



Cerebral microbleeds and blood pressure abnormalities in Parkinson's disease



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ABSTRACT

Blood pressure abnormalities are frequently observed in patients with Parkinson's disease (PD), and are associated with cerebrovascular diseases such as white matter hyperintensities and carotid atherosclerosis. We assessed the relationship between blood pressure abnormalities and cerebral microbleeds (CMBs), a marker of cerebral small vessel disease, in 128 patients with PD. We examined supine and orthostatic blood pressures and used 24-hour ambulatory blood pressure monitoring to assess the presence or absence of orthostatic hypotension (OH), supine hypertension (SH), nocturnal hypertension (NH), and loss of nocturnal blood pressure dips (non-dipping). CMBs were found in 13 (10.2%) patients, and the median number of CMBs was 1 (range: 1 to 10). Six of these patients had deep or infratentorial CMBs, six had strictly lobar CMBs, and one had mixed CMBs. Linear regression analysis indicated that presence of both OH and SH was independently associated with greater numbers of CMBs in deep or infratentorial regions, independent of age, sex, cardiovascular risk factors, and white matter hyperintensities. NH and non-dipping were not associated with CMBs in deep or infratentorial regions, and there was no association between blood pressure and CMBs in lobar regions. Our results suggest that the presence of both OH and SH may be related to deep or infratentorial CMBs in patients with PD.

1. Introduction

Blood pressure abnormalities are common in Parkinson's disease (PD), and may manifest as orthostatic hypotension (OH), supine hypertension (SH), nocturnal hypertension (NH), or loss of nocturnal blood pressure dips (non-dipping), all of which frequently coexist [1]. In patients with PD, these blood pressure abnormalities are associated with cerebrovascular diseases, such as white matter hyperintensities [2–4] and carotid artery atherosclerosis [5].

Cerebral microbleeds (CMBs) are small round hypointense lesions seen on T2*-weighted magnetic resonance imaging (MRI) [6], and are associated with cognitive impairment [7] and recurrence of both ischemic and hemorrhagic stroke [8]. Histopathological studies indicate that CMBs represent previous extravasation of blood and are related to bleeding-prone microangiopathy [9]. Deep or infratentorial CMBs are associated with hypertension, while lobar CMBs reflect the presence of cerebral amyloid angiopathy [10,11]. CMBs have mainly been studied

in the general population, in patients with stroke, and in those with Alzheimer's disease [12], while few studies have investigated CMBs in patients with PD [13–15]. Nevertheless, it has been reported that CMBs occur more frequently in patients with PD with dementia compared to those without dementia. Indeed, patients with PD with CMBs have been found to have a poorer performance in the attention domain compared with those without CMBs [13]. Furthermore, comprehensive neuropsychological evaluation showed no significant association between the presence of CMBs and cognitive function in patients with PD without dementia [14]. We previously reported that OH is associated with deep or infratentorial CMBs in patients with PD [15]. However, whether coexisting SH, NH, or non-dipping is related to CMBs remains unanswered. Here, we evaluated supine and orthostatic blood pressure and used 24-hour ambulatory blood pressure monitoring (ABPM) in patients with PD to assess the relationship between blood pressure abnormalities and CMBs.

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2. Patients and methods

2.1. Study population

We enrolled patients diagnosed with PD according to the U.K. Parkinson's disease Society Brain Bank criteria [16]. Participants were recruited consecutively between January 2014 and September 2016 from the Department of Neurology at Juntendo University School of Medicine. One hundred and forty-three patients underwent blood pressure measurements and brain MRI. Three patients were excluded due to unreliable ABPM data and twelve were excluded due to incomplete blood pressure evaluations. Therefore, 128 patients with PD were examined in the present study.

We collected clinical information regarding age, sex, disease duration, current medications, body mass index, laboratory data, hypertension, and diabetes mellitus. We also determined whether the patients had histories of stroke, coronary artery disease, or cigarette smoking. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mm Hg, a diastolic blood pressure (DBP) ≥ 90 mm Hg in the sitting position, or treatment with antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dL, a glycated hemoglobin level $\geq 6.5\%$, or the use of insulin or oral hypoglycemic agents. Subjects were considered current smokers if they had smoked at least one cigarette per day within the previous year. The mean levodopa equivalent daily dose was calculated for each participant [17]. This study was approved by the Institutional Review Board of Juntendo Hospital. Informed consent was obtained from all patients.

2.2. Blood pressure measurements

OH and SH were assessed using the Schellong test. Patients were studied after they had rested in the supine position for 15 min. The patients' blood pressure and heart rate were measured in the supine position, and then measured in the upright position using an electronic sphygmomanometer (ES-H55 or ES-H55B, Terumo). OH was defined as a fall in SBP ≥ 20 mm Hg, or a fall in DBP ≥ 10 mm Hg within 3 min after rising from a supine to a standing position according to the consensus statement [18]. SH was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg according to the criteria of the American Heart Association [19].

ABPM was performed using an FB-270 device (Fukuda Denshi) every 30 min throughout the day (7:00 AM to 10:00 PM), and every 60 min during the night (10:00 PM to 7:00 AM). Mean SBP, DBP, and heart rate during the daytime, nighttime, and over a 24-hour period were evaluated. Nocturnal BP dip (%) was calculated as $(\text{mean daytime SBP} - \text{mean nighttime SBP}) / \text{mean daytime SBP} \times 100$. Patients with $< 10\%$ nocturnal fall in mean BP were considered "non-dippers" according to the consensus guideline [20]. NH was defined as an average nighttime BP $\geq 120/70$ mm Hg according to the 2007 European Hypertension Society/European Cardiology Society guidelines [21].

2.3. MRI protocol and assessment

Brain MRI was performed using a 3.0 T MR system (GE Healthcare, Discovery MR750w). The whole brain was scanned at a slice thickness of 5 mm with an interslice gap of 1 mm. Twenty-four axial images were obtained. The imaging protocol consisted of T1-weighted (repetition time [TR] = 2800 ms; echo time [TE] = 18 ms; field of view [FOV] = 22×22 cm, matrix = 288×352), T2-weighted (TR = 4427 ms; TE = 85 ms; FOV = 22×22 cm, matrix = 320×448), fluid-attenuated inversion recovery (FLAIR) (TR = 10,000 ms; TE = 120 ms, inversion time = 2570 ms; FOV = 22×22 cm, matrix = 224×288), and T2*-weighted gradient echo sequences (TR = 520 ms; TE = 15 ms; flip angle [FA] = 15° , FOV = 22×22 cm, matrix = 192×256).

CMBs were defined as small, homogeneous, round foci of low signal intensity on T2*-weighted images with diameters < 5 mm. Basal ganglia calcification and vascular flow voids were excluded. The Microbleed Anatomical Rating Scale [22] was used to guide this process and identify the locations of the CMBs. Deep and periventricular white matter hyperintensities were graded from zero to three according to the method described by Fazekas et al. [23]. Periventricular hyperintensities of grade 3 or deep white matter hyperintensities of grade 2 or 3 were defined as advanced white matter hyperintensities [24]. The images were analyzed by a trained observer who was blind to the patients' clinical data.

2.4. Statistical analysis

Continuous variables were compared using Student's *t*-tests or Mann-Whitney *U* tests, as appropriate. The frequencies of categorical variables were compared using χ^2 tests. We performed linear regression analysis to assess the relationship between the number of CMBs and blood pressure abnormalities. Models were adjusted for age and sex (model 1), and additionally adjusted for hypertension, diabetes mellitus, history of stroke, antiplatelet treatment, and the presence of advanced white matter hyperintensities (model 2). The statistical analyses were performed using JMP Version 12.0 software (SAS Inc. Cary, NC, USA). *P*-values < 0.05 were considered to be statistically significant.

3. Results

One-hundred and twenty-eight patients with PD (mean age, 64.4 ± 9.7 years; 56 males) were included in this study. The mean duration of motor symptoms was 10.7 ± 6.0 years, and the mean Hoehn and Yahr stage score was 2.9 ± 0.9 . The clinical characteristics of patients according to the presence of CMBs are shown in Table 1. Thirteen patients (10.2%) had CMBs, in whom the median number of CMBs was 1 (range: 1 to 10). Six of these patients had deep or infratentorial CMBs, six had strictly lobar CMBs, and one had mixed CMBs.

Of the total 128 patients, 60 patients (46.9%) had OH and 20 patients (15.6%) had SH (Table 2). In patients with OH or SH, the mean ages were higher in those without such blood pressure abnormalities. The frequency of diuretic use was significantly higher in patients with OH than in those without OH. SH was found in 26.7% of patients with OH. Forty-four patients (34.3%) had OH only, four had SH only (3.1%), and sixteen (12.5%) had both OH and SH. Among the patients with SH, 80% of patients had OH. Mean SBP and DBP levels were higher in patients with OH or SH than those without, at daytime, nighttime, and over the entire 24-hour period. However, the frequencies of NH and non-dippers were not different between these groups.

On ABPM, 80 patients (62.5%) had NH and 96 patients (75.0%) were non-dippers (Table 3). Mean age was similar between patients with and without NH and non-dipping. In patients with NH, mean supine SBP and DBP levels were higher, and the magnitude of the fall in SBP levels during orthostasis was greater compared to those without NH. The frequencies of OH and SH were, however, not different between patients with NH and those without NH.

The results of blood pressure measurements according to the presence of CMBs are shown in Table 4. Mean supine ($p = 0.03$), 24-hour ($p = 0.02$), and daytime ($p = 0.02$) SBPs were higher in patients with CMBs than in those without CMBs. When we divided the patients into groups based on CMB location, the magnitudes of the falls in SBP ($p = 0.02$) and DBP ($p = 0.02$) during orthostasis were greater in patients with deep or infratentorial CMBs than in those without deep or infratentorial CMBs. When the patients were classified into 4 groups according to the presence or absence of OH and SH (non-OH and non-SH group, OH-only group, SH-only group, and both OH and SH group), the prevalence of these groups was significantly different between patients with deep or infratentorial CMBs and those without deep or infratentorial CMBs ($p = 0.01$). The mean 24-h SBP ($p = 0.03$), daytime

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