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Association between cerebral small vessel diseases and mild parkinsonian signs in the elderly with vascular risk factors

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ABSTRACT

Introduction: The aim of this study was to examine the association between mild parkinsonian signs (MPS), cerebral small-vessel disease (SVD), and total SVD burden in patients with vascular risk factors.
Methods: We performed a cross-sectional study among 268 patients with vascular risk factors but without parkinsonism or dementia (71.0 ± 7.8 years, 63% male). MPS was evaluated via Unified Parkinson's Disease Rating Scale Part III. Brain MRI was used to determine SVD (cerebral microbleeds [CMBs], lacunar infarctions [LIs], and white matter hyperintensities [WMH]). The presence of each SVD feature was indicated by the total SVD score. Logistic regression analyses were performed adjusting for age, sex, history of stroke, hypertension, diabetes mellitus, and dyslipidemia.
Results: In a multivariate analysis, we found that the presence of CMBs, deep CMBs, mixed (in the basal ganglia and thalamus) LIs, periventricular hyperintensities (PVH), and deep WMH (DWMH), and total SVD score were significantly associated with MPS, whereas strictly lobar CMBs and other LIs (in strictly basal ganglia or strictly thalamus) were not. We also found a significant association between mixed LIs, PVH, DWMH and total SVD score and gait/balance function, between PVH and rigidity, and between mixed LIs and bradykinesia. Among elderly participants (≥73years), the association of total SVD score, deep CMBs, mixed LIs, and PVH, with MPS remained significant.
Conclusion: Our results provide additional evidence that SVD including CMBs, and especially total SVD burden, might be a surrogate marker for MPS and support the contribution of hypertensive microangiopathy as the underlying etiology.
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1. Introduction

Cerebral small-vessel disease (SVD) is a leading cause of stroke, cognitive impairment, gait and balance disturbances, and disability [1]. Additionally, previous studies demonstrated an association between SVD, i.e., lacunar infarctions (LIs) and white matter hyperintensities (WMH), and mild parkinsonian signs (MPS), which refer to subtle motor disturbances consisting of bradykinesia, tremor, rigidity, and gait/balance function [2,3]. MPS occur in 15–40% of general elderly population and are associated with functional impairment [4]. The mechanism of MPS is heterogeneous, not completely understood, and appears to depend in part on aging, including age-associated decline in the dopaminergic activity [4]. Moreover, there is an increased awareness of the role played by not only neurodegenerative pathologies but also vascular pathology in accelerating MPS [4], with a recent prospective study raising the possibility that SVD are the initial events in incident parkinsonism including Parkinson's disease (PD) [5].

These studies suggest that the presence of MPS in the elderly might reflect, in part, the accumulation of vascular pathology caused by preventable vascular diseases [2,3]. Thus, it might be useful to identify such a patient for motor impairment at an early stage using imaging markers.

In this context, cerebral microbleeds (CMBs), among the spectrum of SVD, are of particular interest because they frequently

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occur in the elderly population [6]. It is generally considered that the location of CMBs results from 2 underlying pathologies: deep CMBs are related to hypertensive vasculopathy, while strictly lobar CMBs reflect cerebral amyloid angiopathy (CAA) [6]. We hypothesized that the presence of CMBs could reflect a heavier burden of hypertensive or CAA pathology, which could increase the risk of MPS.

Furthermore, although there may be substantial correlations among these SVD features, it is unclear if SVD is a better predictor of MPS than its individual components or global SVD burden, i.e., the combined assessment of total cerebral SVD. Few studies have investigated the SVD components individually and as a whole. We therefore investigated the association between MPS and each SVD feature and total SVD burden in the elderly individuals with vascular risk factors.

2. Methods

2.1. Patients and evaluation of MPS

We prospectively recruited outpatients from Department of Neurology and Stroke center at the Osaka University Hospital, where physicians control risk factors in high-risk patients for primary and secondary prevention of vascular diseases. Subjects were older than 50 years with more than one vascular risk factor, including hypertension, diabetes, dyslipidemia, history of smoking, and documented history of stroke, coronary artery disease, or, atrial fibrillation, and enrolled into this study between October 2012 and December 2013. Patients were excluded from the study if they had experienced a symptomatic vascular event during the previous 6 months. In addition, those with collagen disease, malignant disease, and chronic inflammatory disease were excluded. At entry, 346 outpatients underwent a baseline clinical assessment including medical history, pharmacological treatment history, physical and neurological examination, blood sampling, and brain MRI. We assessed MPS using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III and evaluating 4 categories (bradykinesia, tremor, rigidity, and gait/balance function) [7]. We identified patients as having MPS when they had either (1) 2 or more items with a score of 1; or (2) 1 item with a score of 2 or greater. Parkinsonism was defined as patients having 2 or more items with a score of 2 or greater in 2 or more categories [2,8]. Our intention was to study patients with earliest or suspected movement impairment, but not with overt movement impairment. Thus, the eligible participants basically had no clinically disability on daily life which indicates no sequelae. The patients with distinct parkinsonian signs were excluded from the analysis, as they could be considered as unidentified prevalent cases of parkinsonism. Briefly, participants were considered to have PD or parkinson plus syndrome if 1) they had previously received a diagnosis of PD or parkinson plus syndrome, or 2) they had met the criteria of parkinsonism in UPDRS. In addition, cases of PD or parkinson plus syndrome were identified taking into account multiple sources. Diagnoses were also supported by imaging, such as MRI scan or MIBG cardiac scintigraphy, when available. Furthermore, none of the patients were included drug-induced parkinsonism. Finally, consensus diagnosis of case conferences was made by a panel of neurologists.

Consequently, patients who (1) had insufficient MRI data to evaluate SVD (n = 52), (2) distinct parkinsonian signs (previously diagnoses with PD [n = 8], or parkinsonism [n = 6]), (3) had persistent severe hemiplegia (Manual Muscle Testing: 0/5 to 3/5) or severe spasticity due to stroke history (n = 3), (4) were diagnosed with depression (n = 4) or dementia (n = 5), which could hinder the evaluation of MPS, were excluded from the analysis. Finally, all analyses were based on 268 patients with complete baseline data (Fig. 1). This study was approved by the local ethical review board, and patients provided written informed consent.

2.2. Evaluation of MRIs

MRI was acquired using a single 3.0T scanner. The imaging protocol included T1-,T2-weighted, fluid attenuated inversion recovery (FLAIR), and gradient echo T2*-weighted sequences. The sequence parameters were as follows:axial images, 22–24; field of view, 201–220 mm; echo time, 10–20 ms; repetition time, 600–800 ms; slice thickness, 5.0 mm; interslice gap, 1.0–1.5 mm.

Structural MRI analysis was performed by a single experienced observer blinded to clinical data. CMBs were defined as ≤10 mm of nodular hypointensity lesions on T2*-weighted images [6]. We examined CMBs regions by classifying them into strictly lobar (frontal, parietooccipital, and temporal lobes, and white matter) or deep (basal ganglia, thalamus, and infratentorial), according to previous studies [9,10].

LIs was defined from 3 to 15 mm, with a hypointense lesion and hyperintense rim on FLAIR-images when located supratentorially: in the subcortical white matter, thalamus, or basal ganglia, according to the corresponding hyper- and hypo-intensity on T2-and T1-images, respectively. For the analyses, patients with both basal ganglia and thalamus lacunes were pooled in a single category as mixed LIs. Therefore, we considered the following variables as the location of LIs: strictly basal ganglia, mixed [basal ganglia and thalamus], strictly thalamus. WMH were defined as hyperintense lesions on FLAIR-images, and were scored by the Scheltens and Fazekas scale [11,12]. In accordance with slightly modified Scheltens scale [11], periventricular hyperintensities (PVH) were evaluated using 3 regions (frontal caps, occipital caps, and lateral bands) and scored on a scale of 0–2 (range, 0–6). Deep white matter hyperintensities (DWMH) were evaluated using 4 regions (frontal, parietal, occipital, and temporal lobe) and scored on a scale of 0–6 (range, 0–24). We also both graded on a scale of 0–3 according to the Fazekas scale [12].

For the analysis of total SVD severity, based on the recently described score with slight modifications [13], we rated the total SVD burden, by counting the presence of each SVD features (LIs, CMBs, DWMH, and PVH). The presence of LIs and CMBs were defined as the presence of ≥1 LIs (1 point if present) or ≥1 CMBs (1 point if present). Presence of DWMH was defined as either early confluent deep WMH (Fazekas score 2 or 3) or irregular PVH extending into the deep white matter (Fazekas score 3) (1 point if present). The sum of ratings was used as a total SVD score (range,

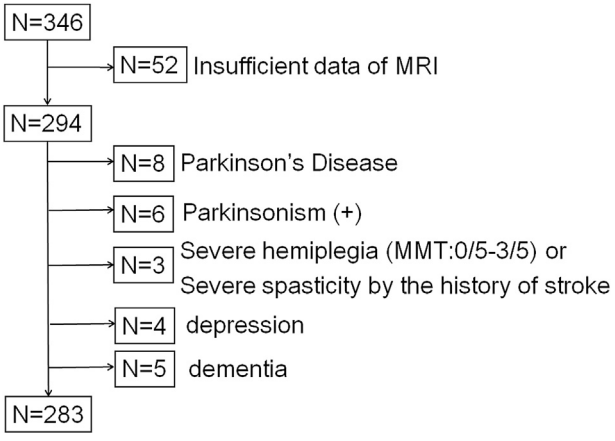

Fig. 1. Flowchart of patient recruitment in this study.

0–4) [13].

2.3. Definition of vascular risk factors

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive drug. Diabetes mellitus was defined as fasting plasma glucose level ≥ 126 mg/dl, HbA1c (NGSP) level ≥6.5%, or use of hypoglycemic drug/insulin injection. Dyslipidemia was defined as low density lipoprotein cholesterol level ≥140 mg/dl, high density lipoprotein cholesterol level ≤40 mg/dl, triglyceride level ≥150 mg/dl, or use of hypolipidemic drug. Patients were categorized as having a history of coronary heart disease (ie, myocardial infarction, hospitalization for angina pectoris, arterial revascularization procedure), stroke (ischemic or hemorrhagic), or atrial fibrillation if they had previously received each diagnosis. Stroke was defined as an acute disturbance of focal neurological dysfunction with symptoms and a result of either cerebral infarction or hemorrhage with imaging evidence. Smoking was evaluated based on current habits. Body mass index was calculated from height and weight measured.

2.4. Statistical analysis

The baseline characteristics were presented as number (percentage), mean ± standard deviation or median (interquartile), and compared between patients with MPS and those without MPS by the χ^2 test, Student-t test, or Mann–Whitney U test. Logistic regression analysis was used to estimate the association between MPS and SVD (CMBs [any, deep, and strictly lobar]), LIs [any, strictly basal ganglia, strictly thalamus, mixed (basal ganglia and thalamus)], PVH, DWMH and total SVD: adjusted for age, sex, intervals of MRI (duration between baseline examination and brain MRI), hypertension, diabetes mellitus, dyslipidemia, and history of stroke, which were generally associated with SVD. All these analyses were repeated to explore the relationships between the 4 categories of MPS and SVD. Moreover, since aging can considered to be a strong confounder in the relation between SVD and MPS, we also estimated the association between SVD and MPS, as according to whether ≥73 years, because the median age of subjects with MPS is 73 years in our cohort. A two-tailed P value of <0.05 was considered statistically significant. All analyses were performed using JMP pro 11.0 (SAS Institute Inc., Cary, N.C., USA).

3. Results

3.1. Characteristics

The characteristics of participants are shown in Table 1. The mean age was 71.0 ± 7.8 years, and 63% were male. Eighty-two percent of subjects in the whole cohort had hypertension, 75% had dyslipidemia, and 36% had a history of stroke. Among 268 subjects, 58 (21.6%) had ≥1 CMBs (42 participants [15.7%] deep CMBs, and 16 [6%] strictly lobar CMBs). LIs were present in 39% (62 [23.1%] strictly basal ganglia, 11 [4.1%], strictly thalamus, and 16 [6%] mixed).

3.2. MPS and SVD

The number of patients who were diagnosed with MPS was 131 (48.8%) (bradykinesia; 31 [11.6%], tremor; 0 [0%], rigidity; 97 [36.2%], and gait/balance impairment; 28 [10.4%]), respectively. In the univariate analysis (Table 1), patients with MPS were significantly older and had a baseline history of stroke, with more severe SVD (mixed LIs, CMBs, deep CMBs, PVH, DWMH, and total SVD score) than patients without MPS. In the multivariable analyses adjusting for age, sex, intervals of MRI, hypertension, diabetes, dyslipidemia, and history of stroke, we found that CMBs, deep CMBs, mixed LIs, PVH, DWMH, and total SVD were significantly associated with MPS, whereas the relationship between strictly lobar CMBs and other LIs (strictly thalamus, or strictly basal ganglia) and MPS was not significant (Fig. 2). Regarding each relevant category, it was difficult to evaluate the category of tremor because it was absent. Therefore, we investigated the remaining 3 categories. In the multivariable analyses, we found a significant association between mixed LIs, PVH, DWMH, and total SVD score and gait/balance function, between PVH and rigidity, and between mixed LIs and bradykinesia (Table 2).

According to whether ≥73 years, a univariate analysis is shown in Supplementary Tables. Although no significant difference between age and MPS was observed among patients ≥73 years, total SVD score, CMBs, deep CMBs, mixed LIs, or, PVH was significantly associated with MPS (Supplementary Table 1). Subsequently, we analyzed the risk of MPS via multivariate analysis. Among patients ≥73 years, the association between total SVD score, deep CMBs, mixed LIs, and PVH, and MPS remained significant. Moreover, total SVD score, deep CMBs, and WMHs remained significant among patients <73 years (Supplementary Table 2).

4. Discussion

Our results add to the accumulating clinically relevant evidence that SVD significantly contributes to the presence of MPS in patients with vascular risk factors, independent of age, vascular risk, and stroke. Deep CMBs, mixed LIs, PVH, as well as, total SVD score were independently associated with MPS at any age. In particular, although aging can be considered as a strong confounder in the risk of both SVD and MPS, we confirmed that the association remained significant among patients ≥73 years. This suggests that patients with MPS have indeed a substantial load of SVD, which could be as potential surrogate marker for MPS.

As commonly observed with LIs and WMH, CMBs may disrupt the connections of functionally important basal ganglia-thalamofrontal cortical circuits relevant for MPS, ultimately leading to the damage of neural networks superimposed to the effects of other often coexisting SVD. In contrast, we did not identify a significant relationship between MPS and strictly lobar CMBs (reflecting CAA), even in the univariate analysis. This is in line with an earlier study on the relationship between only deep CMBs and gait disturbances [14]. Furthermore, deep CMBs were more frequent than strictly lobar CMBs in patients with PD [15]. Our findings therefore support the contribution of hypertensive microangiopathy as the underlying etiology of MPS, which might be a preventable syndrome.

As expected, we also found that age, history of stroke, as well as mixed [basal ganglia and thalamus] LIs, were significantly associated with MPS, whereas the relationship between strictly thalamus LIs, or strictly basal ganglia LIs and MPS was nonsignificant. This suggests the impact of the basal ganglia and thalamus on MPS, reflecting not only location-specific but also dose-dependent effect.

Regarding the risk of category, there were independent associations between mixed LIs, WMHs, global SVD, and gait/balance, possibly reinforcing not only shared pathophysiology but also an independent contribution by SVDs to gait/balance disturbance. Moreover, the relationship between mixed LIs and bradykinesia is in line with a previous study [3], supporting its pathophysiological role and the vulnerability of vascular burden in the basal ganglia–thalamocortical circuits. However, despite independent associations between CMBs and MPS, we were unable to demonstrate an association between CMBs and the category of MPS, partly due

Table 1
Baseline characteristics with respect to MPS.

	All (n = 268)	MPS (−) (n = 137)	MPS (+) (n = 131)	*P value*
Age (years)	71.0 ± 7.8	68.8 ± 7.9	73.3 ± 7.0	<0.001
Male	168 (63)	88 (64.2)	80 (61.1)	0.59
Body mass index	23.4 ± 3.0	23.6 ± 2.9	23.1 ± 3.1	0.13
Current smoker	21 (8)	9 (7)	12 (9.1)	0.49
Hypertension	221 (82)	108 (78.8)	113 (86.2)	0.11
Systolic blood pressure (mmHg)	129.7 ± 11.1	129.6 ± 11.9	129.8 ± 10.3	0.89
Diastolic blood pressure (mmHg)	74.4 ± 9.4	74.8 ± 9.3	74.0 ± 9.5	0.51
Diabetes mellitus	76 (28)	38 (27.4)	38 (29.1)	0.82
HbA1c (NGSP) (%)	6.05 ± 0.76	6.07 ± 0.84	6.03 ± 0.68	0.70
Dyslipidemia	201 (75)	105 (76.6)	96 (73.3)	0.53
Low density lipoprotein (mg/dL)	108.9 ± 27.4	112.2 ± 27.1	105.4 ± 27.4	0.051
High density lipoprotein (mg/dL)	56.4 ± 15.8	56.3 ± 15.0	56.2 ± 16.4	0.98
Triglyceride (mg/dL)	123.1 ± 64.8	126.4 ± 59.0	119.5 ± 70.3	0.39
Coronary artery disease	27 (10)	9 (6.6)	18 (13.7)	0.07
Atrial fibrillation	19 (7)	9 (6.6)	10 (7.6)	0.81
History of ischemic stroke	95 (35)	42 (30.7)	53 (40.5)	0.094
History of cerebral hemorrhage	11 (4.1)	1 (0.7)	11 (7.6)	0.004
Any CMBs	58 (21.6)	18 (13.1)	40 (30.5)	0.0005
Deep CMBs	42 (15.7)	11 (8.0)	31 (23.7)	<0.001
Strictly lobar CMBs	16 (6.0)	7 (5.1)	9 (6.8)	0.41
Any LIs	106 (39.6)	47 (34.3)	59 (45.4)	0.07
LIs in basal ganglia	62 (23.1)	31 (22.6)	31 (23.7)	0.84
LIs in thalamus	11 (4.1)	5 (3.7)	6 (4.6)	0.70
Mixed LIs: in basal ganglia and thalamus	16 (6.0)	2 (1.5)	14 (10.7)	0.0014
PVH	3 (2–5)	2 (1–4)	4 (2–5)	<0.001
DWMH	6 (2–8)	4 (1–7)	7 (4–10)	<0.001
Total SVD	1 (0–2)	0 (0–1)	1 (0–2)	<0.001

Data represent number (percentage), mean ± standard deviation, or median (interquartile range). P values were calculated by univariate analysis.
Abbreviation: MPS, mild parkinsonian signs; CMBs, cerebral microbleeds; LIs, lacunar infarctions; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities.

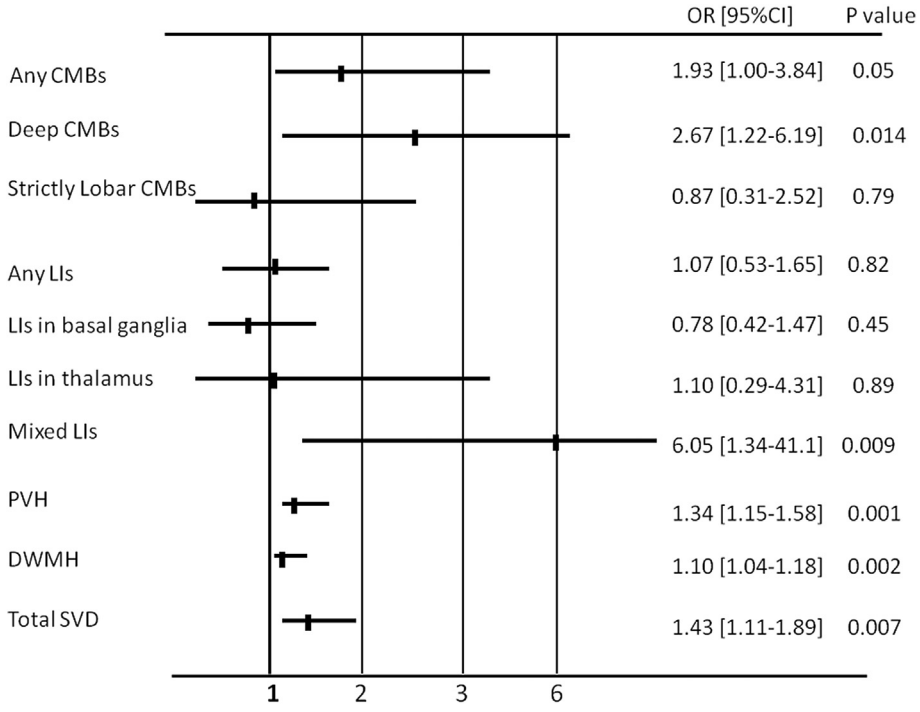

Fig. 2. Association between the presence of MPS and SVD. Logistic regression analysis was used to estimate the association between MPS and each SVD (CMBs [any, deep, and strictly lobar], LIs [strictly basal ganglia, strictly thalamus, mixed (basal ganglia and thalamus)], PVH, DWMH and total SVD: adjusted for age, sex, intervals of MRI (duration between baseline examination and brain MRI), hypertension, diabetes mellitus, dyslipidemia, and history of stroke. Abbreviation: MPS, mild parkinsonian signs; SVD, small vessel disease; CMBs, cerebral microbleeds; LIs, lacunar infarctions; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; OR, odds ratio; 95%CI, 95% confidence interval.

to decreasing statistical power.

We have not introduced simultaneous adjustment for SVD to avoid possible mediating effects, because each SVD often occur together and are highly correlated, despite different pathogenic

Table 2
Association between the presence of each category of UPDRS and each SVD which confirmed significant association with MPS.

	Bradykinesia	Rigidity	Gait/balance
Any CMBs	0.95 (0.35–2.41) 0.93	0.69 (0.36–1.34) 0.28	2.07 (0.80–5.18) 0.131
Deep CMBs	0.87 (0.28–2.40) 0.79	0.53 (0.25–1.10) 0.09	2.09 (0.73–5.79) 0.17
Mixed LIs (in basal ganglia and thalamus)	3.72 (1.08–11.9)* 0.037	0.75 (0.25–2.29) 0.62	4.33 (1.10–15.99)* 0.037
PVH	1.18 (0.93–1.50) 0.170	1.18 (1.01–1.38)* 0.033	1.29 (1.00–1.69)* 0.049
DWMH	1.09 (0.97–1.19) 0.054	1.05 (0.99–1.12) 0.079	1.10 (1.01–1.21)* 0.028
Total SVD	1.00 (0.68–1.45) 0.98	1.16 (0.90–1.49) 0.25	1.65 (1.14–2.40)* 0.008

OR (95%CI) and P values were calculated by logistic regression analysis adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, and history of stroke.
Abbreviation: UPDRS, Unified Parkinson's Disease Rating Scale; MPS, mild parkinsonian signs; SVD, small vessel disease; CMBs, cerebral microbleeds; LIs, lacunar infarctions; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; OR, odds ratio; 95%CI, 95% confidence interval.
*$p < 0.05$.

mechanisms leading to each SVD. Hence, to determine whether these associations can be attributed to a direct effect of individual SVD features or to the accompanying SVD burden, we tested the effect of total SVD score on MPS. The score might provide a potential impact of SVD than each of the SVD separately. Our findings therefore may indicate a more widespread disruption of neuronal networks in subjects with MPS.

Indeed, imaging and pathological cross-sectional studies showed that there was a significant association among the size of WMH, and LIs with MPS, suggesting that cerebrovascular pathologies may play an important role in the etiology of MPS [2,3,16]. However, longitudinal clinical studies investigating the predictive value of combined assessment of both SVD and MPS in the development of incident parkinsonism are currently lacking. Only one recent prospective study supports by providing robust evidence that the relation between SVD at baseline and incident parkinsonism, which showed that a high WMH volume, multiple LIs, and CMBs were associated with an increased 5-year risk of any parkinsonism (n = 20) (including vascular parkinsonism [n = 15]) [5]. Furthermore, they reported a relatively high incidence of parkinsonism, compared to population-based studies, which may also indicate that individuals with a high SVD burden had an increased risk of parkinsonism [5]. Furthermore, these aforementioned associations are indirectly supported by several studies in patients with PD. Comorbid WMH has been associated with gait/balance impairment in PD, probably independently from the degree of nigrostriatal dopaminergic denervation [17]. Given these accumulating evidences, SVD appeared to be important in the development of MPS and parkinsonism, which might be a preventable syndrome in patients with risk factors for SVD. Generally, MPS are common in the elderly not showing neurological disease and associated with significant morbidity, mortality and dementia. However, only a few studies have aimed at evaluating potential risk factors for MPS and it was not elucidated sufficiently whether MPS share the same risk factors as harbinger of PD or whether the occurrence of MPS might largely be associated with vascular risk related to aging. Due to the fact that the pathological features of PD are relatively uncommon in the elderly rather than cerebrovascular pathologies, they cannot account for the full spectrum of MPS. Furthermore, we are not aware of previous prospective study exploring the association between the progression of SVD burden and progression to a higher category of MPS (from normal to MPS, and from MPS to parkinsonism). So far, the exact and direct role of both SVD and MPS in the development of PD is unknown. However, we might be able to investigate this in our follow-up study. Future longitudinal studies are needed to assess to what extent MPS is a predictive marker of the subsequent of distinct parkinsonism.

This study has several limitations. First, although the UPDRS motor scoring is a generally and widely used test for the evaluation of MPS, it is sometimes difficult to distinguish clinically, especially in the elderly. Multiple cerebral and systemic disorders can influence the UPDRS scores, making it difficult to tease out the individual effects of each. For the multivariate analysis, we adjusted the history of stroke as a confounder. Moreover, we tried to overcome this problem by having experienced neurologists evaluate all subjects. After review by the panel, these diagnoses were confirmed. However, despite careful diagnostic workup, some loss of precision is possible, which might lead to underestimation of the association. Second, the cross-sectional design limits causal inferences. Third, our study was limited to a cohort of Japanese individuals with vascular profiles and concomitant SVD burden, and hence, our results may not be generalizable to other races and cohorts. Finally, we did not investigate a detailed neuropsychological examination of global cognition or depressive symptoms, which are unlikely to be precise estimates of the true prevalence of cognition or depression; hence, this might have attenuated the expected association.

Our findings suggest that SVD, including deep CMBs, and in particular, the total SVD score, might be an intermediate marker for MPS, especially gait/balance function. Hence, although the treatment of SVD is still limited and empirical, strategic efforts should be made at least to prevent the progression of SVD through rigorous management of vascular risk factors at midlife, and in turn reduce the risk of motor disturbance in late life. It might also be plausible that an effective control of vascular risk in patients who already have SVD will help reduce the severity of the microvascular pathology, and thereby, mitigate the risk of motor disturbance.

Author's roles

Jun Hatate was involved in the execution of the research project, the acquisition of data and analysis. Kaori Miwa was involved in the execution of the research project, the critiquing of the statistical analysis and interpretation of data, and in writing the final draft of the manuscript and revised manuscript. Mari Matsumoto, Tsutomu Sasaki, and Yoshiki Yagita were involved in the execution of the research project, and the acquisition of data. Manabu Sakaguchi was involved in the execution of the research project, and revising it critically for important intellectual content. Kazuo Kitagawa was involved in the execution of the research project, and the acquisition of data. Hideki Mochizuki was involved in the conception, design of the study, revising it critically for important intellectual content, and final approval of the version to be submitted.

Financial disclosures/conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.02.011.

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