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Impaired peripheral vasoconstrictor response to orthostatic stress in patients with multiple system atrophy

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ABSTRACT

Background and purpose: Most patients with multiple system atrophy (MSA) develop autonomic dysfunction; however, orthostatic hypotension is not always present. Failure of the vasoconstrictor response is thought to be responsible for orthostatic hypotension, but the degree of impairment of this response in patients with MSA is unclear. We assessed autonomic function in patients with MSA by evaluating the vasoconstrictive response during a head-up tilt test and determining its relationship to orthostatic hypotension. As an additional examination, the efficacy of norepinephrine in treating orthostatic hypotension was also assessed.

Methods: The study included 82 patients with MSA and 28 controls. Measures of total peripheral resistance were obtained during a head-up tilt test. Norepinephrine was administered to the patients lacking a vasoconstrictive response to evaluate its ability to treat orthostatic hypotension.

Results: At a 60° tilt, orthostatic hypotension occurred in 47.6% of the patients and 0% of controls. Reduction in total peripheral resistance from baseline at a 60° tilt was observed in 69.5% of the patients and 0% of controls. In patients with MSA, changes in systolic blood pressure from the baseline at a 60° tilt correlated positively with changes in the total peripheral resistance ($r = 0.69$, $p < 0.0001$). Norepinephrine prevented the reduction of total peripheral resistance and development of orthostatic hypotension.

Conclusions: A large number of patients with MSA with and without orthostatic hypotension have an impaired peripheral vasoconstrictive response, suggesting a high frequency of cardiovascular dysautonomia with an associated risk of developing orthostatic hypotension. A norepinephrine infusion was effective for treating orthostatic hypotension.

1. Introduction

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease clinically characterized by parkinsonism, cerebellar dysfunction, pyramidal tract involvement, and autonomic dysfunction [1]. The median time from initial symptom to combined motor and autonomic dysfunction is 2 years [2]. Almost all patients with MSA develop autonomic dysfunction at some point during the course of the disease. This usually manifests as urinary disturbance and orthostatic hypotension (OH), which are important symptoms used in the diagnosis of MSA. However, the frequency of occurrence of OH in MSA is reported to be 41–88% [3–5], so OH does not always occur.

When working normally, peripheral resistance increases to prevent a decrease in blood pressure (BP) during orthostatic stress as a result of the cardiovascular response to sympathoadrenal activation due to gravitational stress [6]. Conversely, neurogenic OH is seen when peripheral vasoconstriction fails to occur under orthostatic stress [7]. This is thought to be related primarily to the loss of sympathetic preganglionic neurons in the intermediolateral column of the thoracolumbar spinal cord in patients with MSA [8–10]. Thus, it is assumed that many patients with MSA have impaired vasoconstrictor response to orthostatic stress, and these conditions increase the risk for OH. In order to manage OH properly, it is important to evaluate the vasoconstrictor response to orthostatic stress in patients with MSA. However, a study investigating

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the frequency of impaired vasoconstrictor response in MSA was not found in the literature.

We investigated changes in the total peripheral resistance and its association with changes of systolic BP (SBP) and cardiac output during head-up tilt. We also evaluated the possibility of differences in the cardiovascular response in patients with the cerebellar variant of MSA (MSA-C) and the parkinsonian variant (MSA-P). As an additional experiment, patients with MSA who demonstrated an impaired vasoconstrictor response to orthostatic stress were given low dose norepinephrine in order to determine whether the vasoconstrictor response to norepinephrine infusion is adequate to prevent OH in these patients.

2. Methods

2.1. Subjects

The study consisted of 82 patients with probable MSA. Of these, 47 had MSA-C and 35 had MSA-P, which were diagnosed according to the consensus criteria [1]. They were referred to our University Hospital for evaluation by a specialist between April 2007 and September 2014. The clinical phenotype of MSA-C or MSA-P was determined according to the classification assigned at the first visit or at an early stage of the illness. Individuals with diabetes mellitus, any known heart disease, or other neurological disorders were excluded. A control group consisting of 28 age- and sex-matched normal healthy adults was enrolled. The demographic and basic clinical data are shown in Table 1. This study was approved by the ethical committee at Nagoya University, and informed written consent was obtained from all patients with MSA and control subjects.

2.2. Head-up tilt test

All studies were performed at 0900 h in a temperature-controlled clinical laboratory (average temperature 25 ± 2 °C) after an overnight fast. Any drugs that might influence the cardiovascular system, including antiparkinsonian drugs, were discontinued at least 12 h before enrollment. After resting for at least 5 min in a supine position, patients were tilted up to 60° in a stepwise manner (20° for 5 min, 40° for 5 min, and 60° for 5 min). We diagnosed OH when the SBP fell ≥20 mmHg or the diastolic BP (DBP) fell ≥10 mmHg at the fifth minute of the 60° tilt compared to the initial value in the supine position. During testing, each subject's condition was monitored continuously by electrocardiogram.

2.3. Non-invasive cardiac autonomic function evaluation

Noninvasive cardiovascular recordings were performed using a dedicated device (Task Force Monitor, CNSystems, Medizintechnik, Graz, Austria). Electrocardiograms (sampling rate: 1000 Hz) were recorded continuously using 4 spot electrodes. Beat-to beat BP measurements (sampling rate: 1000 Hz) were obtained by finger plethysmography of the index finger on the right hand and continuously corrected to the BP of the brachial artery in the left arm obtained by the oscillometric technique. Impedance cardiography (sampling rate: 1000 Hz) assumes that the thorax can be modeled as a homogenous electrical conductor filled with blood. Volume changes in the cardiovascular system produce impedance variations across the thorax. Surface electrodes constantly deliver a low-amplitude high-frequency current and the measured impedance changes are applied to BP measurements to automatically calculate hemodynamic parameters at every beat. Total peripheral resistance is calculated by using the cardiac output, mean arterial pressure, and central venous pressure. All functions of the Task Force Monitor have been assessed previously, and the instrument has already been used successfully in many advanced clinical and scientific studies [11–13]. Cardiac parameters from impedance cardiography were obtained at every beat, and the average of the last 30 s at baseline and the fifth minute of the 20°, 40°, and 60° tilts were used for analysis. However, if the test was stopped in the middle of the protocol due to severe hypotension, data that had been obtained just before discontinuing the tilt were used.

2.4. Additional examination: norepinephrine infusion test

As an additional examination, patients with MSA who showed vasoconstriction failure in the head-up tilt test were offered to undergo the test again with norepinephrine infusion. Failure of vasoconstriction during orthostatic stress was considered to occur when the total peripheral resistance at the fifth minute of the 60° position was lower than that of 0°. Firstly, after resting for 3 min in a supine position, patients were tilted up to 60° for 3 min without norepinephrine. Next, after resting for at least 5 min in a supine position, we administered norepinephrine intravenously in the forearm at 3 μg/min for 3 min in the supine position. This concentration of drug is usually used to detect denervation supersensitivity to norepinephrine [14]. After 3 min, the patients were tilted up to 60°. We continued the administration of norepinephrine during the 60° head-up tilt for 3 min (total dose, 18 μg). The cardiovascular responses including SBP, DBP, heart rate (HR), total peripheral resistance, stroke volume and cardiac output during head-up tilt with and without norepinephrine infusion were compared.

2.5. Statistical analysis

JMP software, version 11 (SAS Institute, Cary, North Carolina) was used for statistical analyses. Quantitative data are presented as mean ± SD values. Significance was defined as $p < 0.05$ (two-tailed). Categorical variables were analyzed by chi-square statistics. The Mann–Whitney U test was used to compare differences between independent groups. For comparisons of more than 2 groups, analysis of variance (ANOVA) was used. If ANOVA was significant,

Table 1
Characteristics of MSA-C patients, MSA-P patients, and controls.

Characteristic	MSA-C	MSA-P	Control	p value
Number	47	35	28	
Male/female	23/24	16/19	16/12	0.65
Age, mean ± SD (years)	60.6 ± 7.9	61.9 ± 6.6	60.6 ± 11.2	0.89
Disease duration, mean ± SD (years)	2.1 ± 1.3	2.6 ± 1.4	–	0.14
Initial symptoms				
Autonomic, number (%)	13 (27.7)	9 (25.7)	–	0.84
Motor, number (%)	34 (72.3)	26 (74.3)	–	

MSA-C, multiple system atrophy-cerebellar variant; MSA-P, multiple system atrophy-parkinsonian variant.

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