2. Patients and methods

2.1. Subjects

A total of 95 PD patients (48 men and 47 women; mean age, 65.3 ± 7.9 y; mean disease duration, 4.6 ± 4.3 y) who were referred to our University Hospital for evaluation by a specialist between March 2009 and January 2013 were included in the study. Individuals with diabetes mellitus, any known heart disease, or other neurological disorders were excluded. Patients who were taking ergot dopamine agonist, had been diagnosed with a valvular disorder, or were taking selegiline were also excluded. All cases of PD were diagnosed using the UK Parkinson's Disease Society Brain Bank criteria [8]. The severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (*UPDRS*) part III. Seventeen normal healthy controls (8 men and 9 women, mean age, 64.5 ± 11.1 y) were also enrolled. This study was approved by the ethical committee at Nagoya University, and informed written consent was obtained from all patients and control subjects.

2.2. Head-up tilt test and impedance cardiography

All participants abstained from food in the morning. Any drug that might influence the cardiovascular system, including anti-Parkinson drugs, were discontinued at least 12 h before the examination. Tests were conducted successively in the morning. After participants rested for at least 5 min in a supine position, they were tilted up to 60° in a stepwise manner (5 min each at 20°, 40°, and 60°). Continuous non-invasive cardiovascular monitoring was performed using the Task Force Monitor (CNSystems Medizintechnik AG, Austria) as previously described [9]. Electrocardiograms (ECG) were recorded continuously using 4 spot electrodes. Beat-to-beat BP measurements were obtained by finger plethysmography of the index finger on the right hand and continuously corrected to the BP of the brachial artery in the left arm that was obtained by the oscillometric technique. Impedance cardiography was recorded by 3 electrodes placed at the neck and thoracic regions. Impedance cardiography assumes that the thorax can be modeled as a homogenous electrical conductor filled with blood. Volume changes in the cardiovascular system produce impedance variations across the thorax. Surface electrodes constantly deliver a low amplitude high frequency current and measure variations in transthoracic impedance to this current flow [10,11]. Pulsatile changes in blood volume and velocity were measured as impedance changes and were then applied to ECG and BP measurements to automatically calculate hemodynamic parameters at every beat. The bioimpedance technique may not accurately measure absolute values [10,11]. However, this technique accurately determines relative changes over a wide range of conditions [12]. We focused on changes in total peripheral resistance and stroke volume. Total peripheral resistance was calculated as mean arterial BP/heart rate times stroke volume. Systolic BP and heart rate were also recorded every 1 min.

2.3. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy

All PD participants underwent cardiac MIBG scintigraphy. MIBG (111 mBq) was injected intravenously, and delayed images were obtained after 3 h. Regions of interest included the whole heart and the mediastinum in the anterior projection, and the MIBG heart-to-mediastinum (H/M) ratio was calculated and evaluated. We defined H/M ratios <1.7 as cardiac denervation and those ≥1.7 as no cardiac denervation. The delayed image reflects the functional status and displays the neuronal uptake more explicitly than the early image [13,14], and an H/M ratio <1.7 is the value that we had determined to represent cardiac denervation in previous studies [4].

2.4. Definition of vasodilatation/vasoconstriction

Vasodilatation of peripheral vessels was indicated when the total peripheral resistance at the 5th min of the 60° position was lower than that at 0°, while vasoconstriction was indicated when the total peripheral resistance at the 60° tilt was higher than that at 0°. Patients were then divided into 4 groups: cardiac denervated vasodilator group, cardiac non-denervated vasodilator group, cardiac denervated vasoconstrictor group, and cardiac non-denervated vasoconstrictor group. Cut-off values for the change in total peripheral resistance were set to less than 'mean − 2SD' in the vasoconstrictor group and to more than 'mean + 2SD' in the vasodilator group.

2.5. Statistical analyses

SPSS software version 20 (SPSS, Chicago, IL) was used for statistical analyses. Significant differences were defined as $p < 0.05$. Categorical variables were analyzed by chi-square statistics. The Mann–Whitney *U* test was used to compare differences between 2 independent groups. For comparisons of more than 2 groups, analysis of variance (ANOVA) was used. If ANOVA was significant, the Bonferroni post hoc test was used. Relationships with change in total peripheral resistance were analyzed using Spearman's correlation coefficient. Changes in heart rate, systolic BP, stroke volume, and total peripheral resistance from the initial values at 0° were analyzed. Cardiac parameters from impedance cardiography were obtained at every beat, and the average of the last 30 s at baseline and the 5th min of the 20°, 40°, and 60° tilts were used for analysis. However, if the test was stopped in the middle of the protocol due to severe hypotension, data that had been obtained just before discontinuing the tilt were used. We diagnosed OH when there was a reduction in systolic BP of at least 20 mm Hg at the 5th min of the 60° position compared to the initial value in the supine position.

3. Results

3.1. Group classifications

Forty-nine of the 95 PD patients showed decreases in total peripheral resistance during the head-up tilt test and were classified into the vasodilator group. The other 46 patients were classified into the vasoconstrictor group. These 2 patient groups were each further classified into 2 groups according to whether cardiac denervation was exhibited (Fig. 1). As for the change in total peripheral resistance, no participant was excluded in the classification using the cut-off values for change in peripheral resistance as described above. Vasoconstriction was evident in all control group participants. The characteristics and baseline hemodynamics of the 4 PD groups and of the control group are shown in Table 1.

3.2. Hemodynamic changes over time and comparison at the 5th min of 60° tilt

Fig. 2 shows the changes over time for hemodynamics at the 5th min of the 20°, 40°, and 60° tilts. Significant differences in the change over time were detected among groups for systolic BP ($p < 0.0001$), total peripheral resistance ($p < 0.0001$), and stroke volume ($p < 0.0001$) (Repeated measure ANOVA). Table 1 shows a comparison of hemodynamic changes at the 5th min of the 60° tilt. Change in total peripheral resistance was similarly reduced in the cardiac denervated vasodilator and cardiac non-denervated

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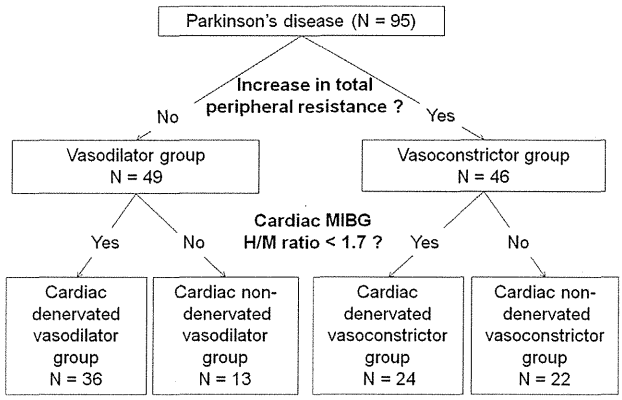

Fig. 1. Flowchart of the classification of patients. MIBG; ^{123}I-metaiodobenzylguanidine, H/M; heart-to-mediastinum.

vasodilator groups. However, the change in systolic BP differed significantly. The cardiac denervated vasodilator group had the highest reduction in systolic BP, while systolic BP was well preserved in the other 4 groups. On the other hand, the change in stroke volume was significantly higher in the cardiac non-denervated vasodilator group than in the other 4 groups.

When PD patients were divided into the cardiac denervated and cardiac non-denervated groups, a significant correlation between the change in total peripheral resistance and the change in systolic BP at the 5th min of the 60° tilt was observed in the cardiac denervated group ($r = 0.62$, $p = 0.001$; Fig. 3A), while no significant correlation was found in the cardiac non-denervated group ($r = 0.23$, $p = 0.18$; Fig. 3B) and control group ($r = 0.08$, $p = 0.76$; Fig. 3C).

OH was observed in 23 patients, all of whom showed cardiac denervation. Among these, peripheral vasoconstriction was shown in only 1 while peripheral vasodilation was evident in the other 22. The frequency of OH was significantly greater in the cardiac denervated vasodilator group than in the other 3 groups ($p < 0.0001$). A scatter plot of the association between cardiac MIBG uptake and change in systolic BP also revealed that OH was mostly limited to the cardiac denervated vasodilator group (Fig. 3D). When clinical characteristics between the patients with and without OH were compared, the UPDRS part III score did not differ between patients with and without OH (19.2 ± 9.9 vs 17.8 ± 11.7, $p = 0.83$). Cardiac MIBG was significantly different between patients with OH and patients without OH (cardiac MIBG H/M ratio; 1.30 ± 0.18 vs 1.83 ± 0.60; $p = 0.001$). As for disease duration, 5 out of the 22 patients with OH in the cardiac denervated vasodilator group had a disease duration of less than 1 year. However, there was a significant difference in disease duration between patients with OH and patients without OH (6.4 ± 5.4 y vs 3.8 ± 3.6 y; $p = 0.040$).

4. Discussion

In this study, we demonstrated that failure to increase total peripheral resistance in response to orthostatic stress is significantly associated with OH in cardiac denervated PD patients. Twenty-two of the 23 patients with OH were in the vasodilator group. Such a lack of increased total peripheral resistance during orthostatic stress has not been reported in PD patients, but has been reported in patients with pure autonomic failure (PAF) [15]. Using impedance cardiography, Chandler et al. found a greater decrease in systolic BP in patients with PAF than in those with multiple system atrophy, and the decreased total peripheral resistance was considered to account for the severe hypotension during orthostatic stress in PAF patients. Autonomic failure in such cases has been linked to the peripheral involvement of sympathetic nerves, and a similar pathological involvement appears to be involved in PD and Lewy body disease [16,17]. Thus, in patients with PD, a similar pathophysiological abnormality as seen in PAF may

Table 1
Demographic data, clinical characteristics, and changes in hemodynamics from baseline to the 5th min of the 60° tilt.[h]

	Cardiac denervated vasodilator group ($n = 36$)	Cardiac non-denervated vasodilator group ($n = 13$)	Cardiac denervated vasoconstrictor group ($n = 24$)	Cardiac non-denervated vasoconstrictor group ($n = 22$)	Control group ($n = 17$)	P*
Clinical features						
Age (y)	65.8 ± 8.0	65.9 ± 7.5	66.4 ± 6.8	62.7 ± 8 0.1	64.5 ± 11.1	0.559
Sex (M/F)	20/16	8/5	13/11	7/15	8/9	0.371
Disease duration (y)	6.0 ± 4.8[a]	2.0 ± 1.7	4.9 ± 4.5	2.6 ± 2.2		0.002
UPDRS part III	22.0 ± 15.0[b]	13.9 ± 5.2	18.8 ± 9.9	13.6 ± 6.0		0.018
L-dopa (mg)	229 ± 218	77 ± 124	175 ± 176	127 ± 134		0.076
Cardiac MIBG H/M ratio (delay)	1.32 ± 0.18[c]	2.40 ± 0.47	1.33 ± 0.16[c]	2.60 ± 0.51		<0.0001
Baseline systolic BP (mm Hg)	128 ± 19[d]	125 ± 19	118 ± 17	123 ± 21	111 ± 13	0.025
Baseline heart rate (beats/min)	68 ± 9	66 ± 155	68 ± 9	67 ± 10	69 ± 15	0.757
CVR-R (%)	2.14 ± 1.11	2.48 ± 1.22	2.27 ± 1.19	2.84 ± 1.34	2.95 ± 1.41	0.130
Head-up tilt test findings						
Orthostatic hypotension	22 (61%)	0 (0%)	1 (0.04%)	0 (0%)	0 (0%)	<0.0001
Change in heart rate (beats/min)	11.2 ± 4.4	9.8 ± 7.8	9.9 ± 7.8	11.1 ± 7.2	11.4 ± 5.3	0.879
Change in systolic BP (mm Hg)	−21.4 ± 15.2[e]	−2.3 ± 10.8	−3.1 ± 11.2	4.3 ± 11.0	8.1 ± 13.6	<0.0001
Change in total peripheral resistance (%)	−13.8 ± 9.6[f]	−13.5 ± 8.4[f]	15.7 ± 13.1	16.0 ± 12.3	17.4 ± 12.3	<0.0001
Change in stroke volume (%)	−13.8 ± 12.0	2.8 ± 12.2[g]	−20.7 ± 8.4	−20.1 ± 11.2	−17.2 ± 12.2	<0.0001

MIBG; ^{123}I-metaiodobenzylguanidine, H/M; heart-to-mediastinum, BP; blood pressure, CVR-R; coefficient of variation of RR intervals.
*ANOVA or chi square test were used to compare among the groups and then post hoc test was used to compare between the groups.
[a] vs cardiac non-denervated vasodilator group, $p = 0.011$; vs cardiac non-denervated vasoconstrictor group, $p = 0.009$.
[b] vs cardiac non-denervated vasodilator group, $p = 0.030$.
[c] vs cardiac non-denervated vasodilator and cardiac non-denervated vasoconstrictor groups, $p < 0.0001$.
[d] vs control group, $p = 0.019$.
[e] vs other four groups, $p < 0.0005$.
[f] vs cardiac denervated and cardiac non-denervated vasoconstrictor groups, and control group, $p < 0.0001$.
[g] vs other four groups, $p < 0.0005$.
[h] The values are expressed as means.

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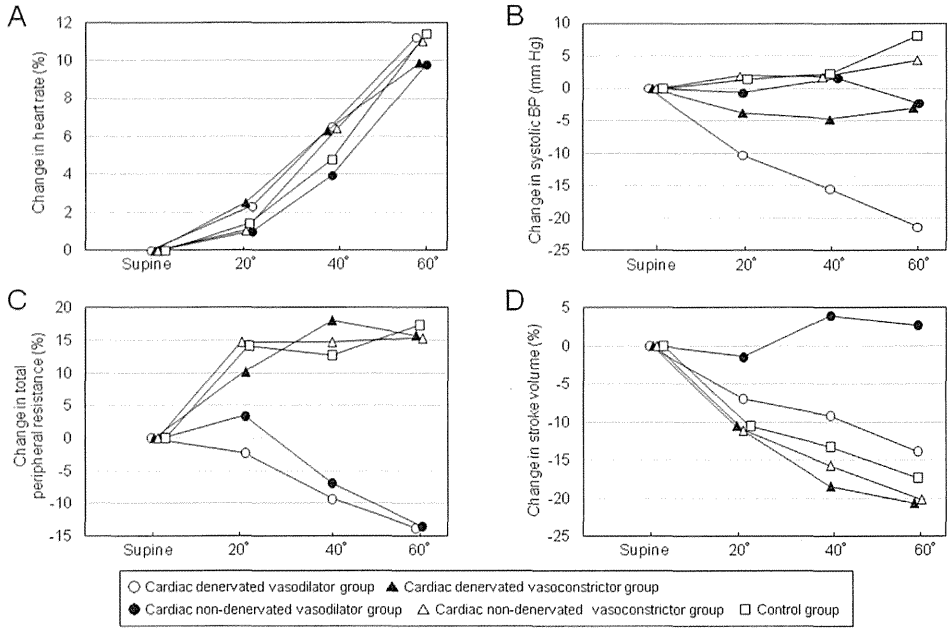

Fig. 2. Change over time in hemodynamics during the head-up tilt test. A. Change in heart rate. B. Change in systolic BP. C. Change in total peripheral resistance. D. Change in stroke volume. BP; blood pressure.

cause OH. However, the pathophysiology of OH in PD remains incompletely understood. Peripheral postganglionic failure, cardiac denervation, and a central-mediated impaired vasoconstrictor mechanism caused by degradation of certain nuclei and cell clusters within the brainstem, including the raphe nuclei, solitary nucleus, and dorsal motor nucleus of the vagus, which impair the outflow of signals important to a normal baroreceptor reflex response, are all considered to be responsible for OH in PD [18–20]. Several previous studies have evaluated the association between OH and cardiac MIBG, but the results were inconsistent. Spiegel et al. reported reduced H/M ratios of cardiac MIBG uptake in PD patients with OH compared to those without [21]. In addition, cardiac uptake of 6-[18F]-fluorodopamine, which can also detect cardiac sympathetic denervation, was reported to be much lower in

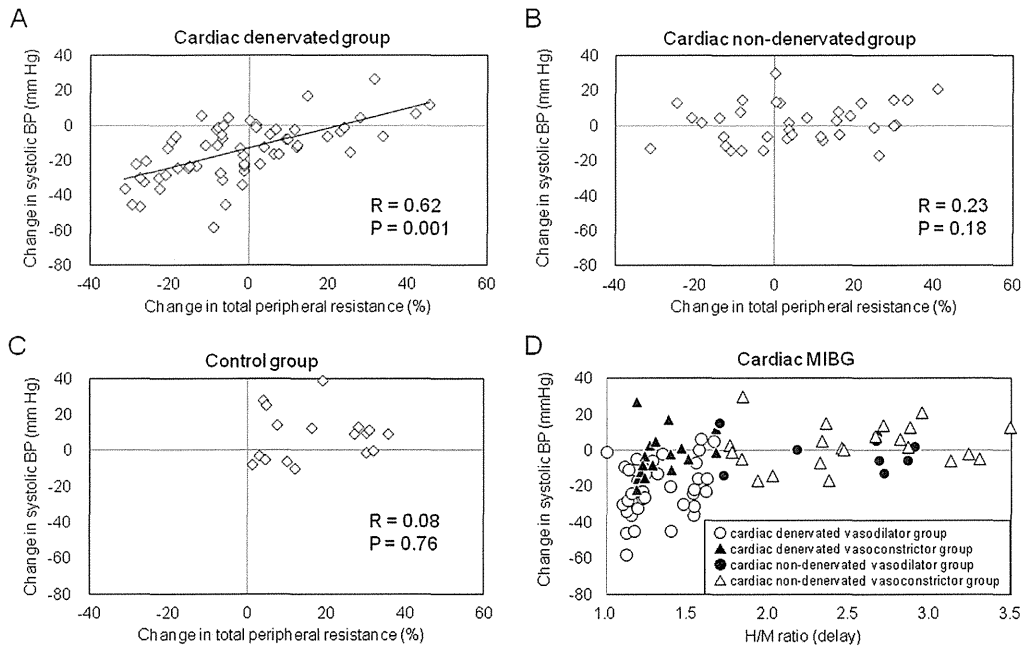

Fig. 3. Scatter plot of the association with change in systolic BP at 5th min of 60° tilt and cardiac parameters. A. Correlation with change in total peripheral resistance in cardiac denervated group. B. Correlation with change in total peripheral resistance in cardiac non-denervated group. C. Correlation with change in total peripheral resistance in control group. D. Association with cardiac MIBG H/M ratio. BP; blood pressure, MIBG; ^{123}I-metaiodobenzylguanidine, H/M; heart-to-mediastinum.

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patients with OH than those without [22]. On the other hand, others reported no significant differences in cardiac MIBG H/M ratios between PD patients with and without OH [23–25]. This lack of consensus about the relationship between OH and cardiac MIBG may be because in those studies patients were simply divided into 2 groups, those with OH and those without, and cardiac MIBG uptakes were compared without consideration of the vasoconstrictor mechanism. Haensch et al. also evaluated the relation between cardiac MIBG and BP response in tilt-table testing but could not find any correlation and speculated that not all components of the autonomic nervous system are uniformly affected at the same time in the course of PD and that the cardiovascular autonomic control and reactivity system may be impaired in different ways at multiple sites [26]. The data in Fig. 3D demonstrate that just the existence of cardiac denervation does not cause OH, but that cardiac denervation in combination with an impaired vasoconstrictor response is associated with OH in PD patients.

In addition, we showed that cardiac sympathetic nerves may play a role in the regulation of BP under orthostatic stress. The significant increase in stroke volume observed in the cardiac non-denervated vasodilator group suggests that a positive inotropic response occurs when a reduction in total peripheral resistance occurs in patients whose cardiac sympathetic nerves are not denervated, resulting in a well-preserved systolic BP, although the decrease in total peripheral resistance was similar to that in the cardiac denervated vasodilator group. Conversely, in patients who had vasoconstrictor responses, we observed a decrease in stroke volume rather than an increase. At the same time, the change in systolic BP did not differ significantly between the cardiac denervated group and cardiac non-denervated group. These cardiovascular changes were similar to those in the control group. Such hemodynamic changes are in agreement with those in previous studies reporting a reduction in stroke volume along with an increase in total peripheral resistance to maintain BP during the head-up tilt test in normal healthy subjects [15]. A previous review also speculated on why PD patients with cardiac denervation do not have OH [19]. That is, they hypothesized that there is sufficient peripheral adrenergic innervation to elicit an increase in total peripheral resistance through vasoconstriction that would mask a potential cardiac denervation effect and would maintain a normal BP response [19]. Results in the cardiac denervated vasoconstrictor group were consistent with this speculation. Furthermore, to understand this mechanism, the cardiovascular response in patients with heart transplantation would be helpful. Previously, increased systemic vascular resistance, decreased stroke volume, and well preserved systolic BP without OH were observed in heart transplant patients during the head-up tilt test and their ability to maintain systemic BP during this postural stress was unaffected [27]. Overall, our results showed a significant correlation between change in total peripheral resistance and change in systolic BP in the cardiac denervated group, while no correlation was observed in the cardiac non-denervated group and control group (Fig. 3A–C). These results indicate that when there is cardiac denervation, the degree of decrease or increase in systolic BP depends on the degree of decrease or increase in total peripheral resistance. On the other hand, when cardiac sympathetic nerves are preserved, systolic BP is maintained against various changes in total peripheral resistance due to cardiac sympathetic function.

In this study, we evaluated the cardiovascular response using impedance cardiography. More direct methods could quantify the response in vascular resistance and might provide more appropriate data. There are at least two methods to measure peripheral responsiveness directly. One is venous occlusion plethysmography, which measures calf blood flow and can quantify the response in vascular resistance. However, as for the head-up tilt test, it was reported that only up to 30° was applicable and the quality of the plethysmographic tracing worsened as the incline increased [28]. Another method to measure peripheral responsiveness directly is a leg blood flow examination using Doppler ultrasound. Groothuis et al. used this method to compare the vascular resistance in the leg, which was calculated as the arterial-venous pressure gradient divided by blood flow, among PD patients with and without OH and controls during the 60° head-up tilt test. They hypothesized that PD patients with OH would have decreased leg vascular resistance; however, leg vascular resistance was increased in all groups and the increase did not differ between groups [29]. Our results were not consistent with their results in that 22 out of 23 patients with OH had decreased total peripheral resistance. It is not clear whether the difference between the assessment by Doppler ultrasound that examined vascular resistance in the leg and our impedance cardiography that assessed systemic vascular resistance could cause such a dissociation. Further investigation using both assessment of leg vascular resistance and total peripheral resistance may be helpful.

The study has some potential limitations. We used impedance cardiography, which accurately determines relative changes, but there is a debate as to whether this method accurately measures cardiac parameters. Thus, we did not compare the absolute value of cardiac parameters and decided to compare relative changes among the groups. Baseline data on these parameters did not provide reliable absolute values; thus, when there were differences in cardiac parameters at baseline, these differences might influence the result. Medication was stopped 12 h before the study instead of the 5 half-lives that are widely accepted to eliminate effects of a given drug. Because some of our patients were at risk of hypotension, we did not consider it safe to withhold their medications for an extended period. Thus, some of the drugs might have influenced BP or peripheral vasoconstriction. Our study results showed comparisons among groups not observations of individual subjects. To study the functional mechanisms of cardiac denervation precisely and to investigate the association of cardiac denervation with changes in total peripheral resistance and stroke volume, an evaluation of individual subjects is required.

In conclusion, in PD patients, failure to increase total peripheral resistance with cardiac denervation under orthostatic stress is associated with systolic BP reduction leading to OH. However, if sympathetic cardiac nerves are not denervated, a significant positive cardiac inotropic response occurs when total peripheral resistance does not increase and systolic BP is maintained. This response may be important in preventing these PD patients from developing OH.

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Potential of a new MRI for visualizing cerebellar involvement in progressive supranuclear palsy

Kazuhiro Hara [a], Hirohisa Watanabe [a], Mizuki Ito [a], Takashi Tsuboi [a], Hazuki Watanabe [a], Ryoichi Nakamura [a], Jo Senda [a], Naoki Atsuta [a], Hiroaki Adachi [a], Ikuko Aiba [b], Shinji Naganawa [c], Gen Sobue [a,*]

[a] Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Aichi, Japan
[b] Department of Neurology, National Hospital Organization Higashinagoya National Hospital, Nagoya, Japan
[c] Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

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ABSTRACT

Objectives: We assessed the usefulness of differential diagnosis of parkinsonism by evaluating lesions of the decussation of the superior cerebellar peduncle (SCP) in patients with progressive supranuclear palsy (PSP) using a new MRI procedure known as readout segmentation of long variable echo-trains (RESOLVE).

Methods: We evaluated 100 cases, consisting of 20 with PSP, 24 with Parkinson's disease (PD), 13 with multiple system atrophy with predominant parkinsonism (MSA-P), 18 with multiple system atrophy with predominant cerebellar ataxia (MSA-C), and 24 controls. All patients were scored on the Unified Parkinson's Disease Rating Scale Part III and the Scale for the Assessment and Rating Scale of Ataxia, and MRI using RESOLVE was conducted.

Results: Images acquired by this MRI procedure clearly showed high intensity areas corresponding to the decussation of the SCP in all controls, PD, and MSA patients. In contrast, ten of the 20 PSP patients exhibited abnormal iso intensities of the decussation of the SCP, while the other 10 showed high intensity signals. Among the PSP patients, there were no differences in clinical features between those with and those without visualization of the decussation of the SCP. Iso intensity signals had a sensitivity of 50% and a specificity of 100% for differentiating PSP from PD, MSA, and controls.

Conclusion: This MRI procedure (RESOLVE) shows a potential for detecting the involvement of the decussation of the SCP in PSP, and can be used for discriminating PSP from PD and MSA-P.

1. Introduction

Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disorder characterized by loss of balance, supranuclear ophthalmoplegia (particularly in the vertical direction), pseudobulbar palsy, dysarthria, nuchal dystonia, and dementia [1]. Involvement of the dentate nucleus and superior cerebellar peduncle (SCP) are the common postmortem findings in patients with PSP [2]. However, it is generally difficult to detect the clinical cerebellar signs except in patients with PSP with cerebellar ataxia [3–6].

In contrast, several MRI procedures, including proton density weighted imaging, fluid attenuation inverted recovery, voxel based morphometry, and diffusion tensor imaging validated SCP involvement in PSP [7–17]. Because the SCP is not involved in Parkinson's disease (PD) and may be involved in the later course of illness in multiple system atrophy with predominant parkinsonism (MSA-P) [1,2,18,19], a more convenient and reliable MRI procedure would be useful for early differentiation of PSP from PD and MSA-P.

Readout segmentation of long variable echo-trains (RESOLVE) is a new procedure of diffusion imaging that provides higher spatial resolution with less distortion than conventional methods [20,21]. According to a previous report [21], RESOLVE is expected to visualize structures of the brainstem, including the SCP, in detail by enhancing contrasts between nuclei and fiber tracts. In this study, we compared the decussation of the SCP findings in PSP patients with those in PD and MSA-P patients, and evaluated the usefulness of RESOLVE for differentiating PSP from PD and MSA-P.

* Corresponding author. Fax: +81 52 744 2384.
E-mail addresses: sobueg@med.nagoya-u.ac.jp, sobueg@gmail.com (G. Sobue).

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2. Patients and methods

We studied a total of 100 subjects from April 1, 2011 to September 30, 2012, at Nagoya University Hospital. We investigated 24 non-demented controls, 20 consecutive patients with clinical PSP, 24 consecutive patients with PD, 13 consecutive patients with MSA-P and 18 consecutive patients with multiple system atrophy with predominant cerebellar ataxia (MSA-C). The demographics of all subjects are shown in Table 1. All subjects gave informed, written consent to their participation in the study and the study was approved by the ethics committee of the Nagoya University Graduate School of Medicine.

The clinical diagnoses were based on the clinical criteria of the National Institute of Neurologic Diseases and Stroke-the Society for PSP [22], the UK Brain Bank Criteria for PD [23], and the second consensus statement on the diagnosis of MSA [24]. All PSP and MSA patients fulfilled clinically probable criteria. All clinical phenotypes of PSP patients were classified as Richardson syndrome. The 24 control subjects had no medical histories of stroke, traumatic brain injury, psychiatric disorders, or neurological manifestations.

All patients were scored on the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) and Scale for the Assessment and Rating of Ataxia (SARA). MRI, including T1-weighted (T1), T2-weighted (T2), Fluid-attenuated inversion recovery (FLAIR), and RESOLVE imaging were conducted immediately after.

2.1. MRI acquisition

All scans were performed on a 3.0 T unit using a 32-channel phased array head coil (Verio, Siemens, Erlangen Germany). Scan parameters for readout-segmented multi-shot echo-planar imaging (rs-EPI) included the following: axial slices parallel to the bilateral cisternal segment of the trigeminal nerves; repetition time (TR), 3800 ms; echo times (TE), 81 ms for b-factor of 700 s/mm^2; 4 times of averaging; 12 slices of 4-mm thickness with 0.4-mm gap; 320 × 256 matrix; unidirectional motion-probing gradient (MPG) in slice selective direction (superior-inferior, S–I); GRAPPA (auto-calibrating partially parallel acquisitions) parallel imaging technique with acceleration factor of 2; number of k-space segmentation, 21; square field of view (FOV), 163 mm; scan time of 6–7 min. Voxel size was 0.5 mm × 0.6 mm × 4 mm [21].

To assess lesions of the decussation of the SCP on RESOLVE and of the SCP itself on FLAIR imaging, an experienced neurologist, blinded to the clinical diagnosis, evaluated the presence of high intensity signals in the areas corresponding anatomically to the decussation of the SCP and to the SCP. As shown in Fig. 1, an image with an iso signal intensity in the area of the decussation of the SCP (Fig. 1A.1, A.2, A.3) was classified as "invisible", and another with a high signal intensity (Fig. 1B) was classified as "visible". We evaluated the SCP lesions in two slices through the midbrain parallel to the bilateral cisternal segment of the trigeminal nerves in each subjects, at the level of the superior colliculus and inferior colliculus. A normal sign was determined visually when there was a high intensity area of the decussation of SCP in either of the two slices. FLAIR imaging was used to assess abnormalities of the SCP as previously described [8]. To verify the reliability of these evaluations, another neurologist, blinded to the clinical diagnosis, also conducted the same evaluations. The Cohen's kappa coefficient between the two examiners was 0.682 ($P < 0.001$). An abnormal finding was defined as present if both raters found a definite abnormality.

Table 1
Demographic and clinical data of subjects studied.

Group (n)	Gender (M/F)	Age (years)	Duration (years)	UPDRS-III	SARA
Control (24)	11/13	62.0 ± 11.2			
PSP (20)	10/10	69.5 ± 6.8	3.8 ± 2.0	40.2 ± 20.0	18.0 ± 11.1
PD (25)	11/14	70.6 ± 10.8[a]	7.6 ± 5.6[b]	33.4 ± 16.7	10.9 ± 5.6
MSA-P (13)	6/7	64.6 ± 5.3	3.5 ± 1.9	40.7 ± 20.0	16.0 ± 10.3
MSA-C (18)	8/10	61.7 ± 8.3	2.8 ± 1.8	31.4 ± 21.0	18.2 ± 9.5

PSP = progressive supranuclear palsy, PD = Parkinson's disease, MSA-P = multiple system atrophy with predominant parkinsonism, MSA-C = MSA with predominant cerebellar ataxia, n = number, M = male, F = female, UPDRS III = the Unified Parkinson's Disease Rating Scale Part III, SARA = Scale for the Assessment and Rating Scale of Ataxia.

[a] PD vs. control, $P = 0.013$; PD vs. MSA-C, $P = 0.018$.

[b] PD vs. PSP, $P = 0.021$; PD vs. MSA-P, $P = 0.014$; PD vs. MSA-C $P = 0.002$.

2.2. Statistical analysis

Results of groups were expressed as mean ± standard deviation. Comparisons of the differences in gender were performed using the chi-square test. To compare age at examination and disease duration, we used one-way analysis of variance. To assess the differences in the UPDRS III and SARA scores among PSP, PD, and MSA-P, we used the Kruskall Wallis test. For evaluation of each group, a multiple comparison was used. The Mann–Whitney analysis was utilized to compare the clinical data of the group with normal images with that of the group with abnormal images in PSP. Statistical analysis was performed using SPSS 17.0 software for Windows (SPSS Inc, Chicago, IL, USA). The significance level was set at $P < 0.05$. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using Microsoft Office Excel 2010 (Microsoft Inc, Redmond, WA, USA), and were evaluated by the Fisher exact test.

3. Results

3.1. Clinical features

The clinical features of all participants are summarized in Table 1. There were no significant differences in either the UPDRS III or SARA scores among the various groups of patients.

3.2. RESOLVE findings in PSP, PD, MSA, and control

Fig. 1A–F shows representative RESOLVE images of the decussation of the SCP in a PSP patient, a control subject, and PD, MSA-P, and MSA-C patients. The images from 10 of the patients with PSP (Fig. 1A.1, A.2, A.3) showed iso intensity signals, but no high intensity signals corresponding to the anatomical area of at the decussation of the SCP. Images from the other 10 PSP patients (Fig. 1B) exhibited high intensity signals. In contrast, all of the control subjects (Fig. 1C), PD (Fig. 1D), MSA-P (Fig. 1E), and MSA-C (Fig. 1F) patients showed high intensity signals at the decussation of the SCP.

There were no significant differences in age, disease duration, the UPDRS III or SARA scores between the PSP patients with and without high intensities of the SCP.

3.3. Comparison of RESOLVE and FLAIR findings in PSP, PD, MSA, and control

The results of RESOLVE and FLAIR imaging are summarized in Table 2. Nine of 20 patients with PSP (45%) showed high intensity signals on FLAIR images of the SCP. This frequency was similar to that of the RESOLVE findings (Table 2). The majority of control subjects, as well as patients with PD, MSA-P and MSA-C showed low intensity FLAIR signals (a normal sign) of the SCP, while some

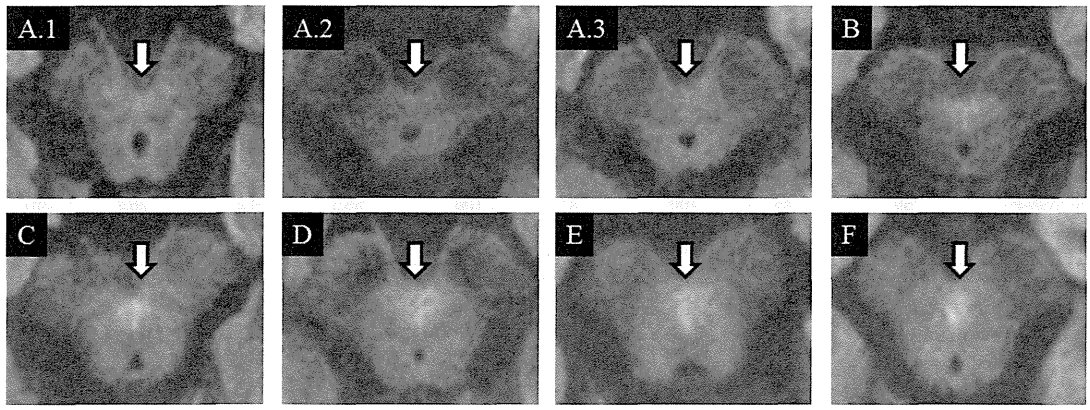

Fig. 1. The absence or presence of high intensity signals in the decussation of the superior cerebellar peduncle was assessed. 10 of the patients with PSP (A.1, A.2, A.3) showed iso intensity signals (arrows). The other 10 PSP patients (B), the controls (C), patients with Parkinson's disease (D), multiple system atrophy with predominant parkinsonism (E), and multiple system atrophy with predominant cerebellar ataxia (F) exhibited high intensity signals (arrows).

controls and PD and MSA patients (15.4–20.8%) also showed high intensity FLAIR signals (an abnormal sign) in the SCP (Table 2).

3.4. Efficacy of RESOLVE and FLAIR images to differentiate PSP from PD, MSA-P, and MSA-C

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of RESOLVE and FLAIR images to differentiate PSP from PD, MSA-P, and MSA-C are shown in Table 3. RESOLVE demonstrated only moderate sensitivity and NPV but extraordinarily high specificity and PPV (100% for both). In contrast, the sensitivity, specificity, PPV, and NPV of FLAIR imaging were inferior to those of the RESOLVE imaging.

4. Discussion

To our knowledge, this is the first study to evaluate findings of the decussation of the SCP findings in PSP patients using RESOLVE sequences on brain MRI. Interestingly, 50% of PSP patients showed iso intensity signals in this region, while all controls, PD, MSA-P, and MSA-C patients showed high intensity signals. Thus, iso intensity signals on RESOLVE images demonstrated 100% specificity and 100% PPV for differentiating PSP from PD, MSA-P, MSA-C, and control. On the other hand 50% of PSP patients showed high intensity RESOLVE signals. The high intensities in the SCP lesions in PSP patients tended to be paler than those in controls; however, these changes of differences in intensity were rather subtle. If we can more quantitatively evaluate these subtle changes, the inter-rater reliability might be higher. This point might explain the low sensitivity.

Table 2
Ratios of abnormal RESOLVE and FLAIR findings.

Group (*n*)	RESOLVE	FLAIR
	Iso intensity of the decussation of SCP	High intensity of SCP
Control (24)	0/24 (0%)	5/24 (20.8%)
PSP (20)	10/20 (50%)	9/20 (45%)
PD (25)	0/25 (0%)	5/25 (20%)
MSA-P (13)	0/13 (0%)	2/13 (15.4%)
MSA-C (18)	0/18 (0%)	3/18 (16.7%)

PSP = progressive supranuclear palsy, PD = Parkinson's disease, MSA-P = multiple system atrophy with predominant parkinsonism, *n* = number, SCP = superior cerebellar peduncle, RESOLVE = readout segmentation of long variable echo-trains.

RESOLVE is a form of readout-segmented multi-shot echo-planar imaging (EPI), which is usually performed as diffusion tensor imaging (DTI) with numerous numbers of motion-probing gradient (MPG) directions; therefore, scan time for DTI acquisition is usually quite long and misregistration by distortion or motion between the scans with different MPG directions obscures the small structures [21]. Diffusion weighted neurography using unidirectional MPG and single-shot EPI has been proposed as a robust technique for brachial or sacral plexus visualization due to the lack of misregistration between the images with different MPG directions [25]. Though single-shot EPI provides excellent time efficiency in terms of signal-to noise ratio~~(SNR)~~, it suffers from severe distortion near bone and air [21]. Naganawa et al. reported that small structures in the brainstem and cisterns were described more clearly by RESOLVE images than by single-shot EPI images, both using unidirectional MPG [21]. As the fibers aligned parallel to the MPG in slice selective direction (superior–inferior, S–I), such as the corticospinal tract, exhibit low signals on RESOLVE, the contrast between the fibers and the nuclei is emphasized, resulting in a clear demonstration of fibers running in a caudal to cranial direction as a high intensity signal. Thus, although several anatomical structures are included in the midline portion of the midbrain, the decussation of the SCP, running perpendicularly to the MPG direction, will be mainly delineated as a high intensity signal on RESOLVE.

The SCP is primarily composed of cerebellar efferent fibers from the dentate nucleus. In patients with PSP, the SCP exhibits significant demyelination and gliosis resulting from degeneration of the dentate, red nucleus, and ventrolateral nuclei of the thalamus [1,2]. Tsuboi et al. demonstrated significant shortening of the width of the SCP in PSP patients as compared to controls at autopsy [2]. In contrast, PD patients and controls generally do not show any abnormalities of the SCP [18]. Although advanced MSA-C patients may show SCP involvement followed by middle cerebellar involvement [19], MSA-C patients did not show iso intensity signals of the decussation of the SCP in our study. This is possibly associated with the background of MSA-C patients, with short disease durations (mean disease duration, 2.8 ± 1.8 years). Based on previous pathological findings of PSP [1,2], PD [18], and MSA [19], characteristic histopathological changes in the decussation of the SCP are responsible for the disappearance of high intensity RESOLVE signals in this area in PSP.

Clinically, PSP patients do not show cerebellar signs except for those with PSP with cerebellar ataxia (PSP–C) [3–6]. In our study, no patients exhibited apparent cerebellar ataxia. Although the PSP

Table 3
Sensitivity, specificity, PPV, and NPV of RESOLVE and FLAIR findings.

Group compared	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		*P* value	
	RESOLVE	FLAIR	RESOLVE	FLAIR	RESOLVE	FLAIR	RESOLVE	FLAIR	RESOLVE	FLAIR
PSP vs. PD	50	45	100	80	100	64.3	71.4	64.5	<0.001	0.072
PSP vs. MSA-P	50	45	100	84.6	100	81.8	56.5	50	<0.01	0.081
PSP vs. MSA	50	45	100	83.9	100	64.3	75.6	29.7	<0.001	0.024
PSP vs. PD and MSA-P	50	45	100	81.6	100	56.3	79.2	26.2	<0.001	0.031
PSP vs. PD and MSA	50	45	100	82.1	100	47.4	84.8	19.3	<0.001	0.016
PSP vs. Control, PD and MSA	50	45	100	81.3	100	37.5	88.9	14.5	<0.001	0.018

PSP = progressive supranuclear palsy, PD = Parkinson's disease, MSA-P = multiple system atrophy with predominant parkinsonism, MSA-C = MSA with predominant cerebellar ataxia, PPV = positive predictive value, NPV = negative predictive value.

and MSA-C patients had slightly higher SARA scores than the PD or MSA-P patients, there were no significant differences among the groups. In addition, there were no significant differences in SARA scores between the PSP patients with iso intensity or high intensity RESOLVE signals of the decussation of SCP. Recently, Shirota et al. reported that cerebellar inhibition was electrophysiologically reduced in PSP patients with no cerebellar symptoms, supporting the presence of severe dentate nuclear involvement in PSP [26]. Taken together, PSP rarely shows cerebellar signs and symptoms, but RESOLVE can distinguish the cerebellar dentate nuclei and SCP involvement.

Several radiological semi-quantitative approaches have been examined to evaluate changes in the SCP. One method is measuring SCP width and volume by volumetric [9] and morphometric [10] ways. Another is measuring pathological changes of SCP by the apparent diffusion coefficient (ADC) [11–13], diffusion tensor imaging (DTI), and tractography (DTT) [14–17]. Those methods have high sensitivity and specificity for distinguishing PSP. It was also reported that simultaneously analyzing multiple brain regions with DTI distinguishes PSP from PD, and MSA. Analyzing multiple regions with DTI has a higher sensitivity than analyzing a single region [17]. There are reports that the magnetic resonance parkinsonism index (MRPI), calculated as pons area/midbrain area × middle cerebellar peduncle width/superior cerebellar peduncle width, help to differentiate PSP from PD and to predict development of PSP in the future [27–30]. However, these methods are time consuming and complicated. In addition, volumetric and morphometric methods as well as the evaluation of DTI and ADC values are generally suitable for group comparisons between PSP and controls or other parkinsonism but not for individual abnormalities in clinical practice. As representatives of qualitative MRI, proton density weighted MRI [7] and fluid-attenuated inversion recovery [8] approaches can assess the individual findings of SCP but are hampered by low sensitivity and specificity. In this study, FLAIR imaging showed low specificity and reproducibility compared to RESOLVE. RESOLVE is an easy and efficient MRI technique.

Our study was somewhat limited by the fact that the diagnoses of subjects were not confirmed pathologically. There were also significant differences in the average age and disease duration among the groups. Finally, the evaluations of neurologists are sometimes inconsistent with one another because RESOLVE is a qualitative approach.

In conclusion, RESOLVE imaging can demonstrate the pathological involvement of the decussation of the SCP in patients with PSP. For discriminating PSP from PD and MSA-P, RESOLVE demonstrated 100% specificity and PPV. Thus, RESOLVE is expected to provide significant diagnostic value for PSP if the normally high intensity signal of the decussation of the SCP exhibits, instead, an iso intensity signal. Further studies, however, are needed.

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Reliability of the Japanese version of the scales for outcomes in Parkinson's disease-autonomic questionnaire

Masaaki Matsushima*, Ichiro Yabe**, Makoto Hirotani, Takahiro Kano, Hidenao Sasaki

Department of Neurology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

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ABSTRACT

Objective: The Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaire was used to assess autonomic dysfunction in patients with neurological disorders. The aim of this study was to evaluate the reliability of the Japanese version of the SCOPA-AUT.
Methods: We translated the SCOPA-AUT from English to Japanese. Thirty-one patients with diseases involving autonomic symptoms completed the form twice. The reliability was assessed by Cronbach's coefficient alphas and intraclass correlation coefficients (ICCs).
Results: The average (standard deviation, SD) total scores of the first and second assessments of the SCOPA-AUT were 15.7 (SD, 7.1) and 13.6 (SD, 6.5), respectively. The Cronbach's coefficient alphas were globally high, but the ICCs were moderately high. The valid response rates for the questions about sexual dysfunction were 36.7% in men and 26.6% in women.
Conclusions: The Japanese version of the SCOPA-AUT had high internal consistency. However, the questions about sexual dysfunction showed less valid response rates.

1. Introduction

Some neurological disorders involve autonomic dysfunction. Reliable objective scales of these diseases have not been developed for use in clinical trials. The Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaire was developed for assessing autonomic dysfunction in patients with Parkinson's disease (PD) [1]. It consists of 25 items (gastrointestinal dysfunction, urinary dysfunction, cardiovascular dysfunction, thermoregulatory dysfunction, pupillomotor dysfunction, sexual dysfunction for men, and sexual dysfunction for women), and patients choose the applicable options on the form. Each item is scored from 0 (no symptoms) to 3 (severe), and the total score ranges from 0 to 69 for both men and women. The English and Portuguese versions of the SCOPA-AUT have been validated [2], but the Japanese version of the SCOPA-AUT has not been published nor tested for its reliability. The SCOPA-AUT can be applied to patients with various neurological disorders because it has recently been used to assess non-PD patients, such as those with multiple system atrophy (MSA) and Huntington's disease [3,4]. Thus, we prepared the Japanese version of the SCOPA-AUT. The purpose of this study was to confirm its reliability in patients with diverse neurological disorders.

2. Materials and methods

We conducted this prospective, single-institution, observational study with hospitalized patients and outpatients of the Department of Neurology of Hokkaido University Hospital between October 2012 and November 2012. All study patients had been diagnosed with some kind of neurological disorder that was accompanied by autonomic dysfunction. We set the target sample size as "31 patients." This was because the intraclass correlation coefficients in the two evaluations were expected to be ~0.85 at 95% confidence interval, which had an accuracy of 0.2 in 31 persons. Previous studies about SCOPA-AUT were conducted in a larger population; however, the validation study of Scale for the Assessment and Rating of Ataxia (SARA) was performed in a smaller group ($n = 27$), and the validity was confirmed [5]. This study was approved by the institutional review board of Hokkaido University Hospital. Prior to the study, written informed consents were obtained from all participants. Those who disagreed to participate in the study or who had severe cognitive impairment making no sense of questionnaires were excluded.

The SCOPA-AUT was translated by native Japanese speakers from English to Japanese. The Japanese version of the SCOPA-AUT was translated back into English by native English speakers. The

* Corresponding author. Tel.: +81 11 706 6028; fax: +81 11 700 5356.
** Co-corresponding author.
E-mail addresses: mmasaaki@huhp.hokudai.ac.jp (M. Matsushima), yabe@med.hokudai.ac.jp (I. Yabe).

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Table 1
Statistical parameters of the Japanese version of the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaire.

Item	First assessment			Second assessment			ICC	Cronbach's coefficient alpha
	Mean	SD	Missing answers	Mean	SD	Missing answers		
1 Swallowing/choking	0.677	0.832	0	0.581	0.620	0	0.550	0.888
2 Sialorrea	0.321	0.541	0	0.321	0.541	0	0.667	0.890
3 Dysphagia	0.387	0.715	0	0.226	0.425	0	0.591	0.887
4 Abdominal fullness	0.500	0.731	1	0.677	0.909	0	0.611	0.888
5 Constipation	1.548	1.060	0	1.355	1.018	0	0.341	0.889
6 Straining for defecation	1.452	1.207	0	1.194	1.046	0	0.550	0.888
7 Fecal incontinence	0.194	0.601	0	0.194	0.601	0	0.911	0.891
8 Urinary urgency	0.800	0.805	1	0.600	0.724	1	0.653	0.888
9 Urinary incontinence	0.742	0.855	0	0.552	0.632	2	0.740	0.886
10 Incomplete emptying	0.645	0.950	0	0.467	0.571	1	0.597	0.889
11 Weak stream of urine	1.129	0.957	0	1.167	0.910	1	0.677	0.886
12 Urinary frequency	1.032	0.912	0	0.900	0.662	1	0.428	0.886
13 Nocturia	1.710	0.902	0	1.621	0.942	2	0.653	0.891
14 Lightheadedness (standing up)	1.000	1.095	0	0.742	0.815	0	0.663	0.888
15 Lightheadedness (standing for some time)	0.774	0.921	0	0.633	0.809	1	0.803	0.888
16 Syncope	0.000	0.000	0	0.000	0.000	0	[a]	0.896
17 Hyperhidrosis (day)	0.452	0.723	0	0.548	0.810	0	0.199	0.891
18 Hyperhidrosis (night)	0.433	0.728	1	0.323	0.653	0	0.369	0.892
19 Oversensitive to bright light	0.419	0.620	0	0.355	0.551	0	0.624	0.890
20 Cold intolerance	0.387	0.615	0	0.267	0.521	1	0.392	0.896
21 Heat intolerance	0.484	0.677	0	0.516	0.769	0	0.222	0.890
22 Erection problem	1.571	1.134	8	1.667	1.211	9	0.942	0.883
23 Ejaculation problem	1.600	1.517	10	2.000	1.414	11	1.000	0.884
24 Vaginal lubrication	0.000	0.000	12	0.000	0.000	11	[a]	0.896
25 Problems with orgasm	0.250	0.500	12	0.250	0.500	12	1.000	0.888
Total	15.677	7.208	45	13.580	6.642	53	0.644	0.877
Gastrointestinal	5.065	3.463	1	4.548	3.139	0	0.625	0.882
Urinary	6.032	3.755	1	5.065	3.010	8	0.494	0.883
Cardiovascular	1.774	1.944	0	1.355	1.539	1	0.800	0.887
Thermo	1.742	1.483	0	1.645	1.836	1	0.089	0.888
Pupillomotor	0.419	0.620	1	0.355	0.551	0	0.624	0.890
Sexual function, male	2.714	2.563	18	3.000	2.683	20	0.988	0.883
Sexual function, female	0.250	0.500	24	0.200	0.447	23	1.000	0.888

Items 22 and 23 were intended only for men, and items 24 and 25 were intended only for women.
Abbreviations: SD, standard deviation; ICC: intraclass coefficient.
[a] The ICCs of items 16 and 24 could not be calculated because their variances were zero.

back translation was compared to the English version and then modified. The final translation was established as the Japanese version of the SCOPA-AUT. We obtained permission to use the questionnaire from the SCOPA research group in the Netherlands.

At first, patients or their family (if a patient could not write because of upper limb disturbance) chose the appropriate options on the Japanese version of the SCOPA-AUT, and they completed the form again 1–4 weeks later. Two trials were performed at the neurology ward or clinic.

The amassed data were subjected to linkable anonymizing. Statistical analyses were then performed.

2.1. Statistical analysis

JMP® Pro 10.0.0 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. The total score and every particular item on the SCOPA-AUT were analyzed with Cronbach's coefficient alphas and intraclass correlation coefficients (ICCs). The items were considered to have high internal consistency if the Cronbach's coefficient alphas were more than 0.8. The ICCs were interpreted to be in conformity to the reference as slight (0.000–0.200), fair (0.201–0.400), moderate (0.401–0.600), substantial (0.601–0.800), or almost perfect (0.801–1.000) [6]. The mean values are presented with standard deviations (SD).

3. Results

Thirty-two patients were enrolled, but one patient was excluded because of a schedule conflict. The demographics of the 31 study patients (male/female, 15/16) are shown in Supplementary Table. The mean age was 64.8 ± 12.9 years (range, 30–82 years). The study patients included 9 with MSA, 8 with PD, 5 with myelopathy, and 9 with other diseases. Patients showing severe autonomic dysfunction that significantly affected their activity of daily living and cognitive impairment were not included.

Supplementary Table related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clineuro.2014.07.007.

Table 1 shows the statistical parameters of the SCOPA-AUT Japanese version. The mean total scores for the first and second assessments were 15.677 ± 7.091 (n = 69; range, 6–31) and 13.580 ± 6.534 (n = 69; range, 3–29), respectively. The ICC of the total SCOPA-AUT score was 0.644, and the Cronbach's coefficient alpha was 0.877. Cronbach's coefficient alphas of all of the items were more than 0.8. Total invalid answers were '45' in the first assessment and '53' in the second assessment. '45' meant 3 blank answers + 42 'use catheter' and 'not applicable', and '53' meant 6 blank answers + 47 'use catheter' and 'not applicable'. These invalid answers were not included in the total score. The participants could choose the option "use catheter" in items 8–13 and "not applicable" in items 22–25. In the 4 questions about sexual dysfunction, items 22–25, there were 62 replies in total, and 20 responses in the first assessment and 19 responses in the second assessment were valid. The valid response rates for the questions about sexual dysfunction were 31.5% in total, 36.7% in the men, and 26.6% in the women. The patients who chose "not applicable" were older than the patients providing valid responses, but this difference was not statistically significant (former: 67.6-year-old males and 68.4-year-old females vs. the latter: 58.1-year-old males and 60.3-year-old females).

For the ICC, items 7, 15, 22, 23, and 25 were evaluated as almost perfect. The total score and items 2, 4, 8, 9, 11, 13, 14, and 19 were substantial, items 1, 3, 6, 10, and 12 were moderate, items 5, 18, 20, and 21 were fair, and item 17 was slight. In items 16 and 24, ICCs could not be calculated because none of the participants had symptoms, and, thus, they had zero scores.

There was a significant correlation between each item and the domain. In addition, each domain was positively correlated with the total score. The ICCs were high for the following, as shown in Table 1: sexual dysfunction in women (items 24 and 25), sexual dysfunction in men (items 22 and 23), cardiovascular dysfunction (items 14–16), gastrointestinal dysfunction (items 1–7), pupillomotor dysfunction (item 19), urinary dysfunction (items 8–13), and thermoregulatory dysfunction (items 17, 18, 20, and 21). The Cronbach's coefficient alphas were high in all of the domains.

4. Discussion

This study, which included patients with various neurological disorders, had similar results as those of previous reports of patients with PD. Although the SCOPA-AUT was developed to estimate autonomic dysfunctions in PD patients, it can provide useful data for patients with other neurological diseases.

The SCOPA-AUT has been reported to be helpful for evaluating Asian patients with PD [7]. This study showed that the SCOPA-AUT was useful not only in Asian patients with PD, but also in Asian patients with other neurological disorders.

The Cronbach's coefficient alphas were more than 0.8 for the total score and for all items, suggesting high internal consistency. Cronbach's coefficient alphas of the total score were almost equal before and after excluding the items which had low valid response rates (item 22, 23, 24 and 25). It meant these four items, indeed, had no large effect on SCOPA-AUT overall. However, most of the ICCs were moderate, and the test–retest reliability of the Japanese version of the SCOPA-AUT was substantial. This result was considered equal to those of previous studies (ICCs: 0.71–0.87) [1,2]. The questions about thermoregulatory dysfunction showed low ICCs, suggesting that the participants' feelings of temperature varied because this study was conducted when the seasons changed.

The small number of valid response for items 22, 23, and 25 may have influenced the high ICCs. However, the low ICCs may reflect the inclusion of patients with different diseases compared to those examined in previous studies. The earlier study on the use of the SCOPA-AUT in patients with MSA [3] was more heterogeneous than those studies that included only patients with PD. Thus, the SCOPA-AUT may be suitable for screening nonhomogeneous diseases, such as MSA.

The average total scores of this study were 13.580 and 15.677 for the first and second assessment, respectively. This was lower than those of previous reports (18.8–23.0). Item 16 shows all zeros, indicating that no one fell unconscious in the previous 6 months. This suggested that our study group consisted of patients with less severe dysautonomia. The lower average score in this study compared to those for the English or Portuguese versions suggests the same thing.

There were not many invalid answers, except for questions about sexual dysfunction. This tendency was compatible with previous reports. In this study, there were 0.4–0.8% missing answers, and there were 5.9–6.6% invalid answers for all of the items, which was similar to a previous study (0.8–1.0%) [3]. Invalid answers accounted for more than two-thirds of the questions about sexual dysfunction. The Portuguese version showed "not applicable" data for 56.9% of the women and 10.6% of the men [2]. In the original version, there were 13% missing data, and "not applicable" accounted for 50% [1]. The most feasible reasons for the many invalid responses were presumed to be the lack of a partner and a sense of shame [2]. This study also suggested this because the mean age of the patients with invalid responses was older than those with valid answers. Alternatively, this may imply that the Japanese are more reserved. A more appropriate approach for evaluating sexual dysfunction needs to be developed.

The limitations of this study were as follows: (i) a control group consisting of individuals without any autonomic dysfunction or neurological disorder was not included in this analysis, (ii) severe cognitive impairment were excluded, but mild cognitive impairment may be included because accurate cognitive function tests such as Mini-Mental State Examination were not evaluated, and (iii) analyses based on each disease were not conducted. These two aspects must be explored in detail while conducting a more stringent validation study.

5. Conclusions

The Japanese version of the SCOPA-AUT had high internal consistency, and it may be applied to patients with various neurological disorders other than PD. It is preferable that the SCOPA-AUT is used for screening nonhomogeneous groups, as in this study. However, it is difficult to get a high response rate to questions about sexual dysfunction.

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Conflict of interest

All authors have no conflict of interest.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Reliability of the Japanese Version of the Berg Balance Scale

Masaaki Matsushima, Ichiro Yabe, Hisashi Uwatoko, Shinichi Shirai, Makoto Hirotani and Hidenao Sasaki

Abstract

Objective The Japanese translation of the Berg balance scale (BBS) has previously been published; however, its reliability has not yet been validated. This study aimed to evaluate its reliability.

Methods Patients took the BBS test three times; two neurologists monitored the results. The intraclass correlation coefficients (ICCs) and Cronbach's alpha (α) coefficients were calculated, and the inter-rater and intra-rater reliability were determined.

Patients Thirty-three patients with balance disturbance were recruited.

Results The study participants included 15 men and 18 women with a mean age of 62.8 years (SD, 14.8). For the total BBS score, the inter-rater ICC and Cronbach's α coefficient were 0.9337 and 0.9493, respectively, while the intra-rater ICC and Cronbach's α coefficient were 0.9772 and 0.9416, respectively. Most items had a relatively high ICC. The Cronbach's α coefficients were more than 0.9 for all items.

Conclusion The Japanese version of the BBS was found to have a high inter-rater and intra-rater reliability and internal consistency.

Key words: Berg balance scale, balance disturbance, intraclass correlation coefficient, Cronbach's α coefficient

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Introduction

Balance disturbance is a common symptom of many neurological disorders, such as spinocerebellar degeneration, multiple sclerosis and cerebrovascular disease. The Berg balance scale (BBS) (1), published in 1989, is a widely used clinical test for evaluating balance disturbance. It consists of 14 balance-related tasks or items, such as standing, sitting, transfers and standing on one leg. Each item is scored from 0 to 4, with 0 being severe balance disturbance and 4 being normal balance function; thus, the minimum score that can be achieved is 0, while the maximum score is 56. In other words, as symptoms progress, the scores will progressively decrease.

The BBS was originally developed to estimate the risk of falling among elderly subjects. Previous studies have used the BBS in assessments of elderly patients and patients with acute stroke, as well as of those with orthopedic diseases (2, 3). Recently, the BBS was used in a clinical trial for the assessment of balance in patients with Parkinson's disease (4). The BBS has been translated into many different languages and each version is said to be reliable (4-7). The Japanese translation of the BBS has also been published (8), but its reliability has yet to be validated.

This primary aim of this study was to evaluate the reliability of the Japanese version of the BBS, given its frequent use in estimating balance disturbance among patients with neurological diseases. Furthermore, we attempted to assess the BBS for various neurological diseases rather than limiting it to one particular disease.

Materials and Methods

Patients who were hospitalized in the Hokkaido University Hospital, Department of Neurology between September

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Correspondence to Dr. Masaaki Matsushima, mmasaaki@huhp.hokudai.ac.jp

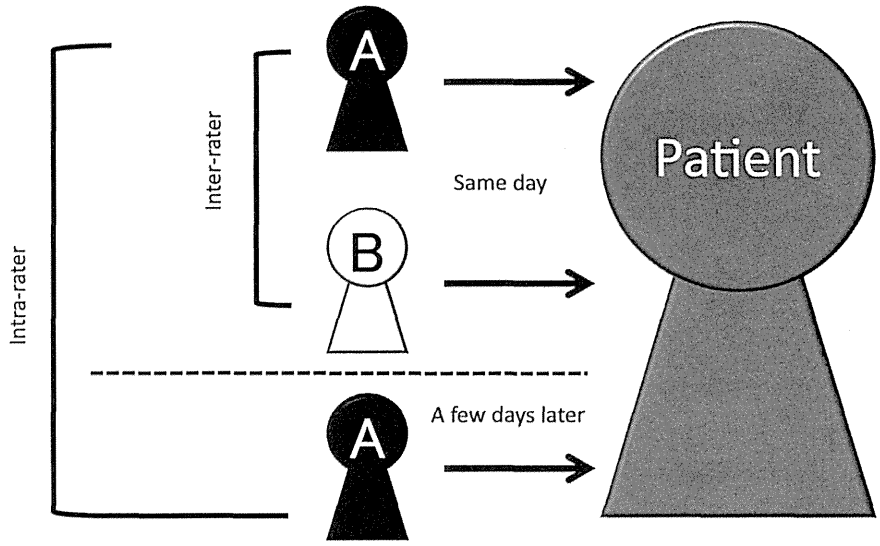

Figure. The assessment procedure used in this study.

2012 and October 2012 were enrolled in this study. Those enrolled were diagnosed with some kind of neurological disorder accompanied by balance disturbance. This study was approved by the institutional review board of Hokkaido University Hospital. Prior to beginning the study, written informed consent was obtained from all participants. Patients with severe cognitive impairment were excluded.

The published Japanese translation of the BBS was used (8); another study that reported on the reliability of the Japanese version of the scale for the assessment and rating of ataxia was consulted for the study design (9). Two neurologists, evaluators A and B, examined each patient separately using the Japanese version of the BBS. Evaluator A carried out the examination first, and evaluator B examined the patients several hours later on the same day. After a few days, evaluator A performed the examination again (Figure).

Each trial was performed blindly and under the same conditions, i.e., during the "on" period in patients with Parkinson's disease, thus avoiding any sudden change in motor symptoms. There were no interventions during the study period except for the prior treatments. Amassed data were anonymized, and the statistical analyses were performed.

Statistical analysis

The JMP® Pro 10.0.0 software program (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. The inter-rater and intra-rater reliability between evaluators A and B was assessed (Figure). The total BBS score and the scores of each item were analyzed based on Cronbach's α coefficients and the intraclass correlation coefficients (ICCs). The items were considered to have high internal consistency if Cronbach's α coefficient was more than 0.8. ICC values were interpreted as follows: slight (0.000 to 0.200); fair (0.201 to 0.400); moderate (0.401 to 0.600); substantial (0.601 to 0.800) and almost perfect (0.801 to 1.000) (10). The mean values are presented with the standard deviation (SD).

Results

Thirty-three patients (15 men and 18 women; age range, 28 to 82 years; mean age, 62.8±14.8 years) were enrolled in this study. The participants had balance disturbance associated with the following neurological diseases: multiple system atrophy (six patients), Parkinson's disease (five patients), amyotrophic lateral sclerosis (three patients), multiple sclerosis (three patients), myasthenia gravis (two patients), Parkinsonism (two patients), and progressive supranuclear palsy, hereditary spinocerebellar degeneration, Creutzfeldt-Jakob disease, clinical isolated syndrome, cerebral infarction, cerebral vasculitis, myelitis, spinal lymphomatoid granulomatosis, human T-cell leukemia virus type 1 associated myelopathy, idiopathic myelopathy, lumbar canal stenosis and peripheral neuropathy (one patient each). The average time needed for each examination was 10.4±2.1 minutes.

The total BBS scores and the scores for each item are shown in Table 1. There were no statistically significant difference between the assessments (p=0.2925 to 1.00). Table 2 shows the distribution of the scores by evaluator A (first assessment). The second and third assessments showed similar scoring values. For item 3 of the BBS, most patients were given a score of "4." As with the other language versions, all items had high item-total correlation coefficients, except for BBS item 3 (data not shown). The ICCs and Cronbach's α coefficients are shown in Table 3. The inter-rater and intra-rater ICCs and Cronbach's α coefficients of the total BBS score were more than 0.9. The inter-rater and intra-rater ICC values for 12 out of the 14 items were over 0.6. The inter-rater ICC of the BBS item 3 could not be calculated due to a software error. The Cronbach's α coefficients of all items were more than 0.9.

Table 1. The Mean Scores ±SD for Each Item and the Total BBS Score

Item		First assessment (A) Score ± SD	Second assessment (B) Score ± SD	Third assessment (A) Score ± SD
BBS1	Sit to stand	3.697 ± 0.521	3.606 ± 0.851	3.576 ± 0.698
BBS2	Standing unsupported	3.394 ± 1.043	3.636 ± 1.010	3.364 ± 1.039
BBS3	Sitting unsupported	3.909 ± 0.378	3.909 ± 0.514	3.909 ± 0.287
BBS4	Stand to sit	3.364 ± 1.096	3.545 ± 0.988	3.424 ± 0.922
BBS5	Transfers	3.636 ± 0.771	3.576 ± 0.780	3.606 ± 0.886
BBS6	Standing with eyes closed	3.212 ± 1.008	3.424 ± 1.016	3.273 ± 1.023
BBS7	Standing with feet together	3.000 ± 1.044	3.182 ± 1.167	3.152 ± 1.019
BBS8	Reaching forward while standing	2.485 ± 1.019	2.645 ± 1.123	2.515 ± 0.957
BBS9	Retrieving object from floor	3.455 ± 1.076	3.455 ± 1.233	3.485 ± 1.158
BBS10	Turning trunk (feet fixed)	3.394 ± 1.099	3.364 ± 1.201	3.394 ± 1.043
BBS11	Turning 360°	2.545 ± 1.373	2.818 ± 1.486	2.727 ± 1.377
BBS12	Placing alternate foot on stool	2.848 ± 1.373	3.121 ± 1.451	3.030 ± 1.359
BBS13	Tandem standing	2.182 ± 1.749	2.091 ± 1.781	2.212 ± 1.719
BBS14	Standing on one leg	1.758 ± 1.634	2.061 ± 1.536	2.000 ± 1.670
Total		42.879 ± 11.793	44.273 ± 12.790	43.667 ± 11.990

The first and third assessments were conducted by evaluator A, and the second assessment was performed by evaluator B.
SD: standard deviation, BBS: Berg Balance Scale

Table 2. Distribution of Scores for Evaluator A (first Assessment)

		Score				
	Item	0	1	2	3	4
Number of assessed patients	BBS1	0	0	1	8	24
	BBS2	2	0	2	8	21
	BBS3	0	0	1	1	31
	BBS4	0	5	1	4	23
	BBS5	0	2	0	6	25
	BBS6	2	0	2	14	15
	BBS7	2	0	6	13	12
	BBS8	2	3	9	15	4
	BBS9	2	1	0	7	23
	BBS10	1	2	4	2	24
	BBS11	3	4	12	0	14
	BBS12	4	2	4	8	15
	BBS13	11	2	3	4	13
	BBS14	13	3	3	7	7
	Sum	42	24	48	97	251
	(%)	(9.09)	(5.19)	(10.39)	(21.00)	(54.33)

BBS: Berg Balance Scale

Table 3. Inter-rater and Intra-rater ICCs and Cronbach's α Coefficients for the BBS

	Inter rater		Intra rater	
Item	ICC	Cronbach's α	ICC	Cronbach's α
BBS1	0.5560	0.9560	0.6930	0.9498
BBS2	0.7814	0.9532	0.8233	0.9458
BBS3	Not calculated	0.9603	0.2099	0.9592
BBS4	0.8127	0.9550	0.8278	0.9478
BBS5	0.8043	0.9543	0.5928	0.9473
BBS6	0.7880	0.9538	0.8859	0.9465
BBS7	0.7377	0.9522	0.7938	0.9448
BBS8	0.7530	0.9539	0.7131	0.9475
BBS9	0.9121	0.9522	0.9411	0.9453
BBS10	0.6771	0.9534	0.7688	0.9472
BBS11	0.8513	0.9529	0.8917	0.9454
BBS12	0.8183	0.9532	0.9218	0.9451
BBS13	0.7493	0.9573	0.9070	0.9499
BBS14	0.8385	0.9569	0.8824	0.9491
Total	0.9337	0.9493	0.9772	0.9416

ICC: Intraclass Correlation Coefficient, BBS: Berg Balance Scale

Discussion

The total score of the Japanese version of the BBS showed a high ICC and Cronbach's α coefficient, indicating good test-retest reliability and internal consistency. Most of the individual items exhibited high ICCs, and all items showed high Cronbach's α coefficients. These findings correspond to those of previous reports of other translations (2, 4-7).

The BBS is mainly used for assessing balance in elderly individuals, patients with stroke and patients with orthopedic diseases. This study demonstrates that the BBS is useful for the assessment of balance in patients with various neurodegenerative diseases associated with balance disturbance. This study differed from previous studies in that all the participants were inpatients.

The related reduction in the activities of daily living may account for the lower scores observed in this study compared to other studies; however, the scores achieved in this study were generally equivalent to those of the previously published data (2, 4-7), and the distribution of scores resembled that reported in previous studies (5, 6).

Regarding item 3 of the BBS, almost all patients could sit safely, i.e., they received a score of "4"; however, the statistical error for item 3 was larger than the dispersion of its score, and thus, the ICC value was negative. Since ICC values are generally displayed as 0 to 1, we could not obtain a relevant value for this item. Previous studies have reported that all participants received a score of "4" in the BBS item 3 (1, 5, 6). Due to the nature of this item, a big difference

may not occur in most populations.

The BBS items 1, 3, and 5 showed low ICC values; their mean scores were higher than 3.5. A few items had low ICC values and a high Cronbach's α coefficient. This may be due to the structure of the 5-point scale. If there was a disagreement between the evaluators in a few items, the Cronbach's α coefficients were high but the ICCs were low; however, the scores of the evaluators were similar for most items.

The BBS is a useful scale, but there may still be room for improvement. That said, items with intra-rater and inter-rater ICC values higher than 0.8 were observed in the latter part of the BBS; those tasks were considered to be relatively difficult to perform. Tasks with high levels of difficulty are likely to be suitable for scales aimed at the differentiation of patients. Previously, brief versions of the BBS have been discussed (11, 12), and several items with high ICCs noted in Table 3 have been included in these versions. It is thought that the ICC values could therefore be useful for developing brief versions of the BBS.

Conclusion

The Japanese version of the BBS was found to have high intra-rater and inter-rater reliability while showing a high internal consistency. Furthermore, the BBS may be a helpful indicator of balance disturbance in patients with neurodegenerative diseases.

The authors state that they have no Conflict of Interest (COI).

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CASE REPORT

Effectiveness of zonisamide in a patient with Parkinson's disease and various levodopa-induced psychotic symptoms

Ichiro Yabe,[1] Midori Ohta,[2] Toshiaki Egashira,[3] Kazunori Sato,[1] Takahiro Kano,[1] Makoto Hirotani,[1] Yasuyuki Kunieda[4] and Hidenao Sasaki[1]

[1]Department of Neurology, Hokkaido University Graduate School of Medicine, Sapporo, [2]Rehabilitation Center, Departments of [3] Psychiatry, and [4] Internal Medicine, Wakkanai City Hospital, Wakkanai, Japan

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Correspondence
Ichiro Yabe
Department of Neurology, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo 060-8638, Japan. Email: yabe@med.hokudai.ac.jp

Abstract

Levodopa and dopamine agonists are useful as Parkinson's disease medications. However, they often induce persistent psychotic symptoms and motor complications, which make Parkinson's disease treatment difficult. This is a case report of a patient with advanced Parkinson's disease accompanied by exacerbation of motor symptoms and psychotic symptoms derived from prolonged use of conventional anti-Parkinson's disease drugs, and in whom adjunctive therapy with a new anti-Parkinson's disease drug, zonisamide, was shown to improve motor symptoms with no exacerbation of psychotic symptoms.

Introduction

As medication for Parkinson's disease (PD), levodopa (L-dopa) and dopamine agonists (DA) are used as the first-line of treatment for PD to activate dopamine neurons. However, they often induce persistent psychotic symptoms including hallucinations and delusions. In addition, after long-term use of L-dopa, some patients experience motor complications, such as wearing-off and the on-off phenomenon, and involuntary movement. In view of these facts, particular caution should be taken in the selection of drugs for the treatment of advanced PD. Zonisamide has been developed as a new anti-PD drug in Japan, and is considered to have various effects on PD. We report a case of an advanced PD patient with exacerbation of psychotic symptoms, and in whom adjunctive therapy with zonisamide proved to be effective.

Case report

A 47-year-old man was diagnosed with early-onset PD with a duration of 19 years. He reported no remarkable family histories.

An overview of clinical symptoms and the medication history of the patient is presented in Figure 1. He noticed gait disturbance as a first symptom 19 years before zonisamide initiation. Four years later, he was diagnosed with early-onset PD and started treatment. After receiving 7 years of treatment with L-dopa and DA, he manifested psychotic symptoms including hallucinations and delusions. Over the next 7 years, although he was treated with L-dopa/carbidopa, DA, anticholinergics and antipsychotics, he was in and out of hospital nine times because of the manifestation and exacerbation of psychotic symptoms (delusions, visual and auditory hallucinations, wandering, gambling problems, emotional disturbance), motor complications and gait disturbance.

He first visited the Department of Neurology, Wakkanai City Hospital in Wakkanai City, Japan, for treatment of his motor symptoms. His main symptoms were muscle rigidity of the left limbs, bradykinesia and freezing of gait, which were severe enough to require wheelchair confinement. No neurological abnormalities were found in the cranial nerves, the cerebellum or the sensory system. Brain magnetic resonance imaging also showed no significant abnormalities.

Although the patient seemed to require an increased dose of anti-PD drugs, increasing the L-dopa dose was deemed inappropriate, as he was already suffering from psychotic symptoms. Instead we initiated adjunctive therapy with 25 mg/day zonisamide, in addition to 300 mg/day L-dopa and 4 mg/day ropinirole. As a result, a marked improvement was achieved in freezing gait, and he could walk by himself within a month of initiation of treatment with zonisamide. Meanwhile, his psychotic symptoms remained stable without aggravation. Six months later, the "off-time" periods were reduced. The patient's daily life improved dramatically to the extent that he could engage in recreational activities with his family. Ten months after zonisamide initiation, improvement of gait freezing persisted, and he could go out on his bicycle during the day. His Unified Parkinson's Disease Rating Scale scores markedly improved (Fig. 1).

Discussion

Zonisamide is used widely as anti-epileptic drug. It was serendipitously found to have beneficial effects on PD, and was

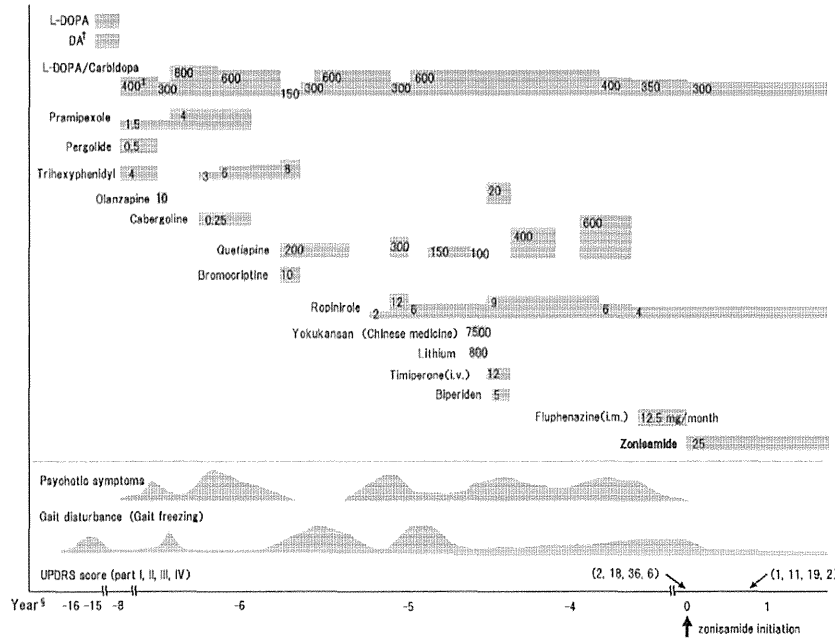

Figure 1 Clinical course showing administration of drugs, symptoms and Unified Parkinson's Disease Rating Scale (UPDRS) scores. †Dopamine agonist (drug name was unknown). ‡The dosage unit of all drugs is mg/day. §Year: Zero-point is when zonisamide was initiated. The UPDRS were scored before and 10 months after zonisamide initiation.

developed as a new anti-PD drug.[1] In the clinical trial, the clinical dose (25 mg/day) of zonisamide showed a low frequency of adverse effects associated with psychotic symptoms.[2] The anti-PD effects of zonisamide are considered to be mediated by inhibition of monoamine oxidase B and the activation of tyrosine hydroxylase. Previous research showed that, when co-administered with L-dopa, it can increase extracellular levels of dopamine in the striatum.[3,4] In addition, another experiment showed that zonisamide inhibited the indirect pathway, but did not act on the direct pathway of the basal ganglia, and this inhibitory mechanism could be mediated by the δ_1 receptor.[5] Furthermore, an examination showed that the mechanism underlying the anti-PD and antitremor effects of zonisamide might be T type calcium channel inhibition, which does not involve dopamine receptors.[6–8] These findings suggest that, unlike other conventional anti-PD drugs whose main action is the activation of the dopamine system, the anti-PD effect of zonisamide could be mediated by various other mechanisms of action.

The present patient experienced repeated manifestation and exacerbation of motor and/or psychotic symptoms, thus requiring adjustment of anti-PD drugs and the administration of antipsychotic drugs. Adjunctive therapy with zonisamide resulted in a sustained anti-PD effect, as evidenced by significant improvement in gait freezing and reduction in "off-time" periods without exacerbation of psychotic symptoms. This finding suggests that zonisamide is less likely to cause psychotic symptoms that are often induced by L-dopa and DA. As the major cause of exacerbation of symptoms was medication non-compliance, making a patient aware of his illness and offering medications that are easy to take is the key to successful treatment. Zonisamide is a convenient, orally administered tablet taken once daily. As shown in the present patient, zonisamide worked so well that just a single tablet changed his life. Selecting a drug that is effective, safe and encourages patient compliance with medication is important when selecting adjunctive therapy for patients with advanced PD requiring multiple medications. There are not so many patients who have an excellent response to zonisamide like this case; however, we consider that it is worth trying zonisamide in patients suffering exacerbation of psychotic symptoms.

The present findings suggest that the use of zonisamide is less likely to result in the psychotic symptoms that are often induced by L-dopa and dopamine agonists, and is an important treatment option for patients with advanced PD.

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