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The presence of cerebral microbleeds is associated with cognitive impairment in Parkinson's disease

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ABSTRACT

Background: Cerebral microbleeds (CMBs) are often observed in Parkinson's disease (PD); however, their association with cognitive decline has been unclear. We performed a retrospective analysis of 124 cases of clinically diagnosed PD to determine the association between the presence of CMBs and cognitive decline.
Results: Of the 124 participants, 21 (16.9%) was diagnosed as PDD in this cohort. CMBs were observed significantly more frequently in the PDD than in the PD (47.6% vs 7.8%, $P < .001$). The presence of both deep/infratentorial (40% vs 14.9%, $P < .05$) and strictly lobar (75% vs 12.9%, $P < .001$) CMBs were associated with PDD. The values of cognitive scales such as Mini-Mental State Examination and the Hasegawa Dementia Scale-revised, were also significantly lower in the presence of each type of CMB. A multivariable logistic regression analysis showed the presence of strictly lobar CMBs as well as a male gender, orthostatic hypotension, periventricular hyperintensity on magnetic resonance imaging were significantly associated with PDD in this cohort.
Conclusions: This study showed the presence of CMBs, especially strictly lobar type, was strongly associated with PDD. We suspect that the burden of small vessel disease and cerebral amyloid angiopathy may be related to the development of cognitive decline in PD, and a prospective study enrolling more cases is warranted.

1. Introduction

Cerebral microbleeds (CMBs) are well-known markers of small vessel disease that can be detected in T2*-weighted gradient echo of magnetic resonance imaging (MRI). [1] CMBs are often observed in elderly populations [2], but they are associated with cerebrovascular diseases and cerebral amyloid angiopathy (CAA) [3, 4]. Deep and infratentorial CMBs are frequently observed in ischemic and hemorrhagic stroke, but lobar CMBs are detected in lobar-type intracerebral hemorrhage (ICH) [5]. In Alzheimer's disease (AD), a majority of CMBs show cortico-subcortical predominance, which is related to the presence of CAA [6]. A histopathological analysis showed that CMBs result from old extravasation of blood and related to blooding-prone microangiopathy of different origins [7]. These microangiopathies have been shown to promote cognitive decline in elderly populations and associated with poor prognosis in AD patients [8, 9].

Parkinson's disease (PD) is a well-known neurodegenerative disorder that manifests as progressive motor symptoms, including bradykinesia, muscular rigidity, tremor at rest, and postural or gait disturbance [10, 11]. Cognitive decline and dementia are important factors affecting the prognosis of PD [12–14]. Approximately 30% of PD patients will develop dementia, and age, older age at onset, akinetic-rigid subtypes, and non-motor symptoms such as visual hallucination, rapid eye movement sleep behavior disorders, and orthostatic hypotension have been shown to be independent risk factors for cognitive decline in PD [15]. Small-vessel disease detected by MRI also affects the cognitive decline in PD [16]. We recently reported that CMBs were frequently observed in patients with PD [17]. However, few studies have assessed the association between the presence of CMBs and cognitive decline in PD. In the present study, we assessed whether or not

Abbreviations: ABPM, ambulatory blood pressure monitoring; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CMBs, cerebral microbleeds; DLB, dementia with Lewy bodies; DWMH, deep white matter hyperintensity; HDS-R, Hasegawa dementia scale-revised; H-Y stage, Hoehn and Yahr stage; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; OH, Orthostatic hypotension; OR, odds ratio; PD, Parkinson's disease; PDD, PD with dementia; PVH, periventricular hyperintensity; SH, supine hypertension

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the existence of CMBs is a risk factor for cognitive decline in PD and evaluated the relationship between the location of CMBs and cognitive decline.

2. Methods

We used a retrospective cohort to analyze the association between abnormal nocturnal blood pressure monitoring and dementia in PD [18]. One hundred and thirty-seven patients with PD admitted to Juntendo University Hospital for a diagnostic assessment, drug adjustment, or evaluation for deep-brain stimulation between January 2014 and July 2016 were analyzed. We excluded patients with PD admitted for the treatment of acute illnesses, such as acute infection, ileus, and heart failure. Among them, 13 patients without T2*-weighted images on MRI were also excluded, leaving 124 patients to be analyzed. The diagnosis of PD was made according to the UK Brain Bank criteria [10]. After obtaining informed consent, patients were assessed for their blood pressure (BP) patterns using ambulatory blood pressure monitoring (ABPM), and orthostatic hypotension and details were determined as described in a previous report [18]. We also calculated the levodopa equivalent daily dose (LEDD) for each participant [19].

The study protocol was approved by the ethics committee of Juntendo University Hospital.

2.1. Detection of CMBs and cerebrovascular lesions

Brain MRI was performed using a 1.5-T MR system (Vistart RX; Toshiba). The whole brain was scanned at a slice thickness of 5.5 mm with an interslice gap of 1 mm; 20 axial images were obtained. The imaging protocol consisted of axial T2*-weighted gradient echo sequences (echo time [TE] = 15 ms; repetition time [TR] = 580 ms; flip angle [FA] = 20°, field of view [FOV] = 18 × 21 cm, matrix = 192 × 256) for CMBs and fluid-attenuated inversion recovery (FALIR) images for periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH). The Microbleed Anatomical Rating Scale (MARS) [20] was used to guide the identification and describe the location of the CMBs.

CMBs were defined as small, homogeneous, round foci or low signal intensity on T2*-weighted images with a diameter of 2-10 mm. Basal ganglia calcification and vascular flow voids were excluded. Other cerebrovascular lesions, such as PVH and DWMH, were also assessed with MRI using semiquantitative visual scales [21].

The images were analyzed by a trained observer who had been blinded to the patients' clinical data.

2.2. Ambulatory blood pressure monitoring (ABPM)

All patients underwent ABPM for 24 h using an automated system (FB-270; Fukuda Denshi, Tokyo, Japan) as described previously [18]. Nocturnal falls in BP were classified as follows: a) riser: a nocturnal BP fall of < 0%; b) non-dipper: a fall of ≥ 0% and < 10%; c) dippers: a fall of between 10% and 20%; and d) extreme-dipper: a fall of > 20%.

2.3. Orthostatic hypotension (OH) and supine hypertension (SH)

After at least 15 min resting in the supine position, the BP was measured, using an electronic sphygmomanometer (ES-H55; Terumo). The first measurement was taken while the patient remained supine, followed by a BP assessment in a standing position. OH was defined as a 20-mmHg drop in systolic BP and/or a 10-mmHg drop in diastolic BP within the first 3 min after standing. Among the participants, eight had previously been diagnosed with OH and were already being treated with midodrine hydrochloride, droxidopa or fludrocortisone acetate. SH was defined as a systolic BP of ≥ 140 mmHg, or a diastolic BP of ≥ 90 mmHg, when in a supine position.

2.4. Cognitive assessment and diagnosis of dementia

The cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Hasegawa dementia scale-revised (HDS-R) [22]. We enrolled PD with dementia (PDD) patients but not dementia with Lewy bodies (DLB) patients based on the "one-year rule" [23], and the diagnosis of PDD was based on the diagnostic criteria and procedures from the Movement Disorder Society Task Force [24, 25]. Based on these criteria, we used the cut-off of MMSE for cognitive decline as < 26 and the notion that cognitive decline should be sufficient to impair daily life and not attributed to motor or autonomic symptoms.

2.5. Statistical analyses

Continuous variables were compared using either Student's *t*-test or a one-way ANOVA with Dunnett's multiple comparison post hoc test. The frequency of categorical variables was compared using the χ^2 test. We performed multivariate logistic regression analyses to evaluate the association of dementia with OH and ABPM parameters. Clinical variables that were significant following a univariate analysis were included. The statistical analyses were performed using the JMP Version 12.0 software program (SAS Inc. Cary, NC, USA). A value of $P < .05$ was considered to be statistically significant.

3. Results

3.1. Baseline demographics and risk for dementia in PD

Table 1 presents the baseline demographics and the presence of risk factors for PDD in the included PD patients. Of the 124 participants, 21 (16.9%) was diagnosed as PDD. Gender, age, Hoehn and Yahr (H−Y) stage, a history of stroke, OH, SH, cerebrovascular lesions such as PVH, and DWMH, and the use of oral anticoagulants were significantly associated with PDD. An abnormal nocturnal blood pressure pattern (dipper and riser) was also associated with PDD, as reported previously [18]. CMBs were significantly more observed in PDD patients than in PD patients (47.6% vs. 7.8%, $P < .0001$), and this trend was preserved in each location of CMBs (19.1% vs. 5.8% for deep and infratentorial CMBs, $P = .04$, 28.6% vs. 1.9% for strictly lobar CMBs, $P < .0001$).

3.2. A comparison of the clinical features and cognitive decline according to the presence or absence of CMBs

The characteristic of the patients with and without CMBs are shown in Table 2. The age and H–Y stage were significantly higher in the patients with CMBs than in those without CMBs ($P < .0001$ and $P < .005$, respectively). PDD was significantly more common in patients with CMBs than in those without CMBs (55.6% vs. 10.4%, $P < .0001$), concomitant with significantly lower scores on the HDS-R and MMSE. The severity of cerebrovascular lesions on MRI ($P < .0001$) and the prevalence of hypertension ($P < .05$), diabetes mellitus ($P < .05$), a history of ischemic stroke ($P < .005$), coronary artery disease ($P < .05$), OH ($P < .01$), SH ($P < .05$), and antiplatelet ($P < .005$) or antihypertensive ($P < .005$) medication use were significantly higher in the patients with CMBs than in those without. Furthermore, we compared these associations based on the location of CMBs. The age ($P < .005$), PDD (45.5% vs. 14.2%, $P < .01$), severity of cerebrovascular lesions on MRI ($P < .001$), the history of stroke ($P < .05$), and the rate of OH ($P < .005$) were significantly higher in the patients with deep or infratentorial CMBs than in those without CMBs, whereas the age, PDD (71.4% vs. 13.7%, $P < .0001$), H−Y stage ($P < .005$), cerebrovascular lesions on MRI (especially PVH, $P < .05$), coronary artery disease ($P < .0001$), or antihypertensive ($P = .0001$) medication use were significantly higher in patients with strictly lobar CMBs than in those without CMBs. Interestingly, both scores of cognition was lower in patients with strictly lobar CMBs than those in deep or