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The effect of small vessel disease on motor and cognitive function in Parkinson's disease

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ABSTRACT

Objectives: Small vessel disease (SVD) has been associated with motor and cognitive impairments in neurodegenerative diseases. We investigated SVD markers using brain magnetic resonance imaging (MRI) and the global SVD score in Parkinson's disease (PD).

Patients and methods: Seventy-one patients with PD were assessed for vascular risk factors, motor severity, and motor phenotype. Global cognition was evaluated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Based on the MoCA score, we categorized cases into normal (> 23) or cognitively impaired (≤ 23). We calculated the total SVD score (range, 0–4) based on white matter hyper intensities (WMHs), lacunae, cerebral microbleeds (MBs), and enlarged perivascular spaces (PVSs). In addition, we evaluated global brain atrophy.

Results: There were no significant associations with total SVD score and vascular risk factors, PD severity, and motor phenotype. Increasing age and reduced MMSE and MoCA scores were associated with increased SVD burden. Logistic regression analyses demonstrated that periventricular WMH (PVH), PVS in the basal ganglia (BG-PVS), and atrophy were predictors of cognitive impairment in PD.

Conclusion: The contribution of SVD may be important in elderly patients with PD. Impaired cognition due to SVD-related brain changes was associated with BG-PVS and PVH. These measures suggest that PD with PVS can provide novel insights into SVD.

1. Introduction

Cognitive impairment and dementia are recognized consequences of the neurodegenerative processes that underlie Parkinson's disease (PD). In addition, these symptoms may relate to comorbid cerebrovascular disease. Clinical imaging and pathological studies highlight the adverse impact of cerebrovascular disease and vascular risk factors, including diabetes, hypertension, and dyslipidemia, on cognition and motor tasks, particularly gait [1,2]. The progression of neurodegeneration in the advanced stages of PD has been widely recognized as responsible for cognitive impairment; however, white matter hyperintensity (WMH) may be a contributing factor [3,4]. In addition, subclinical white matter cerebrovascular disease has been linked to increased motor severity and gait impairment [2,5,6].

The occurrence of cerebrovascular disease in the elderly, such as cerebral small vessel disease (SVD), plays a role in the development of cognitive and motor impairments [7–12]. Intrinsic features of SVD include small perforating arterioles that can be visualized on conventional MRI as lesions, WMHs, lacunae, microbleeds (MBs), enlarged perivascular spaces (PVSs), and subcortical atrophy [13]. Measurements of total SVD burden were first used in ischemic stroke patients [7] and, more recently, in cerebral amyloid angiopathy [14]. We hypothesize that this measurement can be used to define patients that are at risk of cognitive and gait impairments in PD.

WMH in PD can be assessed using a semi-quantitative visual rating scale or automated method. Subsequently, the contradictory results of previous PD studies may be due to differences in WMH assessment methods using MRI. In addition, the pathological substrates of WMH,

Abbreviations: BG-PVS, basal ganglia periventricular space; MB, microbleeds; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; SVD, small vessel disease; TD, tremor-dominant; PD-D, Parkinson's disease with dementia; PD, Parkinson's disease; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NCI, Parkinson's disease with no cognitive impairment; PIGD, postural instability gait difficulty; PVH, periventricular white matter hyperintensity; WMH, white matter hyperintensity

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including lacunae, MBs, and PVS, have not been fully investigated [4]. Several studies have assessed the importance of SVD as a contributing factor in PD [15–17]; however, to the best of our knowledge, no study has examined the importance of SVD burden in PD symptoms, including motor and cognitive impairments.

Therefore, we conducted a retrospective study to investigate whether total SVD burden, assessed using the SVD score, was correlated with vascular risk factors in PD. Furthermore, we assessed the correlation between motor and cognitive features of PD and each SVD component.

2. Material and methods

2.1. Study design and patients

We carried out an observational, crossed-sectional, monocenter evaluative study of patients with PD recruited from the Neurology clinic in the Department of Internal Medicine, Tokyo Women's Medical University Medical Center East, between January and December 2017. Patients with PD were diagnosed according to the diagnostic criteria described previously [18]. Patients were excluded if they (1) were < 55 years old at evaluation; (2) unable to complete assessments due to aural or vision loss, dementia, severe systemic disease, or malignant tumor; and (3) did not provide consent for assessments.

2.2. Clinical assessment of PD

The participants' socio-demographic information, including age, sex, years of education, disease duration, and vascular risk factors were recorded. The severity and stage of Parkinsonism was assessed for each patient using Hoehn and Yahr (HY) staging and the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (UPDRS 3) [19]. Tremor and postural instability gait difficulty (PIGD) scores, which were derived from the ratio between mean tremor and PIGD scores, were used to define tremor-dominant (TD; ratio ≥1.5), PIGD (ratio ≥1), and indeterminate (1 < ratio < 1.5) phenotypes [20]. Levodopa equivalent doses were calculated using established formulae for dose equivalence [21]. Global cognitive performance was evaluated using the Mini-Mental State Examination (MMSE) [22] and Montreal Cognitive Assessment (MoCA) [23], which was adjusted for years of education. Predetermined diagnostic cut-offs in the MoCA were used to categorize cases into normal (> 23: PD with no cognitive impairment, PD-NCI), mild cognitive impairment (22–23 or > 22 without functional impairment: PD-MCI), and dementia (< 22 with functional impairment: PD-D) co-morbidities to reflect the core criteria for PD dementia defined by the Movement Disorder Society Task Force [24,25].

2.3. Brain MRI acquisition

All MRI examinations were performed using a MAGNETOM Avanto 1.5 T (Siemens Medical Solutions, Erlangen, Germany). The imaging protocol consisted of T1-weighted spin-echo (inversion recovery: repetition time/echo time (TR/TE) = 450/11 ms), T2-weighted fast spin-echo (TR/TE = 3370/84 ms), T2*-weighted gradient-echo (TR/TE = 550/18 ms), and fluid-attenuated inversion-recovery (FLAIR; TR/TE = 8000/102 ms) sequences in the axial (T1, T2, and T2*-weighted images) and coronal (FLAIR images) plane, with a slice thickness of 5 mm.

A trained neurologist who was blinded to the patient's clinical symptoms and related information, assessed for SVD scores using the semi quantitative visual rating total SVD scale created by Staals et al [7]. We rated the total burden of SVD on an ordinal scale from 0 to 4 based on the description in a previous study. Briefly, we counted the presence of the 4 MRI features of SVD. Periventricular and deep WMH were rated using the Fazekas scale [26] (0–3) from T2- and FLAIR weighted images. One point was awarded on the SVD scale when (early) confluent deep WMH (Fazekas score of 2 or 3) and/or irregular periventricular WMH extending into deep white matter (Fazekas score of 3) were present. One point on the SVD scale was awarded when ≥1 lacunae were present. The presence of ≥1 MBs in deep or lobar cerebral region was awarded 1 point on the SVD scale. PVS was defined as small (< 3 mm) punctate hyperintensities on T2-weighted images in the centrum semiovale and basal ganglia enlarged perivascular spaces (CS-PVS and BG-PVS) [27]. These were rated on a scale from 0 to 4: 0 = no PVS, 1 = < 10 PVS, 2 = 11–20 PVS, 3 = 21–40 PVS, and 4 = > 40 PVS. One point on the SVD scale was awarded when moderate to severe (grade 2–4) BG-PVS was present. In addition, we evaluated global brain atrophy using the bicaudate ratio [28].

2.4. Statistical analysis

We performed a regression analysis to assess the comparison between SVD scores (0–4). Pearson χ^2 test was used to compare the categorical variables. We performed multivariate logistic regression analyses correcting for age, vascular risk factors, PD clinical features, and MRI findings related to SVD to study the influence of these variables as predictors for PD-NCI and PD-MCI/PD-D. Results were considered statistically significant if $p < 0.05$. We used the statistical package, JMP® Pro 13.1 (SAS Institute Inc., Cary, NC, USA) to perform statistical analyses.

2.5. Patient consent

Informed consent was obtained from all subjects according to the Declaration of Helsinki. This study was approved by the local ethics committees of the hospital.

3. Results

We recruited 71 patients in this study. The clinical characteristics and correlations with the SVD scale and SVD scores in patients with PD are presented in Tables 1 and 2, respectively.

Univariate analysis revealed significant association between total SVD score and increasing age ($p < 0.0001$), reduced MMSE ($p < 0.0001$), and MoCA ($p < 0.0002$). However, there was no significant association with sex, years of education, disease duration, vascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, history TIA/stroke, and cardiovascular disease. There were significant association between total SVD score and MRI findings ($p < 0.003$), which were PVH, DWMH, CS- and BG-PVS, MBs (deep and lobar region) and atrophy. Taken together, this showed that the SVD-MRI findings were associated with the SVD score.

Within the PD group, 37 and 34 participants were classified as PD-NCI and PD-MCI/PD-D, respectively. Comparison of the clinical and MRI data between PD-NCI and PD-MCI/PD-D groups is shown in Table 3. PD-MCI/PD-D patients had significantly greater PVH ($p < 0.0001$), DWMH ($p < 0.01$), CS-PVS ($p < 0.05$), BG-PVS ($p < 0.001$), lacunae ($p = 0.001$), SVD score ($p < 0.0001$), and atrophy ($p < 0.0001$). Univariate analyses revealed that PVH, DWMH, CS-PVS, BG-PVS, lacunae, SVD score, and atrophy were significantly greater among MCI-PD/PD-D participants. Furthermore, logistic regression analysis demonstrated that PVH (OR 15.58: CI 2.953–158.1, $p < 0.01$), BG-PVS (OR 4.062: CI 1.274–18.370, $p < 0.05$), and atrophy (OR 7.77: CI 2.315–5.856, $p < 0.01$) could predict cognitive impairment in PD.

4. Discussion

This study sought to investigate the association between SVD and PD. Vascular risk factors, PD severity, and motor phenotype were not associated with SVD score. In addition, we found that impaired cognition from SVD-related brain changes were associated with BG-PVS in

Table 1
Characteristics of Parkinson's disease (PD) patients and the correlations with small vessel disease (SVD) score.

	N = 71	p*
Clinical feature		
Age, years, mean (SD)	73.2 (8.4)	< 0.0001
Gender, male, n (%)	39 (54.9)	0.068
Education, years, mean (SD)	12.0 (3.0)	0.12
Disease duration, years, mean (SD)	6.4 (4.4)	0.15
Vascular risk factors		
Hypertension, n (%)	23 (32.4)	0.13
Hyperlipidemia, n (%)	28 (39.4)	0.55
Diabetes mellitus, n (%)	22 (31.1)	0.82
Smoking, ever, n (%)	33 (46.5)	0.95
History of TIA/stroke, n (%)	0	
Cardiovascular disease, n (%)	4 (5.6)	0.068
Hoehn and Yahr, mean (SD)	2.5 (0.76)	0.052
UPDRS 3 score	22.1 (8.8)	0.34
PD subtype classification		0.15
TD, n (%)	22 (34.8)	
PIGDD, n (%)	39 (52.2)	
Not determined, n (%)	10 (13.0)	
LED, mg	481.8 (59.0)	0.98
Global cognition		
MMSE	25.3 (4.3)	0.0001
MoCA	22.7 (5.6)	0.0002
SVD related lesions in MRI		
PVH	1.4 (1.1)	< 0.0001
DWMH	0.92 (0.98)	< 0.0001
CS-PVS	2.1 (1.4)	< 0.0001
BG-PVS	2.0 (1.3)	< 0.0001
MBs (deep region)	0.41 (0.79)	< 0.0001
MBs (lobar region)	0.32 (0.19)	0.0026
Lacunae	0.52 (0.89)	< 0.0001
Atrophy	0.19 (0.003)	0.0001

UPDRS 3 score, UPDRS: Unified Parkinson's Disease Rating Scale, TD: tremor dominant, PIGD: postural instability gait disorder, LED: Levodopa Equivalent Dose, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, PVH: enlarged periventricular hyperintensities, DWMH: diffuse white matter hyperintensities, CS: centrum semiovale, BG: basal ganglia, PVS: enlarged perivascular space, MBs: microbeads between.0–4.

* For univariate regression analysis of group comparisons between SVD scores of 0–4.

Table 2
Evaluating total small vessel disease (SVD) score in patients with Parkinson's disease.

SVD Score	0 n = 23	1 n = 15	2 n = 11	3 n = 17	4 n = 5
Lacunae	0	0	5	10	5
MBs	0	3	2	9	5
PVS	0	11	11	16	5
WMH	0	1	4	16	5

MBs: microbleeds, PVS: enlarged perivascular space, WMH: white matter hyperintensities.

addition to PVH.

First, we confirmed that SVD-related brain changes in PD were more prominent in older and cognitively impaired patients. Our study revealed that PVH, BG-PVS, and atrophy were associated with cognitive impairment in PD. This finding is in line with studies that have shown that WMH was associated with cognitively impaired patients with PD [3,29,30]. However, a previous study revealed that the prevalence of vascular risk factors and SVD pathology, assessed using post-mortem examination, was significantly lower in patients with PD than in controls; however, this study did not evaluate cognitive function [31]. Other nonvascular factors, such as PD-associated autonomic dysfunction, may contribute to the progression of dementia in PD in patients with WMH [32].

A previous longitudinal study revealed that the incidence of Parkinsonism with SVD, in particular WMH and lacunae, was higher than the general incidence in the elderly [15]. In mildly symptomatic PD, the prevalence of cognitive impairment is approximately 20%–30%, while in the moderate-severe stage, the prevalence increases to 80%–90% [33]. The prevalence of cognitively impaired patients with PD in this study is consistent with these ranges. In addition, our study revealed that PVH and BG-PVS was important for global cognitive function in PD. WMHs, in particular, PVHs, have been suggested to disrupt cholinergic pathways that originate from the nucleus basalis of Mynert, which are associated with cognitive dysfunction in other non-memory domains, such as executive function [34]. The present study is comparable to studies demonstrating that the spatial distribution of WMH is not homogenous in PD, showing preferential occurrences in the periventricular white matter region [35].

The presence of PVS, particularly in the basal ganglia, is a fundamental component of the histological features of SVD [36]. BG-PVS correlates with many clinical features, including vascular Parkinsonism (VP) [37] and PD [38]. Vascular comorbidity is significantly associated with cognitively impaired and PIGD motor subtype patients with early PD [39]. Gait impairment and falls result from motor dysfunction in PD and are more likely to occur in patients with axial involvement, which is recognized clinically as the PIGD motor phenotype, distinct from TD [2,5]. Patients with VP frequently present with postural instability, gait freeze, and sudden onset stroke [40]. However, a previous pathological study revealed these characteristic features of elderly PD with BG-PVS who had cognitive decline and postural instability [41]. In this study, SVD burden did not have a significant effect on the PIGD motor subtype; therefore, elderly PD patients may have distinct clinical features and MRI finding in BG-PVS.

A recent longitudinal study revealed a link between the progression of WMH with increasing rates of regional grey matter atrophy, demonstrating that grey matter atrophy is a major contributor to whole brain atrophy in symptomatic cerebral SVD [42]. Longitudinal MRI measurements in PD have shown that global atrophy and ventricular enlargement are sensitive to disease progression in PD-MCI when compared with PD-NCI [43]. These measures are required to diagnose PD with PVS and may provide novel insights into SVD. The effect of SVD in elderly patients with PD has important management implications; therefore, a stratified study with a larger population of participants is required to clarify the effect of markers for SVD.

Although previous studies have shown that the characteristic MRI findings of VP were PVH and multiple lacunar lesions in the basal ganglia [37,44], our study revealed that the evaluation of SVD-related changes including these can be more effective for detecting changes in cognitive function especially in PD. Using only MRI findings, it may be difficult to differentiate between elderly PD patients with SVD and VP. Therefore, in addition to using the SVD score, a study of the features using brain SPECT is needed [45] to further clarify the differences of motor and cognitive functions between PD-NCI and PD-MCI/PD-D.

This study has some limitations. First, the findings are based on a small sample size at a single center, and the study has a cross-sectional design. Second, a longitudinal study exploring the progression of SVD and SVD scores, including cognitive ability, in age-matched healthy individuals as the control group would be valuable. Finally, we did not assess all cognitive domains; however, the main purpose of this study was to determine the clinical utility of using the SVD score to compare individual neuroimaging markers in PD and not to identify PD-MCI or PD-D.

5. Conclusions

In conclusion, the results of this study have shown that SVD-related brain changes in PD were more prominent in older and cognitively impaired patients. Impaired cognition owing to SVD-related brain changes was affected by PVH and BG-PVS. These measures suggest that

Table 3
MRI findings in PD-NCI and PD-MCI/PD-D.

	PD-NCI	PD-MCI/PD-D	Univariate analysis	Logistic regression analysis	
	n = 37	n = 34	p	OR (95% CI)	p
Age, mean (SD)	68.3 (7.7)	77.9 (6.3)	< 0.0001		
PVH	0.86 (0.85)	1.90 (1.02)	< 0.0001	15.58 (2.953–158.1)	0.0056
DWMH	0.62 (0.81)	1.31 (1.06)	0.004	0.480 (0.0800–2.586)	0.39
CS-PVS	1.86 (1.40)	2.56 (1.30)	0.036	0.33 (0.0820–0.982)	0.073
BG-PVS	1.60 (1.26)	2.69 (1.02)	0.0003	4.062 (1.274–18.370)	0.033
MBs (deep region)	0.29 (0.71)	0.60 (0.84)	0.117	0.89 (0.156–7.037)	0.9
MBs (lobar region)	0.23 (0.60)	0.47 (0.80)	0.167	1.81 (0.240–12.23)	0.54
Lacunae	0.171 (0.57)	0.97 (1.03)	0.0002	1.58 (0.450–6.931)	0.505
SVD score	1.00 (1.11)	2.21 (1,33)	0.0001	0.28 (0.052–1.197)	0.107
Atrophy	0.170 (0.02)	0.20 (0.03)	< 0.0001	7.77 (2.315–5.856)	0.0025

PD-NCI: Parkinson's disease with no cognitive impairment, PD-MCI: Parkinson's disease with mild cognitive impairment, PD-D: Parkinson's disease with dementia, OR: odds ratio, CI: confidence interval, PVH: periventricular hyperintensities, DWMH: diffuse white matter hyperintensities, CS: centrum semiovale, BG: basal ganglia, PVS: enlarged perivascular space, MBs: microbleeds, SVD: small vessel disease.

PD with PVS can provide novel insights into SVD. In addition, the effect of SVD in elderly patients with PD has important implications for management of such patients.

Declarations of interest

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