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Sympathetic skin response and heart rate variability as diagnostic tools for the differential diagnosis of Lewy body dementia and Alzheimer's disease: a diagnostic test study

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ABSTRACT

Objective: The purpose of this study is to investigate the usefulness of sympathetic skin response (SSR) and heart rate variability (HRV) for the differential diagnosis of patients with dementia with Lewy bodies (DLB).

Design: A diagnostic test study.

Setting: Single centre in Japan.

Participants: We examined 20 patients with probable Alzheimer's disease (AD) diagnosed with NINCDS-ADRDA criteria and 20 with probable DLB diagnosed with the criteria of the third international DLB workshop.

Methods: For the SSR measurement, surface electrodes were used: the active recording electrode was placed on the palm of the hand and the reference electrode was placed on the dorsum of the same hand. SSR was induced by a median nerve electrical stimulation at an amplitude of 20 mA. For the HRV measurement, the A–A intervals were measured twice for 2 min with an interval of 5 min in a sitting position after a rest of 5 min. From the low-frequency power (LF; 0.02–0.15 Hz) and high-frequency power (HF; 0.15–0.50 Hz), the ratio of LF to HF power (LF/HF) was calculated using the maximal entropy method.

Results: SSR and HRV could detect the abnormality of autonomic function in patients with DLB at sensitivities of 85% and 90%, respectively. On the other hand, SSR and HRV detected an abnormality of autonomic function in patients with AD at sensitivities of 15% and 25% ($p<0.05$). The combination of the SSR and the HRV (double-positive) indicated abnormal autonomic function was recorded in only 1 of 20 patients (5%) with AD. In contrast, this combination indicated autonomic abnormality in 15 of 20 patients with DLB by our criteria (75%).

Conclusions: SSR and HRV can be applied to differentiate DLB from AD.

ARTICLE SUMMARY

Article focus

- To investigate the usefulness of sympathetic skin response (SSR) and heart rate variability (HRV) for the differential diagnosis of patients with dementia with Lewy bodies (DLB).

Key message

- SSR and HRV can be applied to differentiate DLB from Alzheimer's disease (AD).

Strengths and limitations of this study

- SSR and HRV could detect abnormalities of autonomic function in patients with DLB at sensitivities of 85% and 90%, respectively. On the other hand, SSR-detected and HRV-detected abnormalities of autonomic function in patients with AD at sensitivities of 15 and 25% ($p<0.05$).
- The combination of SSR and HRV (double-positive) indicated abnormal autonomic function in only 1 of 20 patients (5%) with AD. In contrast, this combination indicated autonomic abnormality in 15 of 20 patients with DLB by our criteria (75%).

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia after Alzheimer's disease (AD).[1] Because of the difficulty of distinguishing DLB from AD owing to overlapping clinical features, ^{123}I-metaiodobenzylguanidine (MIBG) scan is described as a supportive examination in the diagnosis of DLB.[2] MIBG scan is regarded as a useful examination of sympathetic function. However, the utilisation of a radioisotope (RI), high running costs and long testing time prevent the MIBG scan from becoming a routine clinical examination. We investigate the utilisation of other autonomic examinations, that is, sympathetic skin response (SSR) and heart rate variability (HRV) instead of MIBG scan.

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PATIENTS AND METHODS

Patients

This study was approved by the ethics committee of Kanazawa-Nishi Hospital. The patients' consents were obtained using a written consent form. The test was performed from 2009–2010. We tested 20 Japanese patients with probable AD diagnosed with NINCDS-ADRDA criteria[3] and 20 with probable DLB diagnosed with the criteria of the third international DLB workshop[2] (table 1). To detect a difference of a value of 1 at the desired significance level of 0.05 and power of 0.80, 20 patients in each group were required. There were no differences in the Mini-Mental State Examination and the frontal assessment battery scores between the DLB and the AD groups. We evaluated the ratio of heart to mediastinum uptake (H/M) of the MIBG scan using single-photon emission CT. The values of H/M ratio in all the AD patients were greater than 1.70 and those of all the DLB patients were lesser than 1.50. We excluded patients with cardiovascular disease including arrhythmia, diabetes mellitus, other degenerative diseases and peripheral neuropathies. We also excluded patients not willing to participate in the study.

Testing of autonomic functions

Examinations were performed in a quiet room in which the patients relaxed and made themselves comfortable. We also offered patients a rest after the examinations.

For the SSR measurement, surface electrodes were used: the active recording electrode was placed on the palm of the hand and the reference electrode was placed on the dorsum of the same hand. SSR was induced by median nerve electrical stimulation at an amplitude of 20 mA with a 10 s interval. The waveforms of SSR appeared 1.5–2.5 s after the stimulations. Three waves were recorded for each side (right and left). The filters used in the measurement were as follows: high cut, 1 kHz; low cut, 0.1 Hz. The measured amplitude was defined as the peak-to-peak value of the recorded waves. The mean of these six amplitudes was used for the analysis.

For the HRV measurement, the A–A intervals were measured twice for 2 min with an interval of 5 min in a sitting position after a rest of 5 min. For recording and analyses of the A–A intervals, an Artett acceleration plethysmography system (U-Medica, Osaka, Japan) was utilised for analyses of the data, as described earlier.[4] From the low-frequency power (LF; 0.02–0.15 Hz) and the high-frequency power (HF; 0.15–0.50 Hz), the ratio of LF to HF power (LF/HF) was calculated using the maximal entropy method (MEM). The mean of two values from MEM was used. Cut-off value was obtained from a receiver-operating characteristic (ROC) curve using DLB as the positive level and AD as the negative. The coefficient of variation of A–A intervals (CVAA) was also analysed. The examinations were performed by a clinical technician with extensive experience of such work and the results were reviewed by a special neurologist trained for working in an electrophysiological laboratory. The technician was blind to the clinical information of the patients.

For statistical analyses, the data were first tested for a normal distribution using the Shapiro-Wilk test. In the categories with a normal distribution, data were analysed for equality of variance by F test and then Student t test or Welch's t test was utilised. In the categories with a non-normal distribution, Wilcoxon's test was utilised. To detect abnormality in the SSR or HRV examinations, Fisher's exact test was used. Both the SSR and HRV examinations were performed in a quiet room and the patients were kept awake and relaxed during the procedures. The ROC curves of the data were drawn using

Table 1 Comparison of DLB with AD

	DLB (n=20)	AD (n=20)
Gender	10 M and 10 F	10 M and 10 F
Age (mean±SD)	78.7±6.9	78.5±5.0
MMSE (mean±SD)	19.2±4.8	19.3±3.6
FAB (mean±SD)	8.5±4.2	8.6±3.9
H/M of MIBG (mean±SD) (range)	1.20±0.16 (0.95–1.46)	1.85±0.15 (1.71–2.18)
SSR (mean±SD) (cut-off: 0.90 mV)	0.72±0.82* (sensitivity: 85%) (specificity: 85%)	2.33±1.32
HRV (mean±SD) (cut-off: 0.933)	0.597±0.524 (sensitivity: 90%) (specificity: 85.0%)	2.276±1.313

Fisher's exact probability test was used for analysis.
*p<0.01, comparing DLB with AD.
AD, Alzheimer's disease; DLB, dementia with Lewy bodies; F, female; FAB, the frontal assessment battery; H/M, the ratio of heart to mediastinum uptake; HRV, heart rate variability; M, male; MIBG, ^{123}I-metaiodobenzylguanidine imaging; MMSE, Mini-Mental State Examination; SSR: sympathetic skin response.

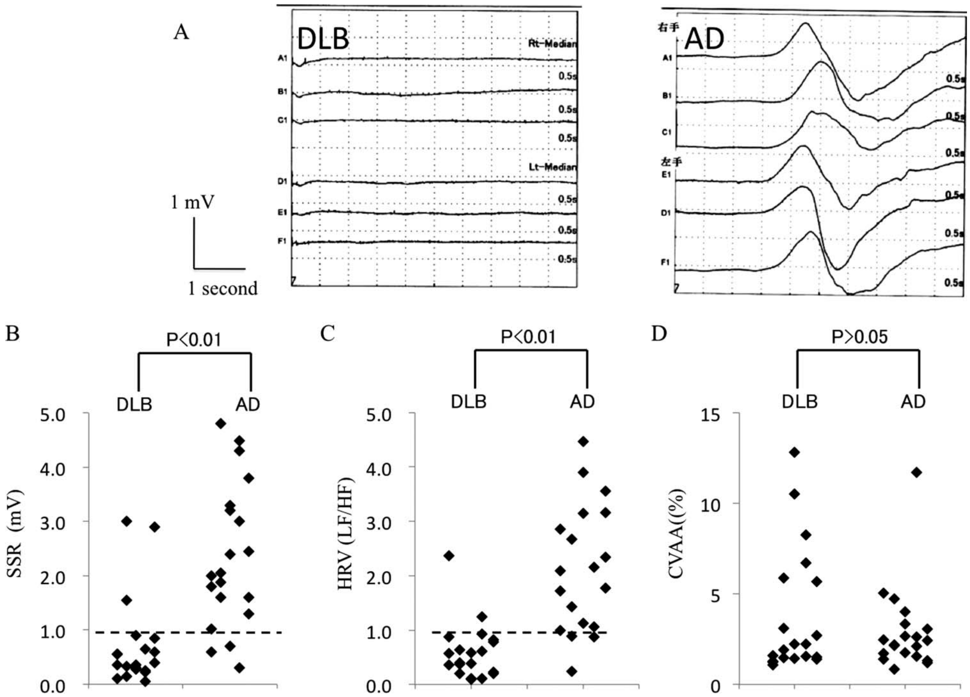

Figure 1 Autonomic examinations. (A) Records of sympathetic skin response (SSR). The left scheme is a typical record of a patient with dementia with Lewy bodies (DLB) and the right scheme is that of a patient with Alzheimer's disease (AD). The SSR of DLB showed almost no response after electric stimulation, while that of AD showed a remarkable response (peak-to-peak amplitude greater than 1 mV). (B) The x–y plotting of SSR of the patients with DLB or AD. The receiver-operating characteristic (ROC) curve was drawn using the data of DLB and AD. Accordingly, a cut-off value was set at 0.90 mV. (C) The x–y plotting of the heart rate variability (HRV) of patients with DLB or AD. The ROC curve was drawn using the data of DLB and AD. Accordingly, a cut-off value was set at 0.933 mV. (D) The x–y plotting of the coefficient of variation of A–A interval (CVAA) of patients with DLB or AD. There was no difference between the values of CVAA of patients with AD (2.91±2.36) and of those with DLB (3.73±3.44).

JMP V.10.0.1 (SAS Institute Inc, Cary, North Carolina, USA). A summary of the ROC curves in this study is available as online supplemental information.

RESULT

There were no adverse events resulting from performing the examinations. Although there was no difference in the data of the CVAA between patients with DLB and AD, the values of SSR and HRV (LF/HF) were significantly smaller in patients with DLB than in those with AD (figure 1A). The cut-off value for SSR was set at 0.90 mV and that of HRV was 0.933. Regarding the 20 patients with DLB, 17 were classified as abnormal for the SSR and 18 were classified as abnormal for the HRV (LF/HF). Regarding the 20 patients with AD, 3 were classified as abnormal for the SSR and 5 were classified as abnormal for the HRV (LF/HF). For the detection of DLB, SSR and HRV had sensitivities of 85% and 90% and specificities of 85% and 85%, respectively. While 15 of 20 patients with DLB (75%) showed double abnormality in SSR and HRV, only 1 of 20 patients with AD (5%) had double-abnormality status. While 20 of 20 cases with DLB (100%) were abnormal in either SSR or HRV, 7 of 20 patients with AD (35%) were abnormal in either SSR or HRV (table 1).

DISCUSSION

Autonomic dysfunction often appears in patients with DLB. MIBG scan is a useful examination for the detection of sympathetic activity and is utilised to distinguish DLB from AD.[5] Since MIBG scans require an RI and a long testing period (more than 3 h), they are not suitable in a routine clinical setting. As an alternative examination, we studied the possibility of utilising SSR and HRV.

SSR reflects sympathetic sweat response.[6] SSR amplitude was found to be severely reduced in DLB. However, there are no reports of a comparison of the data of SSR between DLB and AD. In spite of the poor reproducibility of SSR, this study could show that SSR amplitude in patients with DLB was smaller than that in those with AD.[7] HRV reflects autonomic heart rate response and is detectable by acceleration plethysmography.[4] In an earlier study,[8] there was no significant difference of single LF and single HF between patients with DLB and those with AD. Therefore, we investigated the ratio of LF to HF (LF/HF) instead. The LF/HF is usually used to

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examine sympathetic function.[9] From our results, patients with DLB showed lower values of LF/HF than those with AD. We also analysed the CVAA as a reflection of parasympathetic activity and found no difference between patients with AD and those with DLB. These results suggest that the sympathetic systems are impaired in DLB.

We also investigated the diagnostic accuracy of combination analyses using SSR and HRV. We found 16 patients with a double-abnormal result. The MIBG scan classified them as follows: 15 with DLB and 1 with AD. All the 20 patients diagnosed by an MIBG scan as having DLB could be correctly classified using either SSR or HRV. Thus, the combined analysis using SSR and HRV is useful and could be a substitute for the MIBG scan. The three AD patients with abnormal SSR did not have abnormal MIBG scan. In addition, three AD patients with abnormal HRV did not have abnormal MIBG scan. Only one AD patient had abnormalities of both SSR and HRV. We should follow these patients for their clinical manifestations.

Although this study has a limitation owing to its lack of a normal control, it shows that SSR and HRV can be applied to differentiate DLB from AD.

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Competing interests None.

Ethics approval Ethics committee of Kanazawa-Nishi Hospital.

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Data sharing statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.1k210.

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