the 3 groups. In the post hoc analysis, the TDI score in the anosmia group was lower than those in the hyposmia and normosmia groups. The electrophysiological parameters obtained by conventional TMS and SAI among the 3 groups were described in (Table 2). RMT, CMCT, MEPA and N20 were not significantly different among the 3 groups. In contrast, analysis of the SAI responses in the five inter-stimulus intervals (N20, N20+1 ms, N20+2 ms, N20+3 ms, N20+4 ms) and integrated SAI revealed significant differences among the 3 groups (PD with anosmia>PD with hyposmia>PD with normosmia; p<0.01). In the post hoc analysis, five inter-stimulus intervals and the integrated SAI response of the anosmia group were higher than those of the normosmia group. In Table 3, gait characteristics of the three PD groups, dependent on the degree of olfactory function, were described. Walking time, number of steps, gait speed and stride length were significantly different among the PD groups (p=0.01, <0.001, 0.001 and <0.001, respectively). In the post hoc analysis, the aforementioned gait parameters showed significant differences for the anosmia group than those for the hyposmia and normosmia groups. In the correlation analysis, integrated SAI, TDI score, K-MMSE, UPDRS-III, and age showed significant correlations with the walking speed in PD patients (Table 4A). In multiple linear regression analysis, we corrected the variables related to cholinergic dysfunction (K-MMSE, K-MoCA and integrated SAI). Reduced TDI score was an independent determinant of reduced gait speed, explaining 25% of the variability. TDI score

	PD with anosmia (n=16) ^a	PD with hyposmia (n=19) ^b	PD with normosmia (n=22) ^c	p-value	Post-hoc
	Mean ± SD	Mean ± SD	Mean ± SD		
Age	66.75 ± 12.37	63.47 ± 9.38	64.27 ± 8.76	0.37	
Gender (male/female)	3/13	4/15	8/14		
Disease duration (month)	16.25 ± 12.32	13.31 ± 10.69	13.72 ± 10.08	0.71	
Type of PD (TD/Mixed/AR)	3/10/3	5/8/6	6/12/4		
UPDRS-III	18.31	17.16	13.43	0.11	
Modified H&Y	2.22	2.16	2.02	0.51	
Education (year)	8.37 ± 4.67	8.39 ± 4.58	10.43 ± 4.03	0.21	
K-MMSE	24.25 ± 4.69	25.21 ± 3.30	27.50 ± 2.22	0.02	a=b<c
K-MoCA	18.81 ± 6.64	21.22 ± 5.59	23.32 ± 4.63	0.08	
BDI	15.56 ± 7.02	12.61 ± 6.47	9.27 ± 6.04	0.01	a=b<c
Olfactory function test					
Odour threshold test	3.93 ± 2.66	7.39 ± 1.85	11.70 ± 2.73	<0.01	a<b<c
Odour discrimination test	5.81 ± 1.42	7.68 ± 1.49	10.36 ± 1.55	<0.01	a<b<c
Odour identification test	6.31 ± 1.92	8.00 ± 1.97	9.95 ± 2.33	<0.01	a<b<c
TDI score	16.06 ± 3.43	23.13 ± 1.92	32.11 ± 3.50	<0.01	a<b<c

PD: Parkinson's Disease; UPDRS-III: Unified Parkinson's Disease Rating Scale Part III; H&Y: Hoehn and Yahr Stage; TD: Tremor-Dominant; AR: Akinetic-Rigid; BDI: Beck Depression Inventory; K-MMSE: The Korean Version of Mini-Mental State Examination; K-MoCA: Korean Version of Montreal Cognitive Assessment; TDI: The Sum of the Olfactory Threshold Score, Odour Discrimination Score and Odour Identification Score; post-hoc: Kruskal Wallis Test

Table 1: Demographics and olfactory function test in PD patients.

	PD with anosmia (n=16) ^a	PD with hyposmia (n=19) ^b	PD with normosmia (n=22) ^c	p-value	Post-hoc
	Mean ± SD	Mean ± SD	Mean ± SD		
RMT (%)	68.37 ± 11.58	72.50 ± 13.08	65.00 ± 10.36	0.17	
CMCT (ms)	7.03 ± 1.03	7.09 ± 1.40	7.14 ± 1.16	0.66	
MEPAR (%)	0.34 ± 0.17	0.31 ± 0.27	0.27 ± 0.17	0.10	
N20 (ms)	14.68 ± 3.89	15.16 ± 4.58	17.16 ± 5.00	0.17	
SAI (%): N20	67.08 ± 12.77	65.91 ± 12.02	54.26 ± 12.06	<0.01	a=b>c
SAI (%): N20+1 ms	60.51 ± 11.73	56.73 ± 12.97	46.50 ± 9.64	<0.01	a=b>c
SAI (%): N20+2 ms	53.85 ± 14.49	48.50 ± 13.93	39.96 ± 8.78	<0.01	a=b>c
SAI (%): N20+3 ms	64.91 ± 14.31	59.02 ± 13.39	50.74 ± 11.44	<0.01	a=b>c
SAI (%): N20+4 ms	73.26 ± 15.46	68.37 ± 1.60	58.90 ± 13.66	<0.01	a=b>c
Integrated SAI	63.92 ± 12.71	59.70 ± 12.26	50.07 ± 10.34	<0.01	a=b>c

These values represent the mean with the standard deviation

TMS: Transcranial Magnetic Stimulation; SAI: Short-Latency Afferent Inhibition; PD: Parkinson's Disease; RMT: Resting Motor Threshold; CMCT: Central Motor Conduction Time; MEPAR: Motor Evoked Potential Amplitude Ratio; post-hoc: Kruskal Wallis Test

Table 2: Comparison of electrophysiological parameters obtained by conventional TMS study and SAI.

	PD with anosmia (n=16) ^a	PD with hyposmia (n=19) ^b	PD with normosmia (n=22) ^c	p-value	post-hoc
	Mean ± SD	Mean ± SD	Mean ± SD		
Walking time (s)	11.44 ± 2.10	9.87 ± 1.28	9.47 ± 0.95	0.01	a>b=c
Number of steps (n)	21.63 ± 3.57	19.11 ± 2.35	17.85 ± 1.94	<0.01	a>b=c
Gait speed (m/s)	0.90 ± 0.17	1.03 ± 0.12	1.07 ± 0.10	0.01	a<b=c
Stride length (m)	0.47 ± 0.07	0.53 ± 0.06	0.57 ± 0.06	<0.01	a<b=c
Stride time (s)	0.53 ± 0.04	0.52 ± 0.03	0.53 ± 0.05	0.53	

Table 3: Gait parameters among different PD groups during 10 m gait.

remained a significant determinant of gait speed after controlling for K-MMSE, K-MoCA and integrated SAI (Table 4B).

Discussion and Conclusion

In this study, gait disturbance is strongly associated with olfactory dysfunction, and olfaction demonstrates a distinct association with SAI, which reflects cholinergic function quantitatively in early PD. The anosmia group shows more serious gait disturbance than the hyposmia and normosmia groups in this study. Gait disturbance and freezing of gait are very important issues in PD because they are directly related

to injury [18], loss of mobility [19], admission to nursing homes [20] and ultimately increased mortality. It is worthy of notice that this study demonstrates the associations among gait, olfaction, and the central cholinergic system in the early stage of PD.

It has been reported that SAI is an independent predictor of gait speed in PD compared to control subjects [7]. In other words, central cholinergic dysfunction influences gait disturbance in PD. There are two major cholinergic pathways that can affect gait disturbance: First is the cortical system from the nucleus basalis of Meynert (nbM) to the basal forebrain and cerebral cortex. Neuropathology including

Independent	R	p
SAI 20ms	-0.286	0.016
SAI 21ms	-0.355	0.003
SAI 22ms	-0.343	0.004
SAI 23ms	-0.410	0.001
SAI 24ms	-0.359	0.003
TDI score	0.416	0.001
K-MMSE	0.377	0.002
K-MoCA	0.337	0.06
H-Y stage	-0.203	0.065
UPDRS-III	-0.270	0.021
Integrated SAI	-0.367	0.002
BDI	-0.114	0.201
Age	-0.396	0.001

UPDRS-III: Unified Parkinson's Disease Rating Scale Part III; H&Y: Hoehn and Yahr Stage; BDI: Beck Depression Inventory; K-MMSE: The Korean Version of Mini-Mental State Examination; K-MoCA: Korean Version of Montreal Cognitive Assessment; TDI: The Sum of the Olfactory Threshold Score, Odour Discrimination Score and Odour Identification Score

Table 4A: Correlation analysis of variables for gait speed in PD patients.

Independent	β	p
Model 1		
TDI score	0.293	0.042
UPDRS-III	-0.073	0.589
K-MMSE	0.208	0.361
Age	-0.231	0.145
K-MoCA	-0.124	0.613
Integrated SAI	-0.100	0.493
R ² =0.261, p-value of change=0.01		
Model 2		
Integrated SAI	-0.155	0.262
TDI score	-0.281	0.05
K-MoCA	0.028	0.900
K-MMSE	0.220	0.973
R ² =0.257, p-value of change=0.02		

UPDRS-III: Unified Parkinson's Disease Rating Scale Part III; H&Y: Hoehn and Yahr Stage; BDI: Beck Depression Inventory; K-MMSE: The Korean Version of Mini-Mental State Examination; K-MoCA: Korean Version of Montreal Cognitive Assessment; TDI: The Sum of the Olfactory Threshold Score, Odour Discrimination Score and Odour Identification Score

Table 4B: Multiple regression analysis model and coefficient of variables for gait speed and other variable factors in different PD groups following olfaction.

neurofibrillary tangles, Lewy bodies, or neuronal loss in the nbM leads to impairment of both arousal and selective attention in PD [21] and may also affect gait disturbance [22]. Second, the pedunculopontine nucleus (PPN) supplies the cholinergic input to the striatum, thalamus, cerebellum and brain stem [23]. The cholinergic pathway of nbM is obviously degenerated in PD and this change is associated with cognitive decline, which causes higher level gait disorders [24]. It is known that the cholinergic pathway arising from the PPN resulting in neuronal loss progresses more severely with increasing motor severity in PD [22]. The PPN is connected in more complex ways with SN, subthalamic nucleus (STN) and globus pallidus interna (GPi) and involves posture, locomotion and gait control [25]. Cholinergic neurons of PPN are known to play important roles in gait and control of posture [24]. Greater reduction of cortical cholinergic activity is found in PD patients who experienced falling compared with those of PD non-fallers and controls in a PET study [15].

In this study, the cognitive function measured by the K-MMSE in

anosmia and hyposmia groups is statistically significantly lower than that of the PD normosmia group. In addition, gait disturbance is more severe for the anosmia group than that of the hyposmia and normosmia groups, indicating that the cholinergic system influences cognition, gait and olfaction in the early stage of PD.

Although the olfactory function test is known to reflect cholinergic activity, it may be partially influenced by cognitive or memory functions. The odour discrimination test may be the responsibility of the hippocampus as the test involves working memory [26] because two different odour stimuli cannot be compared simultaneously as in vision, audition, or somatosensory stimulation. In addition, the odour identification test may affect long-term memory's ability to remember the name of the smell, and short-term memory is required in the odor threshold test. Thus, olfactory function is influenced by high levels of cognitive and memory function of the limbic cortex [27,28].

This study has several limitations. First, we cannot evaluate gait function with quantitative kinetic gait analyzer, which may allow us more precise analysis of gait such as the range of motion of the joint. Second, SAI has many confounding factors, especially depending on the state of dopamine medication. There is a possibility that dopaminergic effect has an influence on the SAI response. Despite these limitations, this study suggests that the central cholinergic dysfunction may be responsible for gait disturbance, olfactory dysfunction and cognitive impairment in early stage of PD. Clinicians should pay more attention to cognitive and gait function in PD patients with olfactory dysfunction.

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