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The prevalence and risk factors of cerebral microbleeds in patients with Parkinson's disease

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ABSTRACT

Introduction: Cerebral microbleeds (CMBs) are frequently observed in patients with cerebrovascular disease and Alzheimer's disease. CMBs that are located in the deep or infratentorial regions and those that are present strictly in the lobar regions reflect hypertensive vasculopathy and cerebral amyloid angiopathy, respectively. The development of CMBs can be accelerated by clinical factors. Orthostatic hypotension (OH) has been reported to be associated with cerebral small vessel disease, such as white matter lesions in Parkinson's disease (PD). We investigated the prevalence, location and risk factors, including OH, for CMBs in patients with PD.

Methods: We conducted a retrospective chart review of consecutive patients with PD who were admitted to the Department of Neurology, Juntendo University School of Medicine between January 2010 and July 2014. One hundred and sixty-seven patients with PD who underwent gradient echo T2*-weighted magnetic resonance imaging of the brain were included in the present study. A multivariate logistic regression analysis was performed to investigate the associations between risk factors and the presence of CMBs.

Results: CMBs were detected in 29 (17.4%) patients. Among the patients with CMBs, 19 (65.5%) had deep or infratentorial CMBs and 10 (34.5%) had strictly lobar CMBs. Hypertension, OH and a history of ischemic stroke were independently associated with deep or infratentorial CMBs, whereas antiplatelet use was independently associated with strictly lobar CMBs.

Conclusions: In patients with PD, deep or infratentorial CMBs were more frequent than strictly lobar CMBs, and were associated with hypertension, OH and a history of ischemic stroke.

1. Introduction

Cerebral microbleeds (CMBs) have emerged as an important new manifestation of cerebral small vessel disease which can be detected using gradient echo T2*-weighted or susceptibility-weighted magnetic resonance imaging (MRI) [1]. Histopathological examinations have shown that CMBs are composed of focal hemosiderin depositions in the perivascular space [2]. CMBs are frequently found in patients with both ischemic and hemorrhagic stroke [3] and in patients with Alzheimer's disease [4]. The topographic distribution of CMBs reflects the underlying pathology. Deep or infratentorial CMBs are associated with hypertensive vasculopathy, while strictly lobar CMBs are associated with the presence of cerebral amyloid angiopathy [5,6]. The development of CMBs can be accelerated by clinical factors such as age, hypertension, diabetes and antithrombotic therapy [3].

Orthostatic hypotension (OH) is the most frequent cardiovascular autonomic dysfunction in patients with PD [7]. OH is associated with the presence of cerebral small vessel disease, such as white matter hyperintensity (WMH) on MRI in patients with PD [8] as well as in individuals with late-life depression [9]. We therefore hypothesized that OH contributes to CMBs in patients with PD. In this study, we analyzed the prevalence, location and risk factors, including OH, of CMBs in patients with PD.

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2. Methods

2.1. Study subjects

We conducted a retrospective review of the medical records of consecutive PD patients who were admitted to the Department of Neurology, Juntendo University School of Medicine between January 2010 and July 2014. The clinical diagnosis of PD was made according to the UK Brain Bank criteria [10]. A total of 657 patients with PD were admitted during the study period and 185 patients underwent gradient echo T2*-weighted MRI. Of these 185 patients, we applied the following exclusion criteria: patients whose medical records included no data relating to the presence or absence of OH (n = 12); patients in whom an MRI evaluation was not possible due to the presence of an artifact (n = 2); and patients who were younger than 50 years of age (n = 4). As a result, 167 patients with PD were examined in the present study. The study design was approved by the Institutional Review Board of Juntendo hospital.

Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg in the sitting position or treatment with antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level of ≥126 mg/dL, an HbA1c level of ≥6.5% or the use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as a total cholesterol level of ≥220 mg/dL, a triglyceride level of ≥150 mg/dL or the use of lipid-lowering medications. The subjects were considered to be current smokers if they had smoked at least one cigarette a day within the previous year. The presence of OH was examined in patients with clinical symptoms suggestive of OH. These symptoms included lightheadedness, dizziness or fainting. OH was defined as a reduction in the systolic blood pressure of at least 20 mmHg within three minutes of standing [11]. The stage and severity of PD was assessed using the Hoehn and Yahr scale. Dementia was diagnosed according to the clinical diagnostic criteria for probable dementia associated with PD [12]. The other data that were collected included the patients' daily dose of L-dopa, the quantity and class of their antihypertensive medication, and their use of antiplatelet and anticoagulant agents at admission.

2.2. Brain MRI

Brain MRI was performed using a 1.5 T MR system (Toshiba, Visart RX). The whole brain was scanned at a slice thickness of 5.5 mm and 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). CMBs were defined as small, homogeneous, round foci of low signal intensity on T2*-weighted images with a diameter of 2–10 mm (Fig. 1). Basal ganglia calcification and vascular flow voids were excluded. The Microbleed Anatomical Rating Scale (MARS) [13] was used to guide identification and describe the location of the CMBs. The size of the individual CMBs was assessed by measuring the largest diameter of the lesion. The images were analyzed by a trained observer who was blinded to the patients' clinical data.

2.3. Statistical analyses

Continuous variables are presented as the mean ± SD. Categorical variables are presented as absolute numbers and percentages. Continuous variables were compared using either Student's *t*-test or the Mann–Whitney *U* test, as appropriate, after normality distribution testing. The frequency of categorical variables was compared by the χ^2 test. Multivariate logistic regression analyses were performed to determine the associations between the presence of CMBs and independent variables. Backward stepwise elimination was used to select the independent variables among the potential risk factors which included: age, male gender, hypertension, diabetes mellitus, dyslipidemia, OH, a history of ischemic stroke, a history of CAD, smoking status and the use of medications (L-dopa daily dose, antiplatelet use and anticoagulant use). Antihypertensive medication was not included in this analysis because of the collinear relationship with hypertension. We also assessed the association between the CMB size and medications (antiplatelets and anticoagulants) and smoking status. A Spearman's rank correlation analysis was used to determine the correlation between the CMB size and L-dopa daily dose. The statistical analyses were performed using the JMP Version 9.0 software program (SAS Inc. Cary, NC, USA). A value of $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 68 CMBs were found in 29 (17.4%) patients. Of these, 16 patients (55.2%) had one CMB, 10 patients (34.5%) had 2-4 CMBs, and three patients (10.3%) had ≥ 5 CMBs. The median number of CMBs in the 29 patients was 1 (range: 1 to 15). The location of the CMBs is shown in Supplementary Table 1. Half of the CMBs were located in the basal ganglia and thalamus. Lobar CMBs were most frequently found in the temporal lobes. Among the patients with CMBs, 19 (65.5%) had CMBs in the deep or infratentorial regions

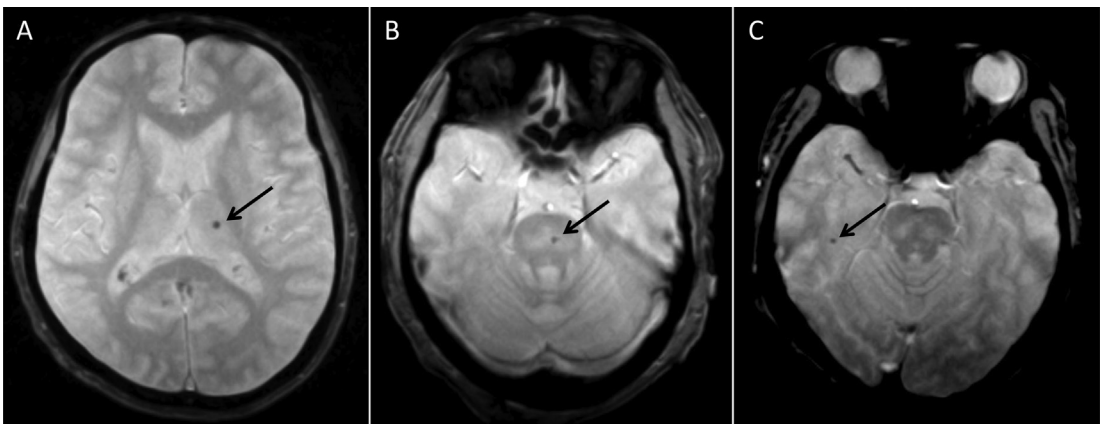

Fig. 1. Representative images of CMBs on gradient echo T2*-weighted MRI. CMBs are seen in the thalamus (A), the pons (B) and the temporal lobe (C).

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