Cardiovascular dysautonomia and cognitive impairment in Lewy body disease

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BMC Neurology  BMC Series

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DOI: 10.21203/rs.2.16373/v2

SUBJECT AREAS  Neurology

KEYWORDS
Orthostatic hypotension, Daily blood pressure fluctuation, Cognitive decline, Parkinson’s disease, Dementia with Lewy bodies
Abstract

Background Cognitive impairment may be correlated with cardiovascular dysautonomia, including blood pressure (BP) dysregulation, in Parkinson’s disease (PD), but the association between these factors in dementia with Lewy bodies (DLB) is uncertain. This study aimed to clarify whether cardiovascular dysautonomia had an influence on cognitive function in Lewy body disease or not. Methods 99 patients with de novo PD (n=75) and DLB (n=24) were evaluated using the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB). Cardiac 123I-metaiodobenzylguanidine (MIBG) scintigraphy, orthostatic hypotension (OH), supine hypertension (SH), postprandial hypotension (PPH), nocturnal BP fall in 24-hour ambulatory blood pressure monitoring (ABPM) and constipation were estimated. Associations of these factors with cognitive and executive dysfunction were examined. Results In DLB, MIBG uptake was reduced and OH, PPH and SH were severely disturbed, compared to PD. The nocturnal BP fall in ABPM was lower in DLB, and the failure of nocturnal BP fall in PD was associated with MMSE, after adjustment for other clinical features. FAB was significantly associated nocturnal BP fall, age and SH in PD, but no significant correlations among factors were found for DLB. Conclusion The significant association between nocturnal BP dysregulation and cognitive or executive decline in PD might be due to impaired microvascular circulation or invasion of $\alpha$-synuclein in the CNS. The lack of a correlation of BP insufficiency with cognitive impairment in DLB suggests initial involvement of Lewy body pathology in the neocortex, regardless of Lewy body invasion of the autonomic nervous system.
Introduction

Parkinson’s disease (PD) is commonly associated with motor symptoms and various non-motor symptoms, including behavioral changes such as depression, sleep disturbance, fatigue, and autonomic dysfunction. Autonomic impairment associated with PD is characterized by clinical features of constipation, sweating, orthostatic hypotension (OH), and postprandial hypotension (PPH), even in the early phase [1]. OH occurs through sympathetic noradrenergic dysfunction and is clinically important in 20% to 50% of patients with PD [1]. Survival depends on the OH status, with a greater risk of death in PD with OH than in PD without OH [2]. OH may also affect cognition [3], daily activities, and quality of life [4]. Patients who have PD with OH have significantly worse sustained attention and visual episodic memory [5] and significantly lower scores on the Mini-Mental State Examination (MMSE) [6] [7]. Abnormal blood pressure (BP) fluctuations are also common in PD [8, 9]. The normal nocturnal BP fall in a healthy person disappears in PD, especially in cases with autonomic dysfunction [10, 11]. Cognitive decline in older people is associated with abnormal BP fluctuations, such as the absence of a normal nocturnal BP fall [11, 12], and cognitive impairment in PD has also been associated with abnormal BP fluctuations [13] (Tanaka et al., 2018). Autonomic dysfunction in dementia with Lewy bodies (DLB) is generally more severe than that in PD [14]. The severity of autonomic failure in DLB is intermediate between that in PD and multiple system atrophy [15]. OH is likely to be severer in DLB than in PD because it is ascribed to Lewy body involvement in the rostral ventrolateral medulla and medullary raphe, which may control sympathetic outflow [15]. However, it is unclear whether cognitive dysfunction in DLB correlates with blood circulatory insufficiency, such as
OH and abnormal BP fluctuations, as occurs in PD.

The aims of this study were to examine the associations of cardiovascular dysautonomia and cognitive impairments in de novo PD and DLB on the basis of the $^{123}$I-metaiodobenzylguanidine (MIBG) uptake by the heart, responses of BP and plasma norepinephrine in a head-up tilt-table test (HUT), a 75-g oral glucose tolerance test (75-g OGTT) for PPH, 24-hour ambulatory blood pressure monitoring (ABPM), and constipation.

Materials and Methods

Study design and participants

The subjects were 75 patients with de novo PD diagnosed using the criteria for PD proposed by the UK Parkinson’s Disease Society Brain Bank [16], and 24 patients with de novo DLB central features and two or more core features of the diagnostic criteria, which is sufficient for a diagnosis of probable DLB [17]. All patients were examined at Daisan Hospital, Jikei University School of Medicine, between January 2012 and March 2018. At least two neurologists performed the diagnosis. We also used a 1-year rule to distinguish DLB from PD with dementia [17]. Patients with overt diabetes or clinically relevant cardiac disease, and those who had been received tricyclic antidepressants, tetracyclic antidepressants, serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors were excluded from the study. None of the patients had received levodopa, other anti-Parkinson drugs, or treatment for OH. Global cognition and executive function were evaluated using the MMSE and the Frontal Assessment Battery (FAB). No patient had atrophy of the putamen, brainstem, or cerebellum on brain MRI. If patients were already receiving antihypertensive drugs, such drugs were withdrawn at least 48
hours before the evaluation of OH. All patients received levodopa or a dopamine agonist for their parkinsonism after this study, and all had a good response. The motor severity of PD was assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS) motor score. The patients were divided into tremor-dominant, akinetic-rigid, and mixed-type subgroups based on the tremor and non-tremor scores, which were obtained using part III of the UPDRS [18]. This study was approved by the Ethics Committee of The Jikei University School of Medicine, and all subjects provided written informed consent before enrollment.

**Cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy**

Cardiac sympathetic denervation was evaluated using MIBG scintigraphy. The ratios of the average pixel count in the heart (H) to that in the mediastinum (M) (H/M ratio) were calculated 15 min (early) and 3 hours (delayed) after injection of 111 MBq $^{123}$I-MIBG (Fujifilm RI Pharma Co., Ltd. Tokyo, Japan) [19].

**Olfactory assessment**

Olfactory function was assessed by the odor stick identification test Japan (OSIT-J) (Daiichi Yakuhin Sangyo Co. Ltd., Tokyo, Japan), as described in our previous study [20]. The number of correct responses for the 12 odorants was defined as the OSIT-J score, which has been shown to significantly correlate with the responses on the University of Pennsylvania Smell Identification Test (UPSIT) and the cross-cultural, smell identification test (CC-SIT) [21, 22].

**Head-up tilt-table test (HUT)**

All subjects underwent HUT in a silent room maintained at an ambient temperature
of 23°C to 26°C. After an overnight fast, the test was started at 9:00 am. After resting for 20 min in the supine position, the subject was tilted to a 60° upright position for 3 min. Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an automated sphygmomanometer after 20 min of rest in the supine position and every 1 min after the subject was tilted for up to 3 min. The maximum decreases in SBP and DBP during tilt were evaluated. Plasma norepinephrine concentrations in serum (NE, μg/ml)) were measured with the subjects in a supine position after 20 minutes of rest and after 10 min in a tilted position. OH was defined as a fall in SBP by ≥20 mmHg [23]. Supine hypertension (SH) was defined as SBP >140 mmHg or DBP >90 mmHg, as measured after 20 min of rest in the supine position [24]. Neurogenic SH was defined as OH with SBP >140 mmHg or DBP >90 mmHg in the supine position [25].

24-hour ambulatory blood pressure monitoring (ABPM)

24-hour ABPM was performed using a noninvasive automated portable recorder in hospitalized patients and outpatients. BP was measured every 30 min during the day (7:00-21:00) and every hour at night (22:00-6:00). SBP was used as an indicator of BP. The nocturnal fall in BP was calculated as: \( \text{SBP}_{\text{day}} - \text{SBP}_{\text{night}}/\text{SBP}_{\text{day}} \times 100 \) (%), where \( \text{SBP}_{\text{day}} \) is the mean SBP during the day, and \( \text{SBP}_{\text{night}} \) is the mean SBP at night. Cases with nocturnal falls in BP of ≥10%, <10%, or no fall were defined as dipper, non-dipper, and riser types, respectively [26, 27].

75-g oral glucose tolerance test for evaluation of postprandial hypotension

After overnight fasting (except for non-caloric liquids), a 75-g OGTT was started between 9:00 and 10:00 am in a quiet room at an ambient temperature of 23° to
26°C. Whenever possible, we performed HUT followed by the 75-g OGTT on the same day. If this was not possible, the 75-g OGTT was performed on the day after HUT. After 20 min resting in the supine position, the subjects drank 75 g of glucose water (calorie content, 300 kcal) and remained resting and awake in the supine position for 120 min. After 20 min and then every 10 min for the next 120 min, brachial SBP and DBP were measured in the supine position with an automated sphygmomanometer. The time to the maximum drop in SBP on the 75-g OGTT was measured. Postprandial hypotension (PPH) was defined as a maximum decrease in SBP of 20 mmHg within 2 hours after glucose intake [28, 29].

**Constipation**

Constipation was defined as the presence of at least one of two criteria: absence of daily defecation, and use of drugs to treat constipation [30].

**Statistical analysis**

Statistical analyses were performed with statistical software (Esumi Co., Ltd., Tokyo, Japan). Differences between groups were compared by the Wilcoxon rank sum test for continuous variables. Pairwise comparisons were made using χ² tests for binary variables. Lepage analysis was used to evaluate differences in the nocturnal fall in BP. Associations of MMSE and FAB scores with clinical variables such as age, gender, symptom duration, UPDRS motor score, motor subtype, olfaction, cardiac MIBG uptake, BP fall on HUT, NE at rest in the supine position on HUT, nocturnal falls in BP in ABPM, PPH, and SH, and constipation were evaluated by multiple regression analysis. P<0.05 was considered to indicate statistical significance.
Results

Cognitive impairment and cardiovascular dysautonomia in PD and DLB

A comparison of the characteristics of the PD and DLB patients is shown in Table 1. DLB patients were older than PD patients, but there was no significant difference in the duration of PD or DLB. PD patients were significantly more frequently female, while DLB patients were more commonly male. There were no significant differences in UPDRS motor scores or motor subtypes between PD and DLB patients. DLB patients had more severely impaired olfaction, lower MMSE and FAB scores, a lower H/M ratio in cardiac MIBG uptake, a lower BP fall in HUT, lower NE in a resting supine position in HUT, and a higher prevalence of OH as compared with PD patients. There was a reduced nocturnal fall in BP on ABPM and a higher proportion of non-dipper/riser types among DLB patients. The BP fall in PPH and the prevalence of PPH were greater in DLB patients. The prevalence of SH did not differ significantly, whereas the prevalence of neurogenic SH was higher in DLB patients. The prevalence of constipation was also higher in DLB patients than in PD patients.

Correlations between cognitive impairment and cardiovascular dysautonomia

In multiple regression analyses, MMSE in PD was significantly associated with a nocturnal fall in BP on ABPM (p=0.0275), after adjusting for age, disease duration, UPDRS motor score, motor subtype, olfaction, cardiac MIBG scintigraphy, BP fall in HUT, NE at rest in a supine position in HUT, PPH, and SH, and constipation (Table 2); and FAB in PD was significantly related to a nocturnal fall in BP (p=0.0395), aging (p=0.0076), and SH (p=0.0037)] (Table 3). In contrast, neither MMSE nor FAB in
DLB was associated with a nocturnal fall in BP or any other clinical variable (Tables 4, 5).

Discussion

In this study, DLB patients clearly had more severe cognitive decline than did PD patients. Olfaction was more impaired in DLB patients, and olfactory dysfunction has been associated with cognitive dysfunction [20, 31]. De novo PD with mild cognitive decline is associated with more olfactory impairment than that found in patients without cognitive dysfunction [32]. This is consistent with the fact that DLB patients with impaired cognition have more severe olfactory dysfunction than that found in PD patients.

MIBG uptake on scintigraphy, indicating cardiac sympathetic denervation, was lower in patients with DLB than in those with PD. Falls in BP on standing were significantly greater, NE at rest was lower, and the BP falls in PPH and SH were greater in patients with DLB. Neurogenic SH differed significantly between patients with PD and those with DLB, but was not related to the prevalence of SH. The prevalence of constipation in DLB was higher than that in PD, suggesting that intestinal autonomic dysfunction might be severer in DLB. Overall, our findings suggest that DLB involves wider spread and severer sympathetic and parasympathetic autonomic dysfunction than PD, which might be caused by peripheral and CNS impairments [14]. Abnormal daily BP fluctuations in PD [33, 34] have been associated with cardiovascular dysautonomia [34], but have rarely been reported in DLB. PD patients with this condition, including reduced or reverse nocturnal BP falls on ABPM, have also been found to have a higher prevalence of OH [33]. Thus, severe cardiovascular autonomic dysfunction in DLB might be linked to more
profound impairment of the nocturnal fall in BP. Cognitive function has previously been linked to abnormal BP fluctuations in PD [11, 13], including an abnormality in the nocturnal BP fall on ABPM. A novel finding in our study was that nocturnal BP abnormality was associated with cognitive and executive dysfunction in early stage and de novo PD after adjusting for other cardiovascular dysautonomic factors, including OH, PPH, SH, and cardiac sympathetic impairment as indicated by MIBG uptake insufficiency.

Several pathogeneses have been suggested for the association of cognitive dysfunction with BP abnormality, but the underlying mechanisms remain unclear. The Braak hypothesis [35] suggests that Lewy body (LB) pathology initially occurs in the olfactory nucleus and dorsal motor nucleus and progressively ascends through the brainstem to the cortex, causing noradrenergic and dopaminergic neuronal degeneration, which results in progression of motor, cognitive, and autonomic impairment. Cognitive declines in PD have been associated with specific patterns of LB density in the entorhinal cortex and anterior cingulate cortex [36], which play a role in autonomic nervous system (ANS) control, including the higher centers of autonomic regulation [37]. Involvement of the anterior cingulate cortex might simultaneously cause cognitive impairment and cardiovascular sympathetic failure. Noradrenergic projection from the locus coeruleus (LC) spreads extensively in the whole brain cortex, including the hippocampus, entorhinal and mediotemporal cortex, cingulate gyrus, and neocortex. Tyrosine hydroxylase immunoreactivity is lost in neurons projecting from the LC owing to the LB pathology in PD [38].

Involvement of the noradrenergic neurons in the LC is increasingly recognized as a potential major contributor to cognitive manifestations in early PD, particularly impaired attention [39]. The LC projects to the parasympathetic neurons of the
dorsal motor nucleus of the vagus nerves (the nucleus ambiguous), while the descending pathway projects to the sympathetic preganglionic neurons in the spinal cord [39]. Therefore, the LC should influence cardiovascular modulation via insufficiency of cardiac parasympathetic and cardiovascular sympathetic function. The LC also regulates part of the wake-promoting circuit with the suprachiasmatic nucleus and dorsomedial hypothalamus [40]. Therefore, spoiling of the LC may cause abnormal daily BP fluctuations in addition to cardiovascular sympathetic failure.

BP insufficiency such as OH, including circadian rhythm failure, is associated with increased white matter hyperintensities (WMHs) on MRI, even in older people [41, 42], and cognitive impairment and WMHs are associated with OH, SH and WMHs in PD. Cognitive impairment and WMHs are common in SH [11]. Our study showed that abnormal BP fluctuation and especially a reduced nocturnal fall in BP were associated with cognitive and executive functions in PD, after adjusting for other autonomic characteristics, including cardiovascular sympathetic function as reflected by cardiac MIBG uptake, OH, PPH, circulatory NE concentrations, and constipation. This suggests that increased lability of daily BP and nocturnal BP is a risk factor for cognitive impairment, even in early de novo PD. Furthermore, FAB scores, but not MMSE scores, correlated with SH and aging in our PD patients. This may indicate that executive dysfunction is caused by prefrontal area damage, which is readily attributable to cerebrovascular circulatory insufficiency of the cortex white matter or age-related changes in the brain in PD [23].

In contrast to PD, we found that cognitive and executive impairments in patients with DLB did not correlate with lability of BP. Our results and those of previous studies suggest that dysautonomia in DLB is severer than that in PD [14, 15]. It
remains uncertain whether PD and DLB including Parkinson’s disease with dementia (PDD) are separate disease entities or parts of the same disease spectrum. LB pathology in PD is restricted to the brainstem and limbic regions, while the pathology more quickly extends to the neocortex in DLB. LB pathology in PD is also not so widely distributed in autonomic nervous organs, as compared with that in DLB. The discrepancy between cardiovascular and cognitive dysfunction in DLB might suggest that regional invasion of LB pathology differs between the neocortex and sympathetic autonomic center. Braak’s hypothesis [35] suggests that α-synucleinopathy initially involves intestinal organs and ascends to the brainstem, including the dorsal motor nucleus of the vagus, LC, medullary reticular formation, raphe nuclei, and peripheral sympathetic nervous system. These organs are associated with modulation of cardiovascular autonomic regulation in early PD. Cognitive dysfunction in PD might be caused by white matter damage resulting from BP dysregulation and noradrenergic decline of the LC [38]. Cognition dysfunction should be associated with cardiovascular autonomic failure if LB pathology involves the ACC or insular cortex. Because cognitive decline has already progressed due to involvement of LB pathology in the brain cortex, cognitive impairment in DLB should not be strongly influenced by BP dysregulation. Alzheimer disease (AD) pathology associated with hyperphosphorylated tau and amyloid-β (Aβ) may also contribute to cognitive declines in DLB and PD. Aβ plaques are significantly more common in cortical and subcortical regions in DLB than in PDD [43, 44], and DLB displays concurrent AD-related pathology as compared with PDD [45]. Cardiovascular dysautonomia including reduced cardiac MIBG uptake and OH is not as impaired in AD as compared with DLB [46]. Thus, AD pathology may not correlate with ANS effects, and increased AD pathology may induce greater dissociation between
cognitive and BP dysregulation in DLB than in PD.

In conclusion, BP dysregulation, especially a reduced nocturnal fall in BP, was associated with cognitive and executive decline in PD, and this may be driven by impaired microvascular circulation or infiltration of α-synuclein from the peripheral ANS to the CNS, such as the LC or ACC. The absence of a correlation between cognitive and BP dysregulation in DLB is due to earlier spread of LB pathology to the neocortex, while ascending LB invasion of the LC or ANS occurs in PD. The more severe AD pathology in the cortex in DLB as compared with that in PD might also contribute to dissociation of cognitive dysfunction and BP abnormality. Therefore, treatment for BP dysregulation may prevent progression of cognitive decline in PD, but not in DLB.

Abbreviations

Alzheimer disease (AD), ambulatory blood pressure monitoring (ABPM), amyloid-β (Aβ), autonomic nervous system (ANS), blood pressure (BP), cross-cultural smell identification test (CC-SIT), dementia with Lewy bodies (DLB), diastolic blood pressure (DBP), Frontal Assessment Battery (FAB), heart (H), head-up tilt-table test (HUT), 123I-metaiodobenzylguanidine (MIBG), Lewy body (LB), locus coeruleus (LC), mediastinum (M), Mini-Mental State Examination (MMSE), 75-g oral glucose tolerance test (75-g OGTT), orthostatic hypotension (OH), Parkinson’s disease (PD), Parkinson’s disease with dementia (PDD), postprandial hypotension (PPH), supine hypertension (SH), systolic blood pressure (SBP), Unified Parkinson’s Disease Rating Scale (UPDRS), white matter hyperintensities (WMHs),

Declarations
Funding

Funding was from institutional sources only.

Competing interests

The authors report no competing interests.

Contributions to the manuscript

Hisayoshi Oka: drafting/revising the manuscript for content, including medical writing; study concept and design; acquisition of data; analysis and interpretation of data. Tadashi Umehara: study concept and design; acquisition of data; review and critique. Atsuo Nakahara: study concept and design; acquisition of data; review. Hiromasa Matsuno: study concept and design; acquisition of data; review. All authors have seen and approved the manuscript.

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Tables

Table 1. Comparison of clinical variables between patients with de novo DLB and patients with PD

| Variables                              | PD (N=75)   | DLB (N=24)  |
|----------------------------------------|-------------|-------------|
| Age (years)                            | 72.2±9.4    | 80.6±5.0    |
| Gender (male/female)                   | 27/48       | 18/6        |
| Symptom duration (years)               | 1.6±1.6     | 1.9±1.7     |
| UPDRS motor score                      | 20.3±10.9   | 21.3±10.8   |
| Subtype (akinetic-rigid/tremor-dominant/mixed) | 45/30       | 19/5        |
| Olfaction                              | 4.1±2.8     | 2.4±2.2     |
| Mini-mental state examination          | 27.7±2.2    | 20.0±4.7    |
| Frontal assessment battery             | 15.1±2.8    | 10.2±3.4    |
| Parameter                                                                 | Value 1     | Value 2     |
|---------------------------------------------------------------------------|-------------|-------------|
| MIBG H/M ratio delay                                                      | 1.44±0.33   | 1.22±0.39   |
| BP fall on head-up tilt-table test (HUT) (mmHg)                           | 23.6±20.0   | 48.5±23.6   |
| Prevalence of OH (-/+                                                    | 44/31       | 1/23        |
| Norepinephrine at rest in supine position on HUT (µg/ml)                 | 217.9±88.2  | 172.8±82.5  |
| Nocturnal fall in BP in ABPM (%)                                          | 8.5±9.4     | -4.4±12.6   |
| ABPM type (dipper/non-dipper or riser type)                              | 37/38       | 4/20        |
| BP fall in postprandial hypotension (mmHg)                               | 18.4±13.1   | 32.8±17.2   |
| Postprandial hypotension (-/+                                            | 42/33       | 6/18        |
| BP in supine hypertension (mmHg)                                          | 134.8±21.5  | 147.5±19.2  |
| Supine hypertension (-/+                                                 | 45/30       | 10/14       |
| Neurogenic supine hypertension (-/+                                       | 56/19       | 12/12       |
| Constipation (-/+                                                        | 25/50       | 1/23        |

\(^a\) Wilcoxon rank sum test and Lepage analysis for continuous variables and \(\chi^2\) test for binary variables.

**UPDRS:** Unified Parkinson’s Disease Rating Scale, MIBG: \(^{123}\)I-metaiodobenzylguanidine, H/M: ratio of the average pixel count in the heart (H) to that in the mediastinum (M), ABPM: 24-hour ambulatory blood pressure monitoring.

Table 2. Relations of MMSE to clinical variables in PD
| Clinical variables                                      | Variable Estimate | Standard Error | p-value |
|--------------------------------------------------------|-------------------|----------------|---------|
| Age (years)                                            | -0.053            | 0.031          | 0.099   |
| Gender (male/female)                                   | 0.260             | 0.594          | 0.664   |
| Symptom duration (years)                               | -0.208            | 0.162          | 0.204   |
| UPDRS motor score                                      | -0.017            | 0.026          |         |
| Subtype (akinetic-rigid/tremor-dominant/mixed)         | -0.906            | 0.528          |         |
| Olfaction                                              | -0.159            | 0.101          |         |
| MIBG H/M ratio delay                                   | -0.0310           | 0.837          |         |
| BP fall on head-up tilt-table test (HUT) (mmHg)        | -0.013            | 0.013          |         |
| Norepinephrine at rest in supine position on HUT (µg/ml)| 0.005             | 0.003          |         |
| Nocturnal fall in BP in ABPM (%)                       | 0.066             | 0.029          |         |
| BP fall in postprandial hypotension (mmHg)             | 0.028             | 0.020          |         |
| BP in supine hypertension (mmHg)                       | -0.180            | 0.013          |         |
| Constipation                                           | -0.018            | 0.622          |         |

\(^a\) Analyses were performed by multiple regression analysis. Abbreviations are as shown in Table 1.

Table 3. Relations of FAB to clinical variables in PD
| Clinical variables                                                                 | Variable Estimate | Standard Error | p-value |
|-----------------------------------------------------------------------------------|-------------------|----------------|---------|
| Age (years)                                                                        | -0.098            | 0.036          | (       |
| Gender (male/female)                                                              | -0.867            | 0.667          | (       |
| Symptom duration (years)                                                           | -0.028            | 0.183          | (       |
| UPDRS motor score                                                                  | -0.012            | 0.02904        | (       |
| Subtype (akinetic-rigid/tremor-dominant/mixed)                                     | -0.551            | 0.595          | (       |
| Olfaction                                                                          | -0.002            | 0.114          | (       |
| MIBG H/M ratio delay                                                               | -0.118            | 0.944          | (       |
| BP fall on head-up tilt-table test (HUT) (mmHg)                                    | 0.018             | 0.015          | (       |
| Norepinephrine at rest in supine position on HUT (µg/ml)                           | 0.002             | 0.003          | (       |
| Nocturnal fall in BP in ABPM (%)                                                   | 0.070             | 0.033          | (       |
| BP fall in postprandial hypotension (mmHg)                                         | 0.002             | 0.022          | (       |
| BP in supine hypertension (mmHg)                                                   | -0.043            | 0.014          | (       |
| Constipation                                                                       | -0.199            | 0.701          | (       |

* Analysis were performed by multiple regression analysis.
Abbreviations are as shown in Table 1.
### Table 4. Relations of MMSE to clinical variables in DLB

| Clinical variables                                      | Variable Estimate | Standard Error |
|---------------------------------------------------------|-------------------|----------------|
| Age (years)                                             | -0.435            | 0.255          |
| Gender (male/female)                                    | -3.063            | 3.454          |
| Symptom duration (years)                                | 0.959             | 0.807          |
| UPDRS motor score                                       | -0.176            | 0.128          |
| Subtype (akinetic-rigid/tremor-dominant/mixed)          | 1.492             | 3.664          |
| Olfaction                                               | 0.566             | 0.651          |
| MIBG H/M ratio delay                                    | 1.136             | 3.243          |
| BP fall in head-up tilt-table test (HUT) (mmHg)         | 0.039             | 0.049          |
| Norepinephrine at rest in supine position in HUT (µg/ml)| -0.024            | 0.019          |
| Nocturnal fall in BP in ABPM (%)                        | 0.095             | 0.143          |
| BP fall in postprandial hypotension (mmHg)              | 0.110             | 0.100          |
| BP in supine hypertension (mmHg)                        | -0.010            | 0.072          |
| Constipation                                            | -6.900            | 5.725          |

a Analysis were performed by multiple regression analysis.

Abbreviations are as shown in Table 1.
### Table 5. Relations of FAB to clinical variables in DLB

| Clinical variables                                | Variable Estimate | Standard Error | p-value |
|---------------------------------------------------|-------------------|----------------|---------|
| Age (years)                                       | -0.326            | 0.188          | 0.114   |
| Gender (male/female)                              | -1.791            | 2.551          | 0.499   |
| Symptom duration (years)                          | 0.221             | 0.596          | 0.719   |
| UPDRS motor score                                 | -0.169            | 0.094          |         |
| Subtype (akinetic-rigid/tremor-dominant/mixed)    | 0.081             | 2.706          |         |
| Olfaction                                         | -0.177            | 0.481          |         |
| MIBG H/M ratio delay                              | 1.731             | 2.395          |         |
| BP fall on head-up tilt-table test (HUT) (mmHg)   | 0.006             | 0.036          |         |
| Norepinephrine at rest in supine position on HUT (µg/ml) | 0.003             | 0.014          |         |
| Nocturnal fall in BP in ABPM (%)                  | 0.016             | 0.106          |         |
| BP fall in postprandial hypotension (mmHg)        | -0.016            | 0.074          |         |
| BP in supine hypertension (mmHg)                  | -0.009            | 0.053          |         |
| Constipation                                      | 1.464             | 4.227          |         |

a Analyses were performed by multiple regression analysis. Abbreviations are as shown in Table 1.