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Comparison of gait parameters between drug-naïve patients diagnosed with multiple system atrophy with predominant parkinsonism and Parkinson's disease

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ABSTRACTS

Introduction: Even though gait symptoms are prominent in patients diagnosed with multiple system atrophy with predominant parkinsonism (MSA-P) compared with Parkinson's disease (PD), the gait patterns of MSA-P were not clearly elucidated. We investigated postural instability and gait disturbances in MSA-P compared with PD.
Methods: We enrolled 34 drug-naïve patients with PD and 26 with MSA-P, and 18 normal controls in this study. Parkinsonism was evaluated by the Unified Parkinson's disease rating scale (UPDRS) part 3 and cognition was assessed with mini-mental status exam (MMSE). All the enrolled subjects underwent Pedoscan and GAITRite to objectively measure postural stability and gait. We compared the results of posturography and gait analysis among 3 groups, and performed correlation analysis of gait parameters with MMSE, UPDRS part 3 and posturography results.
Results: No difference was detected in demographic and clinical variables, except tremor sub-score of UPDRS part 3, urinary symptoms and orthostatic hypotension. MSA-P patients showed larger total anterior-posterior and lateral movement of centre of pressure (COP), and widened base of support than PD patients. In correlation analysis, MMSE score, axial sub-score of UPDRS part 3 and lateral movement of COP were correlated with gait parameters in PD patients, while only axial sub-score was associated in MSA-P patients after controlling for age, sex, height, body weight, education year, and disease duration.
Conclusion: Even at an early stage, MSA-P patients demonstrated more postural instability and gait disturbance compared with PD patients, and the related factors with gait disturbance in PD and MSA-P might be different.

1. Introduction

Multiple system atrophy (MSA) is a neurodegenerative disease with progressive multisystem involvement. Usually parkinsonism in MSA is poorly responsive to levodopa [1], and the prognosis of MSA with predominant parkinsonism (MSA-P) is worse than that of Parkinson's disease (PD) [2]. However, it is difficult to differentiate MSA-P and PD due to similar clinical features including motor and non-motor symptoms, especially in early stages [3]. Dysautonomia is a characteristic symptom of MSA [1], although autonomic nervous system is also commonly involved in PD patients from an early stage [4]. In addition, postural instability and gait disturbance are also more prominent at early stage in MSA-P patients compared with PD patients [5]. Furthermore, gait disturbance and postural instability are closely associated with quality of life [6]. However, the characteristics of gait and postural stability of MSA have yet to be clearly elucidated.

Usually gait and balance could be easily assessed manually at clinic. However, objective measurement is important to compare gait and postural stability between MSA-P and PD patients. Spatial and temporal abnormalities of gait parameters related to Parkinsonism have been studied using various techniques for objective assessment [7,8]. GAITRite is a device comprising carpet instrument, which collects spatio-temporal parameters associated with gait pattern, and is widely used in evaluation of gait disturbances [9]. Additionally, Pedoscan is an automated tool for evaluation of static postural stability [10,11].

Most previous studies recruited PD and MSA-P patients irrespective

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of dopaminergic medications, and failed to eliminate the possible confounding effects of medications. Even though response to dopaminergic medication varied with the disease, this medication affected gait and postural stability in patients with Parkinsonism [12,13]. Therefore, the confounding effect of dopaminergic medications should be minimized to compare the gait and postural stability associated with the diseases. In this study, to investigate the characteristic features of gait and postural stability in MSA-P, we compared the results of gait analysis and posturography between drug-naïve patients with early MSA-P and PD, and evaluated factors correlated to these results.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Board of Samsung Medical Centre and all subjects provided written informed consent. We enrolled drug-naïve, early-stage probable MSA-P and PD patients from September 2014 to June 2016 at the Movement Disorders Clinic in Samsung Medical Centre. MSA-P was diagnosed based on the second consensus diagnosis of MSA [1], and PD according to the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank [14], and using [^{18}F] *N*-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography (FP-CIT PET). Disease duration was defined from the presentation of motor symptoms. Early stage of PD and MSA-P was defined as disease duration less than 4 years. In addition, we recruited normal controls whose age, sex, height, education year and general cognition were matched with PD and MSA-P groups. For PD group, severity of parkinsonism was also matched with MSA-P group. Demographic and clinical data of all enrolled subjects were collected. The motor symptoms were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 and via modified Hoehn and Yahr stage [15], and UPDRS part 3 score was divided into 4 sub-scores for tremor, bradykinesia, rigidity and axial symptoms [16]. General cognition was assessed according to Korean mini-mental status exam score (MMSE) [17]. For autonomic involvements, urinary symptom and constipation were evaluated with clinical history, and orthostatic hypotension with head-up tilt test [18].

We excluded patients with cerebellar symptoms to minimize the bias associated with cerebellar ataxia, especially in the MSA-P group [19]. Cerebellar ataxia was defined by the presence of cerebellar ataxia on items 10 or 13 of Unified Multiple System Atrophy Rating Scale (UMSARS) part 2 [20], or cerebellar atrophy in brain MRI. Additionally, subjects were excluded if the following were detected: structural brain lesions including territorial stroke or white matter changes (age-related white matter change score ≥ 2 on brain MRI) [21], other known neurodegenerative diseases, psychiatric disorders requiring medication, cognitive decline (MMSE score ≤ 24), stroke, head trauma, vestibulopathy, diabetes, symptomatic neuropathy, radiculopathy, or musculoskeletal problems, which affected gait or postural stability.

2.2. Gait and postural stability

All enrolled subjects had undergone DIERS Pedoscan system (DIERS International, Wiesbaden, Germany) and GAITRite walkway system (CIR Systems, Clifton, New Jersey, USA) for the objective measurement of postural stability and gait. Pedoscan is used to measure foot pressure and soles under both feet during standing [11]. To assess postural body swaying, the patients were asked to stand as still as possible on a Pedoscan mat bipedally with their feet in a closed stance and arms by their sides for 1 min. We evaluated the total centre of pressure (COP) movement of anterior-posterior direction (COP-AP) and lateral direction (COP-Lat).

Temporal and spatial gait characteristics were measured using GAITRite. The mat length of GAITRite was 4.6 m, and subjects were required to walk barefoot at preferred and fast speeds along the mat six times [9]. For each cycle, the following spatial parameters were recorded: cadence (steps/min), walking velocity (cm/s), step/stride length (cm), and base of support (cm). Single/double support time (%GC; gait cycle) and swing/stance phase (%GC) for temporal parameters were recorded as spatial gait parameters. Cadence (steps/min), walking velocity (cm/s), single and double support times (s), proportion in gait cycle (%GC) of single support and double support time, %GC of swing time and stance time were assessed as temporal gait parameters. Functional ambulation profile score was calculated to evaluate the gait function [22].

2.3. Statistical analysis

All data were presented as means with standard deviations. Differences among the MSA-P group, PD and normal control groups were evaluated using one-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA with Tukey's test using ranks for post-hoc tests for continuous and ordinary variables, while Pearson's Chi-square test or Fisher's exact test was used for categorical variables. To compare between PD and MSA-P groups, independent Student's t-test or Mann-Whitney *U* test was done. Additionally, the factors related to the gait parameters in each group were identified using partial Spearman correlation analyses in PD group between the objective data from GAITRite, and other clinical data (UPDRS part 3, MMSE scores, and posturography data), with age, gender, height, weight, disease duration and education year as controlled variables. We added autonomic dysfunction as controlled variables in MSA-P group. All statistical analyses were conducted using commercially available software (PASW for Windows, version 23.0; SPSS Inc., Chicago, Illinois, USA).

3. Results

A total of 34 drug-naïve PD and 26 drug-naïve MSA-P patients, and 18 normal controls were recruited for this study. There was no statistically significant difference in demographic data between the three groups (Table 1). However, when we compared clinical data between MSA-P and PD groups, MSA-P patients and less tremor sub-score in UPDRS part 3, and more genitourinary symptoms and orthostatic hypotension. For gait and postural stability, MSA-P patients showed significantly greater impairment of gait and postural stability compared with PD patients (Table 2). When we compared the results from Pedoscan, MSA-P patients showed larger movement of COP in both anterior-posterior and lateral directions than PD patients. In terms of gait parameters, the MSA-P group demonstrated widened base of support compared to PD patients. Although MSA-P patients revealed slower velocity and smaller step length, there was no statistical significance.

The factors related to parameters of gait and postural stability in each group were identified via partial Spearman correlation analysis in PD and MSA-P groups, respectively. In PD group, the MMSE score was correlated with gait velocity, bilateral step/stride length, left single/double support time, and right swing/stance phase (Table 3). Interestingly, even though UPDRS part 3 total score was not correlated with any gait parameters, axial sub-score was associated with velocity, bilateral stride length, left step length and single/double support phase and right swing/stance phase. Additionally, COP-Lat was correlated with bilateral base of support, left single support phase, and right swing/stance phase. Conversely, in MSA-P group, MMSE and UPDRS part 3 total score, COP-AP and COP-Lat were not correlated with gait parameters. Only axial sub-score of UPDRS part 3 was associated with left swing/stance phase ($r = -0.653$ and 0.652, $p = 0.004$ and 0.005, respectively) and right single support phase ($r = -0.608$, $p = 0.010$) in MSA-P patients.

Table 1
Comparison of clinical demographics between PD and MSA-P groups.

	Normal (n = 18)	PD (n = 33)	MSA-P (n = 26)	*p*-value
Age	63.4 ± 10.6	65.0 ± 9.5	65.2 ± 9.6	0.971
Male, n (%)	10 (55.6)	17 (50.0)	16 (61.5)	0.236
Height (cm)	161.4 ± 10.7	160.6 ± 8.7	163.9 ± 8.8	0.555
Body weight (kg)	66.0 ± 11.9	62.3 ± 10.9	62.6 ± 11.2	0.195
Education year	13.6 ± 3.7	11.4 ± 4.0	11.4 ± 3.2	0.507
MMSE	27.5 ± 1.9	26.7 ± 1.9	26.9 ± 2.1	0.340
Orientation	9.8 ± 0.4	9.6 ± 0.8	9.7 ± 0.6	0.682
Attention/calculation	4.0 ± 1.2	3.9 ± 1.1	3.8 ± 1.2	0.584
Recall	1.9 ± 1.0	1.8 ± 1.1	2.0 ± 0.9	0.723
Language	7.8 ± 0.4	7.7 ± 0.5	7.8 ± 0.4	0.727
Visuospatial	1	0.9 ± 0.3	0.9 ± 0.4	0.395
Disease duration (months)		19.3 ± 11.7	18.1 ± 10.1	0.793
UPDRS part 3		21.9 ± 6.7	23.5 ± 10.5	0.724
Tremor		1.7 ± 1.5	0.5 ± 0.8	0.001*
Rigidity		9.1 ± 3.9	10.7 ± 5.5	0.400
Bradykinesia		4.4 ± 2.6	4.1 ± 3.1	0.429
Axial symptoms		6.7 ± 2.5	8.2 ± 3.8	0.146
Hoehn-Yahr stage		1.9 ± 0.6	2.0 ± 0.6	0.215
Dysautonomia				
Constipation, n (%)		17 (51.5)	14 (53.8)	1.000
Genitourinary symptom, n (%)		9 (27.3)	18 (69.2)	0.002*
Orthostatic hypotension, n (%)		2 (6.1)	22 (84.6)	< 0.001*

PD, Parkinson's disease; MSA-P, multiple system atrophy with predominant Parkinsonism; UPDRS, unified Parkinson's disease rating scale; MMSE, mini-mental status exam.

4. Discussion

This study is the first of its kind to investigate gait and postural stability between drug-naïve patients with PD and MSA-P using objective evaluation tools. Unlike previous studies, we enrolled drug naïve patients to eliminate possible confounding factors from medications, and early stage patients with Parkinsonism. Thus, our study is clinically meaningful for differential diagnosis based on these aspects. Especially in early stages of diseases, it is difficult to differentiate MSA-P from PD [3]. MSA is typically characterized by autonomic involvement, although several previous studies reported controversial results [4]. Similarly with dysautonomia, early postural instability and gait disturbance was more prominent in MSA-P patients compared with PD patients [23]. However, there is no consensus on features of gait and postural stability between the two diseases.

In our study, MSA-P patients showed larger COP movement in both anterior-posterior direction and lateral direction than PD patients. Classically, PD patients manifest slow/shuffling gait, a reduction in stride length and an increase in double support time, but not widened base or postural instability [24]. Further, because of early postural instability, MSA patients reported shorter disease duration to falls compared with PD patients [5]. However, both PD and MSA-P are

Table 2
Comparison of postural instability and gait parameters between PD and MSA-P groups.

	Normal (n = 14)	PD (n = 33)	MSA-P (n = 26)	*p*-value	
Postural stability					
COP-AP (cm)	1.2 ± 0.4	1.3 ± 0.6	1.8 ± 1.0	0.039*	Normal = PD < MSA-P
COP-Lat (cm)	0.9 ± 0.5	0.8 ± 0.5	1.7 ± 1.1	0.001*	Normal = PD < MSA-P
Gait parameters					
cadence (steps/min)	103.2 ± 13.2	105.0 ± 9.9	103.7 ± 10.5	0.987	
velocity (cm/s)	89.7 ± 13.9	89.2 ± 18.8	81.8 ± 18.2	0.103	
step time differential (ms)	11.2 ± 9.2	50.6 ± 87.7	30.4 ± 24.9	0.011*	Normal < PD = MSA-P
step length differential (cm)	2.0 ± 1.4	2.2 ± 1.5	2.3 ± 1.8	0.342	
functional ambulation profile	93.9 ± 4.8	92.0 ± 6.7	87.7 ± 10.7	0.035*	Normal > PD = MSA-P
Left					
step length (cm)	50.5 ± 5.1	50.9 ± 7.8	46.9 ± 8.8	0.132	
stride length (cm)	102.3 ± 10.3	102.0 ± 15.9	95.1 ± 16.5	0.221	
base of support (cm)	8.2 ± 2.4	8.7 ± 2.8	10.3 ± 3.0	0.037*	Normal = PD < MSA-P
single support time (%GC)	36.0 ± 1.3	36.1 ± 2.7	37.2 ± 6.1	0.810	
double support time (%GC)	27.6 ± 2.1	27.2 ± 4.7	27.8 ± 4.0	0.934	
swing phase (%GC)	35.9 ± 1.3	35.9 ± 2.7	35.5 ± 2.5	0.493	
stance phase (%GC)	64.1 ± 1.3	64.1 ± 2.7	64.5 ± 2.5	0.462	
Right					
step length (cm)	51.2 ± 5.3	50.6 ± 8.3	47.5 ± 7.9	0.262	
stride length (cm)	102.0 ± 10.2	102.2 ± 16.0	90.5 ± 21.7	0.088	
base of support (cm)	8.2 ± 2.3	8.7 ± 2.9	10.3 ± 2.9	0.037*	Normal = PD < MSA-P
single support time (s)	35.8 ± 1.4	36.0 ± 2.7	35.5 ± 2.6	0.705	
double support time (s)	27.3 ± 2.2	26.6 ± 6.3	27.1 ± 5.9	0.741	
swing phase (%GC)	35.9 ± 1.2	36.2 ± 2.7	36.1 ± 2.0	0.706	
stance phase (%GC)	64.1 ± 1.2	63.8 ± 2.7	63.9 ± 2.0	0.681	

PD, Parkinson's disease; MSA-P, multiple system atrophy with predominant Parkinsonism; COP-AP, movement of centre of pressure (anterior-posterior direction); and COP-Lat, movement of centre of pressure (lateral direction).
**p*-value < 0.05.

Table 3
Partial Spearman correlation analyses of the results using GAITRite and Pedoscan, and MMSE score, with age, gender, height, weight, disease duration and education year as controlled variables, in PD patients.

	Parkinson's disease (n = 33)						MSA-P (n = 26)	
	MMSE		axial sub-score		COP-Lat		axial sub-score	
	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
Gait parameters								
cadence (steps/min)	0.268	0.176	−0.292	0.140	−0.056	0.781	−0.022	0.932
velocity (cm/s)	0.419	0.029*	−0.400	0.039*	−0.248	0.211	−0.223	0.390
Left								
step length (cm)	0.394	0.042*	−0.413	0.032*	−0.298	0.131	−0.325	0.203
stride length (cm)	0.416	0.031*	−0.400	0.039*	−0.331	0.091	−0.339	0.183
base of support (cm)	−0.093	0.646	0.121	0.548	0.387	0.046*	−0.195	0.452
single support time (%GC)	0.402	0.037*	−0.387	0.046*	−0.595	0.001*	−0.031	0.906
double support time (%GC)	−0.384	0.048*	0.453	0.018*	0.373	0.055	0.467	0.059
swing phase (%GC)	0.341	0.082	−0.303	0.125	−0.087	0.667	−0.653	0.004*
stance phase (%GC)	−0.344	0.079	0.303	0.124	0.085	0.673	0.652	0.005*
Right								
step length (cm)	0.430	0.025*	−0.354	0.070	−0.351	0.073	−0.249	0.336
stride length (cm)	0.413	0.032*	−0.399	0.039*	−0.332	0.090	−0.296	0.249
base of support (cm)	−0.103	0.608	0.133	0.508	0.398	0.040*	−0.208	0.424
single support time (s)	0.343	0.080	0.102	0.614	0.247	0.215	−0.608	0.010*
double support time (s)	−0.440	0.022*	0.418	0.030*	0.341	0.081	−0.470	0.057
swing phase (%GC)	0.404	0.037*	−0.461	0.016*	−0.534	0.004*	−0.307	0.230
stance phase (%GC)	−0.403	0.037*	0.465	0.015*	0.536	0.004*	0.306	0.232

PD, Parkinson's disease; MMSE, mini-mental status exam; UPDRS, Unified Parkinson's disease rating scale; COP-Lat, movement of centre of pressure (lateral direction).
**p*-value < 0.05.

neurodegenerative diseases, which are common in elderly people. Postural instability may result from various medical conditions including neuropathy, radiculopathy, or secondary Parkinsonism such as vascular Parkinsonism and so on. Therefore, we excluded possible confounding factors from other medical conditions to focus the effects on postural stability due to each disease per se.

In accordance with larger COP-AP and COP-Lat in MSA-P group, the gait pattern in MSA-P patients was characterized by widened base of support than in PD patients. Consistent with our study, previous studies already reported early postural instability in MSA patients [5]. Although the pattern of MSA-P and MSA with cerebellar ataxia (MSA-C) varied [25,26], these two subtypes of MSA also share common pathophysiology [27]. Even in MSA-P patients, MSA patients could present with minimal or mild cerebellar ataxia, and ataxia and parkinsonism affect each scale of these symptoms [19]. Therefore, even though we enrolled only MSA-P patients without ataxia based on precise evaluation for cerebellar ataxia, the postural instability of MSA-P patients might result from minimal cerebellar involvement in MSA itself.

We found that MMSE score was correlated with both spatial gait parameters and temporal parameters in PD patients, but not in MSA-P patients. Increased stance phase and double support time in PD patients may be attributed to cognitive decline unlike MSA-P patients. Based on our results, we suggest that the pathophysiology of gait varied with the two diseases. In previous studies, cognition was regarded to be associated with gait. Gait disturbance was reported in patients with dementia or mild cognitive decline [28], and even in normal elderly people [29,30]. Similarly, cognition was closely related to gait disturbance in PD patients [31,32], and gait was suggested as a clinical biomarker for cognitive decline in early PD [33]. In accordance with our results, global cognitive function showed a strong correlation with stride velocity [31]. However, considering we enrolled subjects with MMSE score more than 24, our results should be interpreted cautiously.

In terms of parkinsonism, only axial symptoms were associated with gait parameters in both PD and MSA-P groups. Because we recruited early stage patients, enrolled subjects showed mild parkinsonism, thus there might be limited effects from parkinsonism to gait. Further studies with advance patients could be helpful, but it is difficult to match disease stage between advanced PD and MSA-P patients, and differential diagnosis is usually more important in early stage.

The present study has several limitations. First of all, we evaluated static and not dynamic postural stability, which facilitated early detection of balance problems. However, even from early-stage, we could find out more postural instability in MSA-P patients than in PD patients with evaluation of static postural instability. Additionally, previous studies reported the relationship between frontal executive function and gait [29,30]. Compared to previous studies, MMSE is not an appropriate tool to evaluate frontal lobe function or to access each cognitive domain precisely. However, a previous studies also used a scale for global cognitive function to successfully correlate cognition and gait similar to our findings in PD patients [31,32]. Finally, we enrolled only subjects at early stages. Since clinical diagnosis may be changed according to follow-up, the possibility for altered diagnosis existed. To minimize this limitation, all the subjects were followed up after more than 2 years, and all the PD patients in our study showed excellent response to dopaminergic medication and also confirmed with dopamine transporter PET. Furthermore, marked cognitive decline is usually not seen in early stage of disease, and we excluded subjects with possible cognitive impairments. Therefore, the role of cognitive impairments in our study might be limited only for patients with early stage, and further study with patients in advance stage is needed. However, it is difficult to distinguish PD from MSA-P, especially in early stage, we aimed to investigate the clinical implications of objective gait analysis to help the differential diagnosis in early patients.

In conclusion, MSA-P patients manifest greater postural instability and gait disturbance compared with PD patients, and objective measurement of gait and postural stability maybe helpful for the differential diagnosis of PD and MSA-P. Furthermore, global cognitive function and postural instability were related to gait parameters only in PD patients, while axial parkinsonism was associated in both MSA-P and PD groups. Based on our results, the mechanism underlying gait disturbance in PD and MSA-P might vary, and approaches tailored to the individual pathophysiology are needed for the management of gait disturbance and postural instability in patients with Parkinsonism.

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