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Clinical study

Association of orthostatic blood pressure with the symptoms of orthostatic hypotension and cognitive impairment in patients with multiple system atrophy

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ABSTRACT

The degree and frequency of orthostatic hypotension (OH) are high in patients with multiple system atrophy (MSA); however, the association of orthostatic blood pressure (BP) with the symptoms of OH and cognitive impairment in these patients remains unclear. The aim of this study was to clarify whether absolute BP and/or changes in BP during standing are related to OH symptoms and cognitive impairment in patients with MSA. Thirty-two patients with MSA were examined using the head-up tilt and cognitive function tests. OH symptoms were evaluated using a patient-reported scale. The results were compared with those for 15 age- and sex-matched healthy controls. Seventeen of the 32 (53.1%) patients had OH, with eight of them exhibiting OH symptoms, which were related to the absolute BP value at 60° tilt. However, OH symptoms were not related to the degree of decrease in BP during the tilt test, and they were frequently observed in patients with a mean BP of <80 mmHg at 60° tilt (sensitivity, 67%; specificity, 91%). Cognitive dysfunction assessed by the Mini-Mental State Examination (MMSE; $\leq$ 26) was also associated with a low mean BP at 60° tilt (odds ratio, 1.32; 95% confidence interval, 1.04–1.67; p = 0.02). The upright BP value is associated with OH symptoms and the MMSE score in patients with MSA. Thus, careful observation of OH symptoms can enable early management of BP and the detection of cognitive impairment in these patients.

1. Introduction

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease clinically characterized by parkinsonism, cerebellar dysfunction, autonomic dysfunction, and pyramidal tract involvement [1]. Neurodegenerative diseases such as Parkinson's disease (PD) and MSA often complicate orthostatic hypotension (OH), although patients do not necessarily complain of OH symptoms such as dizziness, loss of consciousness, and blurred vision. It is estimated that 30% to 60% patients with PD have OH [2,3], and that OH symptoms are associated with an upright mean blood pressure (BP) of <75 mmHg [2]. In addition, cognitive dysfunction and deep white matter lesions often progress in PD with OH [4]. On the other hand, in patients with MSA, cognitive impairment is mainly attributed to frontal dysfunction and cerebral atrophy in the frontal lobe [5–7], and the impact of OH on cognitive function and deep white matter lesion in MSA is not well known.

This study aimed to clarify whether the absolute mean BP and/or decrease in the mean BP during standing are related to OH symptoms, cognitive function, and white matter lesion in patients with MSA.

2. Materials and methods

2.1. Subjects

The study consisted of 32 patients with probable MSA (21 men and 12 women, 65.5 ± 8.6 years). Of these, 20 had predominant cerebellar ataxia (MSA-C) and 12 had predominant parkinsonism (MSA-P), which were diagnosed according to the consensus criteria [1]. They were referred to our University Hospital for evaluation by a specialist. Individuals with diabetes mellitus, any known heart

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disease or other neurological disorders were excluded. A control group consisting of 15 age- and sex-matched normal healthy adults (9 men and 6 women, 65.6 ± 11.9 years) was also enrolled.

2.2. Clinical assessments

Head-up tilt test was performed as previously described [8,9]. All studies were performed at 0900 h in a temperature-controlled clinical laboratory (average temperature 25 °C ± 1 °C) after overnight fasting. Any drugs that might influence the cardiovascular system, including antiparkinsonian drugs, were discontinued at least 12 h before enrollment. OH was defined by a decrease in systolic BP of at least 20 mm Hg or in diastolic BP at least 10 mm Hg between supine rest for at least 15 min and 60° for 3 min (unless symptomatic or rapid hypotension necessitated return to the supine position before 3 min 60° tilt) [8,10]. Along with the head-up tilt test, cardiovascular recordings were conducted using a non-invasive monitoring device (Task Force Monitor, CNSystems, Medizintechnik, Graz, Austria) [11,12]. Electrocardiograms were recorded continuously using four spot electrodes. Beat-to-beat measurements of BP were obtained by finger plethysmography of the right index finger and continuously corrected to the BP of the brachial artery in the left arm measured via the oscillometric technique.

Symptoms of OH were assessed at 3 min of 60° tilt test using the Orthostatic Hypotension Questionnaire, a validated patient-reported scale [2,13]. Patients were categorized based on the presence or absence of symptoms. Those who reported dizziness, lightheadedness, visual impairment (i.e., blurred vision, tunnel vision, or diminished vision), or pain in the shoulders and back of the neck (coat hanger pain), which correspond to items 1, 2, and 6 of the questionnaire, respectively, were included in the symptomatic group as previously described [2].

After the head-up tilt test, we successively assessed global cognitive function using the Mini-Mental State Examination (MMSE) and frontal lobe function using the Frontal Assessment Battery (FAB) and Japanese version of the Montreal Cognitive Assessment (MoCA-J) for MSA patients. The examinations were conducted in the sitting position, and all patients were carefully observed for orthostatic symptoms during the examinations. If such symptoms occurred, the test was resumed after symptom alleviation to focus on cognitive decline owing to the effect of low blood pressure.

For white matter lesions, brain MRI was examined around 2 weeks of the head-up tilt test. The amount of deep white matter lesions and periventricular hyperintensity white matter lesions on T2-weighted images was scored using the Fazekas score [14]. Periventricular hyperintensity was graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo," and 3 = irregular periventricular hyperintensity extending into the deep white matter. Deep and subcortical white matter hyperintense signals were rated as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas. All scoring was performed consistently by the same neuroradiologist (MU under supervision of TN).

2.3. Statistical analysis

Continuous data are expressed as means ± standard deviations. Differences between groups were assessed using unpaired t tests. Categorized data were analyzed by using the chi-squared test. Correlation analysis (Pearson's coefficient) and simple regression were used to assess the relationship between BP and the patients' characteristics. Sensitivity and specificity to predict orthostatic symptoms were assessed. Multivariate analysis was used to estimate the predictors of OH symptoms, cognition, and white matter lesions. The risk was determined with odds ratios (ORs) and 95% confidence intervals (CIs). SPSS software version 23 (SPSS, Chicago, IL, USA) was used for statistical analyses. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. OH, OH symptoms, and BP during head-up tilt test

The demographic and basic clinical data are shown in Table 1. Ten patients with MSA exhibited hypertension with a systolic BP of ≥140 mmHg or a diastolic BP of ≥90 mmHg at 0° tilt in the head-up tilt test. Systolic BP, diastolic BP, and mean BP at the 3 min of the 60° tilt were not different between MSA patients and controls, but decrease in systolic BP, diastolic BP, and mean BP at the 3 min of the 60° tilt from the 0° was significantly greater in MSA patients than in controls. Seventeen out of 32 MSA patients (53.1%) showed OH, whereas none in the control group showed OH. A total of nine patients exhibited OH symptoms, and eight of them had OH. Among the 23 patients without OH symptoms, nine had OH. OH symptoms were not observed in the controls. We compared the mean BP and the change in the mean BP at the 3 min of the 60° tilt between subjects with OH symptoms and those without. Categorization of patients according to the presence or absence of symptoms revealed a higher decrease in the mean BP at 60° tilt (−24.6 vs −6.0 mmHg, $p < 0.005$; Fig. 1A) and a lower mean BP at 60° tilt (76.1 vs 91.0 mmHg, $p < 0.05$; Fig. 1B) in the symptomatic group. When the subject's age, disease duration, disease type (MSA-P or MSA-C), mean BP, change in the mean BP in the tilt test, and periventricular hyperintensity/deep and subcortical white matter hyperintensity were included as covariates, logistic regression analysis revealed that OH symptoms were only associated with the mean BP at 60° tilt (Table 2). Calculation of receiver operating characteristic curves revealed that OH symptoms were frequent in patients with a mean BP of <80 mmHg (sensitivity, 67%; specificity, 91%) at 60° tilt.

Table1
Demographic data, clinical characteristics, and changes in hemodynamics from baseline to the 3 min of the 60° tilt.

	MSA (n = 32)	Control (n = 15)	p value
Age (years)	65.5 ± 8.6	65.6 ± 11.9	0.97
Male: Female	21:11	9:6	0.71
Disease duration (years)	2.8 ± 2.3		
MSA-P: MSA-C	12:20		
Cognition			
MMSE	26.6 ± 2.6		
FAB	13.6 ± 2.9		
MOCA-J	22.3 ± 4.4		
Brain MRI			
Periventricular hyper-intensity	1.0 ± 0.7	1.3 ± 1.0	0.30
Deep and subcortical white matter hyperintensity	1.7 ± 0.9	1.6 ± 1.2	0.76
Head-up tilt test			
Systolic BP at 0°(mmHg)	123.1 ± 18.4	112.6 ± 15.1	0.09
Diastolic BP at 0°(mmHg)	80.8 ± 15.4	73.2 ± 9.4	0.08
Mean BP at 0° (mmHg)	99.3 ± 16.0	90.3 ± 11.8	0.10
Heart rate at 0°(/min)	69.8 ± 12.0	64.8 ± 11.1	0.13
Systolic BP at 60° (mmHg)	107.8 ± 14.0	114.8 ± 14.1	0.14
Diastolic BP at 60° (mmHg)	73.5 ± 11.5	77.6 ± 9.2	0.49
Mean BP at 60°(mmHg)	86.8 ± 11.6	92.6 ± 10.6	0.29
Heart rate at 60°(/min)	80.7 ± 13.7	73.8 ± 13.7	0.05
Δ Systolic BP (mmHg)	−15.3 ± 22.7	2.2 ± 8.7	0.01
Δ Diastolic BP (mmHg)	−7.3 ± 17.5	4.4 ± 9.6	0.02
Δ Mean BP (mmHg)	−11.3 ± 20.7	2.3 ± 9.4	0.01
Δ Heart rate (/min)	11.0 ± 6.9	9.0 ± 7.0	0.28

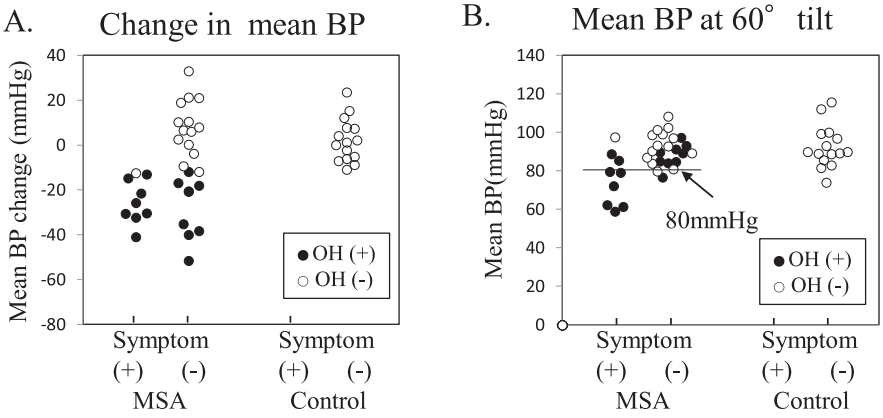

Fig. 1. Change in blood pressure (BP) and BP at 60° tilt in symptomatic orthostatic hypotension (OH) group and non-symptomatic OH group in both multiple system atrophy (MSA) patients and controls. A. Change in mean BP. B. Mean BP at 60° tilt. Horizontal line in B represents a cut-off value that provides the best sensitivity and specificity in identifying symptomatic patients. Black circle represents subjects with OH. White circle represents subjects without OH.

Table 2
Odds ratio and 95% CI of OH symptoms.

	Odds ratio	95% CI	p value
Age	1.06	0.90–1.25	0.47
Disease duration	0.68	0.35–1.30	0.24
Disease type	2.95	0.26–32.9	0.38
Mean BP at 60°	1.16	1.002–1.334	0.046
Change in Mean BP in the tilt test	0.96	0.89–1.03	0.24
Periventricular hyperintensity score	0.20	0.02–2.06	0.39
Deep and subcortical white matter hyperintensity score	0.52	0.12–2.32	0.17

CI = confidential interval.

Table 3
Odds ratio and 95% CI of cognitive dysfunction (MMSE ≤ 26).

	Odds ratio	95% CI	p value
Age	0.93	0.76–1.13	0.46
Disease duration	1.17	0.70–1.95	0.56
Disease type	0.17	0.01–3.14	0.24
Mean BP at 60°	1.32	1.04–1.67	0.02
Change in Mean BP in the tilt test	1.13	1.01–1.26	0.03
Periventricular hyperintensity score	0.25	0.02–3.35	0.30
Deep and subcortical white matter hyperintensity score	0.54	0.07–3.96	0.54

CI = confidential interval.

3.2. Predictors of cognitive dysfunction

The MMSE score showed a correlation with age (r = −0.41, p = 0.01) and the mean BP at 60° tilt (r = 0.36, p = 0.04), whereas it was not correlated with the mean BP at 0° tilt (r = 0.20, p = 0.25) or the change in the mean BP (r = −0.04, p = 0.41). FAB and MOCA-J scores showed no correlation with BP or the change in BP at 60° tilt.

The regression line using MMSE as the outcome variable (y) and the mean BP at 60° tilt as the predictor variable (x) was y = 0.0812x + 19.516. According to this formula, the mean BP at 60° tilt, with an MMSE score of 26 points, was 80 mm Hg. In addition, stepwise regression analysis adjusted for the patient's age, disease duration, mean BP at 0° and 60° tilt, change in the mean BP, OH symptoms, and periventricular hyperintensity/deep and subcortical white matter hyperintensity confirmed that MMSE was independently associated (adjusted r = 0.57) with age (p = 0.01) and the mean BP at 60° tilt (p = 0.02). Logistic regression analysis also showed that the mean BP at 60° tilt (OR, 1.32; 95% CI, 1.04–1.67, p = 0.02) and the change in the mean BP (OR, 1.13; 95% CI, 1.01–1.26, p = 0.03) were the only predictors of an MMSE score of ≤ 26 (Table 3).

A similar analysis using the stepwise method revealed that the FAB score was associated with deep and subcortical white matter hyperintensity (R = 0.47, p = 0.01), while the MOCA-J score was associated with age (R = 0.46, p = 0.03). There was no association between FAB/MOCA-J scores and the mean BP and the change in the mean BP at 60° tilt.

3.3. Predictors of white matter lesion

There were no differences in the score of periventricular hyperintensity or deep and subcortical white matter hyperintense signals between MSA patients and controls (Table 1). In addition, no differences were found in the score of periventricular hyperintensity or separate deep white matter hyperintense signals between MSA patients with OH and those without (0.94 vs 1.00, p = 0.83; 1.82 vs 1.60, p = 0.52, respectively) and between MSA patients with OH symptoms and those without (1.00 vs 0.95, p = 0.88; 1.78 vs 1.70, p = 0.83, respectively). The scores for the white matter lesions did not correlate with the absolute values for the mean BP at 0° and 60° tilt or the change in BP during tilt. Multivariate analysis revealed that age was the only predictor of white matter lesions in both MSA patients (deep and subcortical white matter hyperintensity: R = 0.51, p < 0.01; periventricular hyperintensity: R = 0.63, p < 0.001) and controls (deep and subcortical white matter hyperintensity: R = 0.76, p = 0.01; periventricular hyperintensity: R = 0.86, p < 0.01).

4. Discussion

In the present study, we demonstrated that the absolute value of BP on standing rather than the magnitude of BP decrease during standing is a determinant factor for symptoms of OH in MSA patients. In PD patients, symptomatic OH is reported to be associated with an upright mean BP < 75 mmHg [2]. However, little is known about this association in MSA patients. Our results showed that symptomatic OH was chiefly associated with mean BP < 80 mm Hg at 60° tilt. This value is similar to that in a previous report of PD patients [2].

In addition, we found that an MMSE score of ≤ 26 was correlated with the mean BP at 60° tilt. The regression line derived in the study showed that a mean BP of <80 mm Hg at 60° tilt was a potential risk factor for cognitive decline in MSA patients. Previous studies have reported that cognitive impairment in patients with

MSA correlates with their disease duration [15], severe motor disability [7], and cardiovascular dysautonomia such as reduced ^{123}I-metaidobenylguanidine cardiac uptake [5] or short coefficient of variation of electrocardiographic RR intervals [16]. Hatakeyama et al. evaluated the predictors of cognitive impairment in MSA by performing Schellong Test; however, there was no correlation between MMSE score and the result of the Schellong Test [16]. In the present study, we found that the mean BP at 60° tilt was associated with the MMSE score; this suggests that careful observation of OH symptoms can be helpful in the detection of cognitive dysfunction in MSA patients.

In our study, the disease duration was not relevant to cognition, possibly because our patients exhibited a disease duration of 2.8 years, which is shorter than that (4.2 years) in the study by Hatakeyama et al [16]. We could not find any relation between FAB score and BP during the tilt test. In our results, mean FAB score in MSA patients was 13.6 ± 2.9, which is almost the same as the score previously reported by Hatakeyama et al., who also could not find any relation with Schellong Test [16]. A meta-analysis clarified that cerebral white matter lesions are associated with cognitive dysfunction [17], particularly executive dysfunction [18,19]. Similarly, in the present study, white matter lesions were not related to the MMSE or MOCA-J scores, whereas they were related to the FAB score, which represents executive function. There are only a few studies evaluating cognition using MOCA in MSA [20,21], and there is no report investigating its relationship with OH; therefore, accumulation of further cases is necessary.

White matter score did not correlate with decrease in BP or absolute BP at 60° tilt. Cognitive dysfunction and deep white matter lesions are reported to progress in PD patients with OH [4,22,23]. However, it remains unknown whether OH and white matter lesions are merely associated or causally related to each other, and if so, how OH might contribute to white matter lesions in PD patients [22]. Pathologically, white matter change on MRI scan in MSA reflects the presence of glial cytoplasmic inclusions, located in oligodendrocytes [24]. However, the cause of white matter degeneration is not clear, and there is a possibility that OH or blood flow reduction in the brain relates to white matter degeneration. Thus, further observation is necessary to solve this issue in MSA.

This study has some limitations. Patients with MSA-P show more severe and widespread or rapidly progressive cognitive dysfunction than do patients with MSA-C [16,25]. However, given the small sample size in the present study, we found no differences between patients with MSA-P and those with MSA-C. Therefore, it is necessary to investigate further by increasing the number of cases in the future. Regarding examination of white matter lesions, there was no uniformity in MRI equipment, with 1.5 T or 3 T equipment being used. Therefore, a slight difference in appearance might occur. In addition, although the patients were carefully observed during the examination of cognitive function, actual BP values were not recorded. It is possible that BP may have dropped and affected cognitive function in some cases.

5. Conclusion

In patients with MSA, a decrease in the mean BP while standing to 80 mmHg is a determinant of OH symptoms and may be helpful for the detection of cognitive dysfunction. Thus, careful observation of OH symptoms can enable the early management of BP and cognitive impairment in this patient population.

Ethical guidelines

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government. The study protocol was approved by the ethical committee at Nagoya University, and written informed consent was obtained from all subjects.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.03.040.

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