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Preserved autonomic function in patients with POEMS syndrome

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ABSTRACT

Aim: We systematically performed autonomic testing on patients with polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome (POEMS) to determine whether autonomic function is preserved in such patients.
Methods: We studied 17 POEMS patients, 17 diabetic neuropathy (DN) patients and 17 age-matched normal subjects. Blood pressure responses to the head-up tilt test and heart rate variability were used to evaluate cardiovascular autonomic function. Sweat responses and cutaneous vasoconstriction to several stimuli were recorded via the finger tips to estimate cutaneous sympathetic function. In addition, motor nerve conduction studies were performed.
Results: Although the results of the autonomic testing were normal in POEMS patients, motor disability was severe, and motor nerve conduction studies provided evidence of extensive axonal loss. The DN patients showed significantly impaired autonomic responses despite mild motor dysfunction.
Conclusions: Autonomic function was normal in POEMS patients, indicating the preservation of autonomic fibers and selective involvement of large fibers.

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1. Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome (POEMS) is a disease that causes mixed axonal/demyelinating polyneuropathy with multiple organ involvement and plasma cell dyscrasia. Its major clinical feature is chronic progressive polyneuropathy with predominant distal motor disability [1–3], which is presumably mediated by the overproduction of vascular endothelial growth factor [4]. POEMS syndrome is potentially fatal [2], and immediate treatment, such as using high-dose chemotherapy with autologous peripheral blood stem cell transplantation or thalidomide therapy, is usually required [5,6]. However, early diagnosis is quite difficult, particularly when patients present with polyneuropathy without the associated systemic symptoms or signs such as hyperpigmentation of the skin, peripheral edema, hypertrichosis or organomegaly [7]. In POEMS, motor involvement follows the sensory symptoms which begin in the feet. Sensory and motor symptoms are distal, symmetric and progressive with a gradual proximal spread [7]. Information on the extent of autonomic involvement in this syndrome may be helpful for its early diagnosis. However, no previous reports have focused on autonomic function in patients with POEMS. Therefore, we performed systematic autonomic testing in POEMS patients and compared the results with those in patients with diabetic neuropathy (DN).

2. Methods

We prospectively studied 17 POEMS patients (13 men and 4 women; mean age, 54 ± 9 years; mean disease duration, 3 ± 3 years) in this study. They were consecutive patients who were referred to the Department of Neurology of Chiba University Hospital from 2005 to 2009. All patients fulfilled the published diagnostic criteria for POEMS that were proposed by Dispenzieri. Table 1 shows the clinical profiles of our POEMS patients. Seventeen patients with DN (11 men and 6 women; mean age, 60 ± 10 years; mean disease duration of diabetes, 13 ± 11 years) were included as disease controls. DN was defined by known diabetes mellitus criteria and the presence of symmetric sensory-dominant polyneuropathy [8]. The mean hemoglobin A1c levels in DN patients were 8.3% ± 1.6%. Seventeen healthy controls (13 men and 4 women; mean age, 55 ± 9 years) were also evaluated. No participant received medications that could affect autonomic nervous system activity. Written informed consent was obtained from all patients. The ethics committee of Chiba University School of Medicine approved this study.

Clinical motor disability was assessed using the following overall neuropathy limitation scale: a grade for each upper limb was scaled from 0 (normal) to 5 (most severe) and that for each lower limb was scaled from 0 (normal) to 7 (most severe) [9]. Motor nerve conduction studies were performed on the tibial nerve using conventional procedures with a lower limit of 5.6 mV for the normal range of compound motor action potentials (CMAPs) according to our laboratory data. Autonomic function tests were performed in a quiet room at an ambient temperature of 24–26 °C. Each subject was asked to relax, stay awake

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Table 1
Clinical profiles of patients with POEMS syndrome.

No.	Age (years)	Sex	Disease duration (months)	ONLS		Sensory loss		CMAP* (mV)	SNAP** (μV)	VEGF† (pg/mL)	Therapeutic response		
				Upper limb	Lower limb	Pain	Vibration				Steroid	Thalidomide	Auto-PBSCT
1	43	M	15	1	3	Mild	Severe	NR	NR	7160			
2	58	M	5	0	2	Mild	Severe	2.9	3.7	2040			
3	52	M	44	3	6	Severe	Severe	NR	NR	378	NTR		
4	41	M	7	1	2	Severe	Severe	NR	NR	5110			
5	50	M	34	2	3	Mild	Mild	NR	NR	317	PTR	PTR	TR
6	34	F	48	1	7	Mild	Moderate	NR	10	3990			
7	63	M	49	1	1	Mild	Severe	1.1	NR	470	NTR	NE	
8	55	M	27	2	3	Mild	Mild	0.32	4	499			TR
9	57	M	13	1	4	Mild	Severe	NR	NR	4810	NE	NE	
10	64	F	44	1	2	Severe	Severe	0.15	NR	5570	PTR	NE	
11	46	F	13	2	4	Severe	Severe	NR	NR	9950	NE	NE	
12	57	M	11	1	3	Moderate	Moderate	NR	2	5250			
13	59	M	29	0	3	Mild	Severe	NR	NR	320		PTR	TR
14	53	M	126	0	0	Mild	Mild	NR	7	261	PTR		TR
15	53	M	55	1	2	Mild	Severe	0.5	NR	1310	PTR	PTR	TR
16	65	M	64	1	4	Moderate	Moderate	NR	NR	119	PTR	NE	
17	51	F	52	1	2	Mild	Mild	NR	NR	450	PTR		TR

POEMS = polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes syndrome.
ONLS, overall neuropathy limitation scale (0 indicates no symptoms of neuropathy, most severe grades are 5 in the upper limb and 7 in the lower limb).
CMAP, compound motor action potential in the tibial nerve; SNAP, sensory nerve action potential in the sural nerve.
NR, not recorded; VEGF, vascular endothelial growth factor; Auto-PBSCT, autologous peripheral blood stem cell transplantation.
TR, therapeutic response; PTR, partial therapeutic response; NTR, no therapeutic response; NE, not evaluated.
*Normal > 5.6 mV, **normal > 3.4 μV, †normal < 1000 pg/mL.

and remain supine for at least 20 min before the tests. During the head-up tilt test, systolic and diastolic blood pressure and heart rate were measured using a sphygmomanometer at 1-min intervals. After 5 min of baseline measurements, each subject was tilted to 70° for 10 min on an electrically driven tilt table. Electrocardiography was used to record limb lead (II) measurements during normal breathing in the supine position, and three series of 100 successive R–R intervals were used to obtain the coefficient of variation of the R–R intervals (CV_{R-R}). This coefficient was calculated as the standard deviation divided by the mean R–R interval (%). The average of these three series was used as the CV_{R-R} value. Sweat output was measured on the right thumb fingertip using a sudorometer (model SKD-1000; SKINOS Co., Nagano, Japan), and cutaneous blood flow was recorded on the right index finger tip using a Doppler flow meter (model ALF21D; Advance, Tokyo, Japan). Sweat output and skin blood flow were recorded during a sympathetic activation test that involved deep inspiration, mental arithmetic and exercise. These procedures increased sweat output (sympathetic sweat response) and reduced cutaneous blood flow (skin vasomotor reflex) to the palms [10]. The amplitude of the sympathetic sweat response was measured from the baseline to the peak. The amplitude of the skin vasomotor response was calculated as the percentage of blood flow that fell below the basal blood flow rate (reduction rate).

Analysis of variance (ANOVA) was used to analyze the differences in the parametric values among all three groups. When ANOVA showed a significant difference, a Tukey's test was performed. A Chi-square test or the Mann–Whitney *U*-test was used to analyze differences between the two patient groups. Values were presented as means ± standard deviation.

3. Results

The overall neuropathy limitation scale scores (arm grade = 1.1 ± 0.8, leg grade = 3.0 ± 1.7) for the POEMS patients were significantly higher than those (0.4 ± 0.5, 0.2 ± 0.7, respectively) for the DN patients ($p<0.01$, $p<0.000005$, respectively). In the tibial nerve, CMAPs were absent in 12 (71%) and reduced in five (29%) POEMS patients; none demonstrated normal CMAPs. In the DN group, CMAPs were reduced in nine (53%) and normal in eight (47%) patients; none demonstrated absent CMAPs. The CMAP reduction in the POEMS patients was significantly greater than that in the DN patients ($p<0.05$).

In the head-up tilt test, blood pressures and heart rate in the supine position were comparable between the three groups. None of the patients showed serious bradycardia (heart rate < 50 beats/min) or tachycardia (heart rate > 100 beats/min) in the supine position. One POEMS patient (6%) and 12 DN patients (71%) showed orthostatic hypotension (decrease in systolic blood pressure of > 20 mm Hg or decrease in diastolic pressure of > 10 mm Hg) during the head-up tilt test [11]. The decreases in systolic and diastolic blood pressures recorded during the head-up tilt test were significantly greater in the DN group than those in controls ($p<0.0005$, $p<0.01$, respectively) and POEMS patients ($p<0.0005$, $p<0.001$, respectively); they were not significantly different between POEMS patients and controls. One POEMS patient (6%) and seven DN patients (41%) showed abnormal CV_{R-R} values. The CV_{R-R} values in the DN patients were significantly lower than those in the POEMS patients ($p<0.05$), whereas they were not significantly different between POEMS patients and controls (Fig. 1).

Basal sweat output was comparable between the three groups. Two POEMS patients (12%) and seven DN patients (41%) did not show sympathetic sweat responses to any stimuli. The amplitudes of the sympathetic sweat responses in the DN patients were significantly lower than those in the controls for deep inspiration ($p<0.01$), mental arithmetic ($p<0.05$) and exercise ($p<0.05$), and they were also significantly lower than those in the POEMS patients for mental arithmetic ($p<0.05$) and exercise ($p<0.05$). There were no significant differences between the POEMS and control groups (Fig. 2). The baselines of cutaneous blood flow were comparable between the three groups. Six DN patients (35%) did not show skin vasomotor responses to any stimuli, whereas all POEMS patients presented normal responses. The reduction rates of the skin vasomotor responses in the DN patients were significantly lower than those in the controls for deep inspiration ($p<0.001$) and significantly lower than those in the POEMS patients for deep inspiration ($p<0.001$) and exercise ($p<0.05$). The reduction rates of the skin vasomotor responses were not significantly different between the POEMS and control groups (Fig. 2).

4. Discussion

In our study, POEMS patients had high disability scores and severe motor neuropathies that were demonstrated by nerve conduction studies. However, most showed normal results on the cardiovascular

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