Cutaneous sympathetic function in patients with multiple system atrophy

Introduction

Autonomic disturbance is one of the prominent symptoms in multiple system atrophy (MSA), including striatoniigral degeneration (SND), olivopontocerebellar atrophy (OPCA), and Shy-Drager syndrome (SDS) [1]. Although many investigators have evaluated autonomic dysfunction in MSA patients, there have been few reports on cutaneous sympathetic functions, such as sudomotor function and cutaneous vasomotor function in relation to MSA. Some procedures, such as deep inspiration and exercise, provoke increased sweat output and reduced cutaneous blood flow in the palm; such responses are termed the sympathetic sweat response (SSwR) [2] and skin vasomotor reflex (SVR), respectively [3]. The recording of SSwR and SVR is non-invasive and useful for respective estimation of sudomotor function and cutaneous vasomotor function [2]. We examined cutaneous sympathetic function in MSA patients by measuring SSwR and SVR.

Subjects and methods

Subjects

We studied 40 MSA patients (mean age 59 ± 7 years; 21 females and 19 males), including 26 patients with OPCA (mean age 59 ± 6 years; 15 females and 11 males), 8 patients with SDS (mean age 59 ± 9 years; 3 females and 5 males) and 6 patients with SND (mean age 60 ± 7 years; 3 females and 3 males).
3 females and 3 males). All patients had characteristic clinical manifestations according to the criteria established by the Consensus Statement on the diagnosis of MSA in 1998 [4]. The patients were classified as OPCA, SDS, or SND according to the criteria of Hirayama et al. [5]. The duration of illness was 4.0 ± 2.4 years in the MSA patients (OPCA, 4.4 ± 2.6 years; SDS, 2.8 ± 1.8 years; SND, 3.3 ± 1.2 years). There were no significant differences in age or duration of illness among these 3 clinical subgroups. None of the patients had dementia, tendon areflexia, or prominent gaze palsy. Four SND and 2 SDS patients were prescribed levodopa with a dopa decarboxylase inhibitor (200–600 mg), whereas no patients received a dopamine agonist or anticholinergics. Dopa decarboxylase inhibitors were not discontinued in the levodopa-treated patients. Two SDS patients were treated with 4 mg of midodrine or 5 mg of amezinium for orthostatic hypotension. The midodrine or amezinium was discontinued at least 24 hours before autonomic function tests. Patients taking other medications known to influence autonomic function were excluded. Autonomic function was also examined in 15 age-matched control subjects (mean age 56 ± 11 years; 7 females and 8 males) in good health and not taking any medications. All subjects gave informed consent to participate in the study.

### Autonomic function tests

All experimental procedures were performed in a room with a constant ambient temperature of 24°C. Subjects were encouraged to relax but to remain awake. As indices of cutaneous sympathetic function, SSwR and SVR were recorded first. Next, a head-up tilt test and measurement of R-R intervals were conducted to evaluate cardiovascular function. The subject was placed on a table in the supine position and allowed to rest for at least 15 min before each investigation.

Sweat output was measured on the tip of the thumb (palm side) by a sudorimeter (OS5–100, Kenz), and cutaneous blood flow was recorded on the tip of an index finger (palm side) by a Doppler flowmeter (ALF21D, Advance). The signal, on-line digitized (12-bit A/D-board) at a rate of 100 Hz, was stored on hard disk. Data were analyzed using computer software (BIMUTAS II, Kissei Comtec Co.). We measured sweat output and cutaneous blood flow in the supine position at rest for 3 min and during sympathetic activation procedures that included deep inspiration, mental arithmetic (serial seven test, for 15 sec), exercise (raising both lower limbs for 10 sec), and tactile stimulation (rubbing with the examiner’s finger for 15 sec). These sympathetic activation procedures induced increased sweat output (SSwr) and a reduction of cutaneous blood flow (SVR) (Fig. 1). We considered SSwR and SVR to be absent when there was no response to any of the sympathetic activation procedures. The SSwR amplitude was measured from the baseline to the peak, and the SVR reduction rate (SVR amplitude) was calculated as the percentage of reduced blood flow to basal blood flow ([(reduced flow/basal flow) x100%].

Systolic and diastolic blood pressure and heart rate were measured by a sphygmomanometer and automatically recorded at 1-minute intervals. Each subject was passively tilted on an electrically driven tilt table at 70 degrees for 10 minutes. A drop in systolic blood pressure of >30 mmHg was considered to indicate orthostatic hypotension. The electrocardiogram was recorded with the subject in a supine position as three series of 100 consecutive R-R intervals with an accuracy of 1 msec during normal breathing in each subject, and the coefficient of variation of R-R intervals (CVR-R) was calculated as the standard deviation divided by the mean R-R interval. The CVR-R was taken from the average of three series of measurements and evaluated for abnormality relative to age-dependent values [6].

### Data analysis

Either the Mann-Whitney U test or the chi-square test was used to analyze the differences between the MSA group and controls. The

![Fig.1](image.png) Recording of sympathetic sweat response (upper) and skin vasomotor response (lower) in a normal control subject (57 years old, female). Sweat output was increased by sympathetic activation procedures, including deep inspiration (DI), mental arithmetic (MA), exercise (Ex), and tactile sensation (TS), whereas cutaneous blood flow was reduced.

Kruskal-Wallis test was used to analyze the differences among the OPCA, SDS, and SND subgroups. Spearman’s coefficient of rank correlation was used to determine any correlation between SSwR amplitudes or SVR reduction rates and the postural change of blood pressure or CVR-R values, respectively.

### Results

Means of blood pressure and heart rate in the baseline supine position did not differ between the MSA group and controls, or among the 3 clinical subgroups (Table 1). Orthostatic hypotension (fall of systolic blood pressure >30 mmHg) was seen in 18/40 (45%) of the MSA patients, including 9/26 (34.6%) of the OPCA patients, 6/8 (75%) of the SDS patients, and 3/6 (50%) of the SND patients, whereas no controls showed any evidence of orthostatic hypotension. The incidence of orthostatic hypotension in the MSA patients was significantly higher than that in controls (p < 0.005). The incidence of orthostatic hypotension in the SDS subgroup was high compared with that of other subgroups, although the difference did not appear to be significant. In the head-up tilt test, the mean fall in systolic blood pressure (p < 0.000001) and the mean increment of heart rate (p < 0.05) while standing were significantly greater in the MSA group than in controls. There were no significant differences in those results among the 3 clinical subgroups (Table 1). Abnormally low values of CVR-R were seen in 13/40 (32.5%) of the MSA patients, including 7/26 (26.9%) of the OPCA patients, 4/8 (50%) of the SDS patients, and 2/6 (33.3%) of the SND patients. All controls showed normal values of CVR-R. The incidence