Prolonged Sympathetic Reflex Latency on Skin Nerves in Sporadic Cerebellar Degeneration

Kazumasa Shindo, MD; Shin-ichi Tsunoda, MD; Zenji Shiozawa, MD

Background: Many physiological or pharmacological evaluations of autonomic function have been performed in patients with various types of cerebellar degeneration (CD). Few studies have been done, however, using neurographic recordings in patients with CD, especially of sudomotor or vasoconstrictor nerves.

Objective: To confirm the clinical importance of sympathetic reflex latencies on the skin nerves of patients with various types of CD.

Design and Setting: Case-comparison study at an academic center.

Participants: We studied 12 patients who had sporadic CD (cerebellar cortical atrophy, olivopontocerebellar atrophy, and Shy-Drager syndrome) and 15 healthy volunteers as controls.

Methods: Skin sympathetic nerve activity (SSNA), sympathetic skin response, and skin vasomotor reflex were simultaneously recorded using randomly administered electrical stimuli.

Results: In controls, SSNA reflex latency ranged from 640 to 864 milliseconds. Patients with cerebellar cortical atrophy exhibited slight but significant \((P<.01)\) prolongation of reflex latency to the onset of reflex bursts. In patients with olivopontocerebellar atrophy, latency to the onset and the peak of reflex bursts was significantly prolonged \((P<.001)\). Patients with Shy-Drager syndrome had no SSNA, sympathetic skin response, or skin vasomotor reflex, even with supramaximal electrical stimuli.

Conclusions: Prolonged reflex latency or the absence of reflex bursts on SSNA can be observed in patients with CD with various forms of autonomic dysfunction. The measurement of SSNA reflex latency may be a useful method of evaluating sympathetic function, including the central pathway.

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PATIENTS AND METHODS

PATIENTS AND CONTROL SUBJECTS

We studied 12 patients (5 men and 7 women; mean ± SD age [range], 59.0 ± 7.0 [45-69] years) with CD without a family history of such disorders who had had magnetic resonance imaging. Cerebellar degeneration was diagnosed based on the presence of progressive cerebellar ataxia and obvious cerebellar atrophy without vascular lesions of the brainstem or cerebellum. Patients with cerebellar ataxia due to alcohol poisoning, antiepileptic agents, viral infections, or the effects of cancer were excluded. The clinical duration of CD ranged from 1.5 to 6 (3.5 ± 1.2 [mean ± SD]) years. All patients had mild to severe limb or truncal ataxia. They were divided clinically into the following types: patients who had cerebellar cortical atrophy (CCA) with mild autonomic symptoms; those who had OPCA with moderate autonomic symptoms in addition to pyramidal or extrapyramidal symptoms; and those who had SDS, characterized by severe autonomic symptoms in addition to other neurological signs (Table 1).

The control group consisted of 15 healthy age-matched volunteers (10 men and 5 women; mean ± SD age [range], 52.2 ± 14.6 [28-72] years).

Patients who had CD and the control subjects did not have any other known ailments, including hypertension, cardiovascular disease, cerebrovascular disease, or polyneuropathy. Informed consent was obtained from each subject before study. The study protocol was approved by the ethics committee of Japan Neurography Society. All drugs that would affect the autonomic nervous system were discontinued 2 days before the procedure. No patients with CD were administered anticholinergic drugs, such as amitriptyline hydrochloride.

PREPARATION

All examinations were performed in a semidarkened room with the subject supine and relaxed and with the ambient temperature controlled at 24°C to 28°C. If the measured skin temperature was less than 32°C, the lower limbs were warmed. Subjects ate 3 hours before being examined. All subjects first underwent conventional motor and sensory conduction studies, confirming that conduction velocities and amplitudes in all patients having CD were within the mean ± 2 SDs of those in control subjects. Each subject’s leg length was measured from the L4 vertebra to the internal malleolus.

MICRONEUROGRAPHY

Skin sympathetic nerve activity (SSNA) was elicited and recorded using microneurographic methods as previously described.14,15 Skin sympathetic nerve activity was identified by several characteristics, such as irregularly occurring spontaneous bursts with no pulse synchrony; bursts induced by loud voices, electrical stimuli, or deep inspiration; and a constant relationship between spontaneous bursts and changes in skin blood flow, demonstrated by laser flowmetry or sympathetic skin response (SSR).

With subjects in the supine position, SSNA was recorded directly from peroneal nerve fascicles at the popliteal fossa using 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 AVM-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 resistance capacitance integrating unit (model EI-601G; Nihon Kohden) at a time constant of 0.1 second.

Continued on next page
SSR AND SKIN VASOMOTOR REFLEX

The SSR was recorded based on methods described previously by Shahani et al.\(^1\) and Braune et al.\(^1\) Surface electrodes were applied to the sole and dorsum of the right foot. The band-pass filter was 0.5 to 1000 Hz. Skin blood flow was recorded in the foot using a laser Doppler flowmeter (model ALF21; Advance, Tokyo) to measure the skin vasomotor reflex (SVR) according to the method developed by Low et al.\(^1\) The laser probe was attached to the pulp of the little toe. The SSR and SVR were expressed as the percentage of frequency, which refers to the frequency of occurrence of SSR and SVR after electrical stimulation.

MEASUREMENT AND ANALYSIS

The SSNA, SSR, and SVR were monitored with an oscilloscope (model VC-10; Nihon Kohden), and the data were recorded simultaneously on a thermal array recorder (model RTA1200; Nihon Kohden) at a paper speed of 5 and 25 mm/s. Data recording was preceded by a 15-minute rest. Electrical stimuli used single-square-wave pulses of 0.1 milliseconds, 30 to 90 mA, applied randomly to the skin at the level of the ankle at irregular intervals of 30 seconds or more. Each stimulus was delivered 20 times.

The SSNA reflex latency was determined as the time from a stimulus to the onset of a reflex burst, measured from recordings in which the SSNA reflex burst was easily identified. Investigators who were unaware of the clinical findings in individual patients identified sympathetic reflex bursts by inspecting the mean-voltage neurogram. The data were fed into a computer (model PC-E 550; Sharp, Osaka, Japan), and latencies and amplitudes were measured with a digitizer (DST-4AN model 30; Pentel, Tokyo).

The results are expressed as mean ± SD. Data were evaluated statistically using the unpaired Student t test; P < .05 was considered statistically significant.

COMMENT

We confirmed a consistent relationship between electrical stimulation and reflex bursts of SSNA, SSR, and SVR in control subjects. In contrast to previous reports,\(^1\) no significant correlation was found between SSNA reflex latency and leg length. One reason for this discrepancy is that our control subjects had less variation in leg length than that reported by Fagius and Wallin.\(^1\) Another is that large interindividual differences in burst amplitude are frequently observed in healthy subjects on recordings of sympathetic neurograms. One could speculate that these amplitude differences may obscure a prolonged latency associated with a longer leg.

Patients who had CCA exhibited prolonged SSNA reflex latency, and this was even more prolonged in patients who had OPCA. The possibility that latency is prolonged because of decreased amplitudes of SSNA reflex bursts can be excluded because the latency to the onset and the peak of reflex bursts was prolonged in those with CCA.\(^1\) This finding suggests that latency prolongation can also be caused by decreased amplitudes of SSNA reflex bursts. One could speculate that these amplitude differences may obscure a prolonged latency associated with a longer leg.

Figure 1. Representative recordings (sympathetic skin response [SSR], integrated skin sympathetic nerve activity [SSNA], and laser Doppler flowmetry) in (A) a 50-year-old healthy female volunteer, (B) a 57-year-old woman with cerebellar cortical atrophy, (C) a 63-year-old woman with olivopontocerebellar atrophy, and (D) a 64-year-old man with Shy-Drager syndrome when electrical stimuli (ES) were administered. Each bottom tracing is an expanded record during electrical stimulation.
patients with OPCA. In addition, control subjects with lower amplitudes of reflex bursts did not exhibit prolonged latency.

The SSNA reflex latency was prolonged in proportion to the prominence of autonomic symptoms in patients with CD. Because SSNA reflex bursts reportedly consist of 2 components—an early sudomotor burst and a subsequent vasoconstrictor burst—prolonged latency may reflect the loss of the sudomotor component. Previous studies of autonomic function in patients with CD have shown a tendency for sudomotor function to be affected earlier in the clinical course than vasoconstrictor function. In our study, the SSR tended to disappear earlier than the SVR in proportion to the severity of autonomic symptoms (Table 3).

Another possible mechanism is that SSNA reflex latency was prolonged by latency delay in the spinal cord. Using magnetic stimulation, Uozumi et al reported a latency delay in the central nervous system in an SSR study of a patient with OPCA. A patient with OPCA in our study exhibited the prolonged latency of reflex bursts with evident double peaks. Although all patients with CD had normal results on the motor and sensory conduction study, this does not mean that the slowing of SSNA is not caused by peripheral factors because standard nerve conduction velocity mainly reflects the potentials of large myelinated fibers. Fagius, however, has reported that SSNA reflex latency is not prolonged in patients with autonomic neuropathy. These results suggest a possible latency delay in the central connections.

Resting SSNA characteristically shows large interindividual and intralindividual variability because this activity is easily increased or attenuated by changes in mental and environmental conditions. The SSNA reflex latency in response to electrical stimuli, however, was elicited easily, with good reproducibility in controls and in patients with CD, except in those with SDS. Because no consistent SSNA response to electrical stimuli was elicited in patients with SDS, reflex bursts of SSNA in the legs may progressively disappear in patients who have CD with severe autonomic dysfunction or an absence of SSR or SVR.

In conclusion, because SSR and SVR are effector-organ responses, they show a tendency to disappear due to habituation or to skin or peripheral vascular lesions. The direct recording of neurograms may reflect global and specific sympathetic function, unless patients have peripheral neuropathy. The measurement of SSNA reflex latency by electrical stimuli may be a useful tool to evaluate central autonomic function in degenerative neurological disorders. Further microneurographic studies in other types of CD syndromes or in patients with multiple system atrophy would be necessary to confirm this significance.

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We thank Toshimasa Onaya, MD, and Tadaaki Mano, MD, for helpful suggestions and advice on this work.

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Table 2. Quantitative Data in Controls

<table>
<thead>
<tr>
<th>Subject No./Sex/Age, y</th>
<th>Latency, ms</th>
<th>Burst Amplitude, µV</th>
<th>Frequency of Response, %*</th>
<th>Leg Length, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To Start</td>
<td>To Peak</td>
<td>SSR</td>
<td>SVR</td>
</tr>
<tr>
<td>1/F/28</td>
<td>728</td>
<td>1020</td>
<td>29.7</td>
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<td>2/F/30</td>
<td>800</td>
<td>1072</td>
<td>29.8</td>
<td>90</td>
</tr>
<tr>
<td>3/M/33</td>
<td>712</td>
<td>1080</td>
<td>13.2</td>
<td>100</td>
</tr>
<tr>
<td>4/M/34</td>
<td>640</td>
<td>952</td>
<td>23.8</td>
<td>100</td>
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<tr>
<td>5/F/50</td>
<td>864</td>
<td>1180</td>
<td>11.3</td>
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<td>813</td>
<td>1100</td>
<td>6.5</td>
<td>90</td>
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<td>7/M/54</td>
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<td>1016</td>
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<td>19.0</td>
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<td>11/M/64</td>
<td>696</td>
<td>1008</td>
<td>7.8</td>
<td>100</td>
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<td>1072</td>
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<td>95</td>
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<td>100</td>
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<td>14/M/68</td>
<td>680</td>
<td>968</td>
<td>10.8</td>
<td>100</td>
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<tr>
<td>15/F/72</td>
<td>740</td>
<td>1068</td>
<td>23.0</td>
<td>100</td>
</tr>
</tbody>
</table>

*SSR indicates sympathetic skin response; SVR, skin vasomotor reflex.

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Figure 2. Skin sympathetic nerve activity reflex latency in controls, patients with cerebellar cortical atrophy (CCA), and patients with olivopontocerebellar atrophy (OPCA). The horizontal bars represent the mean ± SD. Asterisk indicates P < .01; dagger, P < .001.
Table 3. Quantitative Data in Patients With Cerebellar Cortical Atrophy (Patients 1-4) and Olivopontocerebellar Atrophy (Patients 5-8)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>To Start</th>
<th>To Peak</th>
<th>Burst Amplitude, µV</th>
<th>SSR</th>
<th>SVR</th>
<th>Leg Length, cm</th>
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<td>800</td>
<td>996</td>
<td>13.6</td>
<td>95</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>928</td>
<td>1176</td>
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<td>90</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>880</td>
<td>1120</td>
<td>35.4</td>
<td>100</td>
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<td>84</td>
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<td>4</td>
<td>816</td>
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<td>5</td>
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<td>1548</td>
<td>8.3</td>
<td>0</td>
<td>40</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>1024</td>
<td>1292</td>
<td>8.6</td>
<td>10</td>
<td>60</td>
<td>75</td>
</tr>
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</table>

* SSR indicates sympathetic skin response; SVR, skin vasomotor reflex.

Table 4. Comparisons of Data in 3 Groups of Controls and Patients With Cerebellar Cortical Atrophy (CCA) and Olivopontocerebellar Atrophy (OPCA)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, y</th>
<th>To Start</th>
<th>To Peak</th>
<th>Amplitude Burst, µV</th>
<th>Leg Length, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA (n = 4)</td>
<td>56.0±10.0</td>
<td>856.0±59.1</td>
<td>1074.0±88.5</td>
<td>15.6±13.6</td>
<td>82.0±4.3</td>
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<tr>
<td>OPCA (n = 4)</td>
<td>59.0±6.9</td>
<td>1083.0±56.7</td>
<td>1469.1±121.3§</td>
<td>7.4±1.5§</td>
<td>78.3±4.0</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD. All P values are derived from patients vs controls.
†P<.01.
‡P<.001.
§P<.05.

Figure 3. Amplitudes of skin sympathetic nerve activity reflex bursts in controls, patients with cerebellar cortical atrophy (CCA), and patients with olivopontocerebellar atrophy (OPCA). The horizontal bars represent the mean ± SD. Asterisk indicates P<.50, dagger, P<.05.

REFERENCES