Journal of the Neurological Sciences 380 (2017) 191–195

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Pre- and postganglionic vasomotor dysfunction causes distal limb coldness in multiple system atrophy

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ARTICLE INFO

Article history:
Received 13 March 2017
Received in revised form 10 July 2017
Accepted 16 July 2017
Available online 18 July 2017

Keywords:
Multiple system atrophy (MSA)
Limb coldness (LC)
Skin sympathetic nerve activity (SSNA)
Skin blood flow
Skin vasomotor dysfunction

ABSTRACT

Background: The detailed pathophysiology of limb coldness in multiple system atrophy (MSA) is unknown.
Methods: We evaluated cutaneous vasomotor neural function in 18 MSA patients with or without limb coldness, and in 20 healthy volunteers as controls. We measured resting skin sympathetic nerve activity (SSNA) and spontaneous changes of the sympathetic skin response (SSR) and skin blood flow (skin vasomotor reflex: SVR), as well as SVR and reflex changes of SSNA after electrical stimulation. The parameters investigated were the SSNA frequency at rest, amplitude of SSNA reflex bursts, absolute decrease and percent reduction of SVR, recovery time, and skin blood flow velocity.
Results: Both the resting frequency of SSNA and the amplitude of SSNA reflex bursts were significantly lower in the MSA group than the control group ($p < 0.001$ and $p < 0.05$, respectively). There were no significant differences between the two groups with regard to the absolute decrease or percent reduction of SVR volume. The recovery time showed no significant difference between all MSA patients and control groups, but it was significantly prolonged in six MSA patients with limb coldness compared with that in the control group and that in MSA patients without limb coldness ($p < 0.01$). The skin blood flow velocity was significantly slower in the MSA group than in the control group ($p < 0.001$).
Conclusion: In MSA patients, limb coldness might occur due to impairments of the peripheral circulation based on prolongation of vasoconstriction and a decrease of skin blood flow velocity secondary to combined pre- and postganglionic skin vasomotor dysfunction.

1. Introduction

Patients with multiple system atrophy (MSA) frequently have various symptoms of autonomic dysfunction in addition to parkinsonian, cerebellar, and pyramidal symptoms [1–3]. Thermoregulatory and vasomotor abnormalities are often detected by structured questionnaires or by physiological testing [4–6]. Several investigators have reported that thermoregulatory dysfunction in MSA patients is due to central autonomic involvement [5–8]. It has been reported that 45–65% of MSA patients have cold hands [9,10] and the "cold hands sign" is one of the supporting features (red flags) for diagnosis of this condition in recent criteria [11]. However, several studies have investigated cutaneous vasomotor function by measurement of blood flow [5,6,12,13], so the detailed pathophysiology of limb coldness in patients with MSA is unknown.

Skin sympathetic nerve activity (SSNA) has an important role in the regulation of skin blood flow and sweating via the thermoregulatory center, and it has recently become easier to record SSNA by microneurography in conventional laboratories [14–16]. However, there have been few investigations of skin vasomotor function (including SSNA) in MSA, and good recordings of SSNA are reported to be difficult to obtain in MSA patients with symptomatic thermoregulatory dysfunction. In the present study, we performed a detailed evaluation of cutaneous vasomotor neural function in MSA patients with or without limb coldness by measuring reflex changes of skin blood flow and SSNA after electrical stimulation, as well as resting SSNA and spontaneous changes of the sympathetic skin response (SSR) and the skin vasomotor reflex (SVR).

2. Materials and methods

2.1. Participants

We studied 18 patients with MSA (5 men and 13 women with a mean [SD] age of 61.9 [6.5] years; range: 48 to 77 years). Their scores

Abbreviations: MSA, multiple system atrophy; SSR, sympathetic skin response; SVR, skin vasomotor reflex; SSNA, skin sympathetic nerve activity.

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http://dx.doi.org/10.1016/j.jns.2017.07.018
0022-510X/

Table 1
Background and clinical findings in patients with MSA.

Patient no.	Age (years)/gender	Duration of the disease (years)	Disability level (UMSARS Part 1/Part 2)	Autonomic symptoms	LC	Subtypes of MSA	Anti-parkinso-nian drugs
1	48/M	2	11/16	C, U	(−)	MSA-C	(−)
2	53/M	3	24/26	C, U, OH	(+)	MSA-C	Levodopa
3	54/F	2	18/22	C, U, OD	(−)	MSA-C	(−)
4	55/F	1.5	18/21	C, U, OD	(+)	MSA-C	(−)
5	57/F	3	18/24	C, U, OD	(−)	MSA-C	(−)
6	57/M	7	27/33	C, U	(−)	MSA-P	Levodopa
7	58/F	3	26/32	C, U, OD	(−)	MSA-C	(−)
8	58/M	5	24/26	C, U, OD	(−)	MSA-P	Levodopa
9	60/F	5	26/34	C, U,	(+)	MSA-C	(−)
10	63/F	4	24/28	C, U, OD	(+)	MSA-C	(−)
11	63/M	2	24/29	C, U	(−)	MSA-P	Levodopa
12	63/F	3	18/24	C, U, OD	(−)	MSA-P	Levodopa
13	65/F	1.5	14/16	C	(+)	MSA-C	
14	65/F	5	24/30	C, U, OD	(−)	MSA-P	Levodopa
15	65/F	1	11/16	C, U	(−)	MSA-C	
16	67/F	1.5	16/20	C, U	(+)	MSA-C	
17	73/M	3	24/36	C, U, OH	(−)	MSA-P	Levodopa
18	77/M	2	20/26	C, U, OD	(−)	MSA-P	Levodopa
Mean ± SD	61.9 ± 6.5 M:F = 5:13	2.6 ± 1.8	20.9 ± 4.7/26.1 ± 5.9			MSA-C:MSA-P = 11:7	

MSA, multiple system atrophy; LC, limb coldness; M, male; F, female; C, constipation; U, urinary urgency; OD, orthostatic dizziness; OH, orthostatic hypotension; SD, standard deviation.

on the Unified Multiple System Atrophy Rating Scale (UMSARS) ranged from 11 to 27 (mean: 20.9 (4.7)) for Part 1 and ranged from 16 to 36 (mean: 26.9 (5.9)) for Part 2. Based on the criteria of Gilman et al. [11], the clinical diagnosis was MSA with predominant parkinsonism (MSA-P) in 7 patients and cerebellar-type MSA (MSA-C) in 11 patients. In all patients, magnetic resonance imaging revealed the pontine hot cross bun sign along with cerebellar atrophy or abnormal linear intensities in the outer putamen. The interval from disease onset to the present study ranged from 0.5 to 7 years (mean ± SD: 2.6 ± 1.8 years). All patients had autonomic symptoms, including constipation, urinary urgency, orthostatic dizziness, and orthostatic hypotension. Six patients had distal limb coldness, which was defined as subjective sensitivity to cold, pallor of the fingers of both hands, and palm skin temperature < 28 °C, especially during the winter. Sixteen patients were on medications for urinary urgency or constipation, but none of them were using vasopressors. Five patients had orthostatic hypotension (defined as a decrease of systolic blood pressure by ≥20 mm Hg or a decrease of diastolic blood pressure by ≥10 mm Hg on standing), but MSA patients with severe autonomic symptoms (such as typical cold hands sign, heat intolerance due to anhidrosis, or episodes of syncope due to OH) were excluded from the present study. Eight patients were taking levodopa (Table 1).

None of the patients had dyspnea at rest and they did not have concurrent disorders such as hypertension, cardiovascular disease, or cerebrovascular disease. They continued routine antiparkinsonian drugs during the study to prevent exacerbation of neurological symptoms, and most recent dose of medication was taken 2 to 3 h before assessment. Other drugs that could affect the autonomic nervous system, such as muscle relaxants, vasodilators, or antidepressants, were discontinued 2 days before the examination.

The control group consisted of 20 subjects, including 5 men and 15 women with a mean ± SD (range) age of 59.8 ± 8.5 (41–74) years. Limb coldness in cold winter season or autonomic symptoms in association with postganglionic dysfunction in limbs was not found in control subjects.

2.2. Physiological examinations

Informed consent was obtained from each subject before the study. The study protocol was approved by the ethics committee of the Japan Microneurography Society. All examinations were carried out in a semidarkened room with the subject relaxed in the supine position. The below measurements were performed from September to October for three years intensively. Subjects ate 3 h before being examined. The room temperature was maintained at 24 °C to 26 °C. If the skin temperature was <32 °C, the lower limbs were warmed. Subjects ate a meal at 3 h before being examined. All subjects first underwent conventional motor and sensory conduction studies of the median, ulnar, peroneal, and tibial nerves, which confirmed that the conduction velocities and amplitudes of the MSA patients were within the mean ± 2 SD range for the control subjects.

SSNA was elicited and recorded by using the microneurographic method described previously [15]. SSNA was identified on the basis of multiple characteristics such as irregular occurrence of spontaneous bursts without pulse synchrony; bursts induced by a loud voice, electrical stimulation, or deep inspiration; and a constant relationship between the spontaneous bursts and changes of skin blood flow demonstrated by laser flowmetry or SSR.

With the subject in the supine position, SSNA was recorded directly from peroneal nerve fascicles at the popliteal fossa by tungsten microelectrodes. The electrodes were connected to a preamplifier (model LI-75A; NF Circuit Design Block, Yokohama, Japan) with a gain of 100 and to an amplifier (model AVN-10; Nihon Kohden, Tokyo, Japan) with a gain of 500. A band-pass filter of 500 to 2000 Hz was used. To obtain a mean-voltage neurogram, the filtered neurogram was fed into a

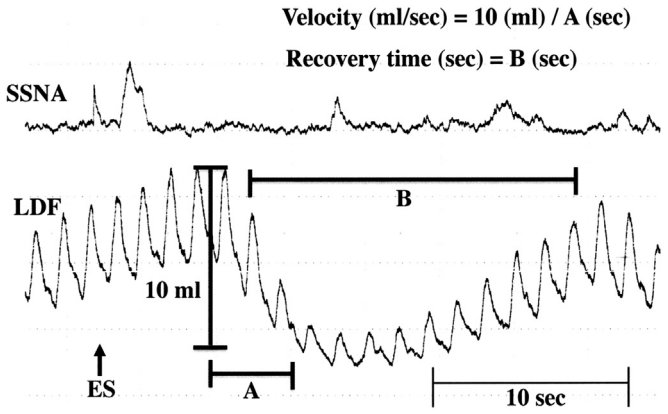

Fig. 1. The measurement method of the skin blood flow velocity calculated from the interval when the reduced response after electrical stimulation (ES) was obtained is shown. SSNA, skin sympathetic nerve activity; LDF, laser Doppler flowmetry.