Association Between Cerebral Small Vessel Disease and Central Motor Conduction Time in Patients with Vascular Risk

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Background and Purpose: Cerebral small vessel disease (CSVD) is related to motor function disturbance. It includes several types: lacunar infarction, white matter hyperintensity, cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVS). Transcranial magnetic stimulation (TMS) has been successfully used to evaluate the function of the pyramidal tract. Central motor conduction time (CMCT) is one of the indicators of pyramidal tract dysfunction in motor evoked potential (MEP). The aim of this study was to investigate the association between each type of CSVD and CMCT. *Methods:* We enrolled 350 patients with vascular risk factors or a history of cerebrovascular events, who showed signs of CSVD in magnetic resonance imaging in the prospective registry. Among them, 138 patients agreed to the evaluation of MEP. CMCT, resting motor threshold (RMT), and silent period are indicators of the function of motor pathways in MEP. A total of 276 hemispheres were divided into 45 symptomatic hemispheres with a history of pyramidal tract dysfunction and 231 without it. Correlation between each type of CSVD and CMCT were examined in total, symptomatic, and asymptomatic hemispheres. *Results:* The mean age was 70.5 ± 10.3 (mean ± SD) years, and 89 (65%) were men. In the symptomatic hemisphere, CMCT and RMT were significantly higher than in the asymptomatic hemisphere. In the symptomatic hemisphere, significant association was observed between the number of EPVS in the white matter and CMCT ($R^2 = 0.201$, $p < .01$). *Conclusions:* In the symptomatic hemispheres, CMCT was associated with the number of EPVS in the white matter. The EPVS in the white matter may be involved in the motor disturbance due to CSVD.

Key Words: Cerebral small vessel disease—motor evoked potential—central motor conduction time—enlarged perivascular spaces

Introduction

Cerebral small vessel disease (CSVD) includes several types: lacunar infarction (LI), white matter hyperintensities (WMH), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVS). Recently, CSVD has been attracting much attention due to its relationship with stroke, cognitive impairment, mood and behavioral, and urinary disturbances.[1,2] Further, CSVD is related to motor function disturbance, typically vascular Parkinsonism.[3,4] However, the mechanisms of CSVD underlying motor dysfunction remain unclear.

Transcranial magnetic stimulation (TMS) has been successfully used to evaluate the function of the pyramidal tract in many neurological diseases, such as multiple sclerosis, motor neuron disease, and stroke.[5] Central motor conduction time (CMCT), resting motor threshold (RMT), and silent period (SP) are indicators of the function of motor pathways involved in motor evoked potential (MEP), which have been widely measured.[6,7] Previous studies have extensively showed that CMCT was prolonged in patients with acute stroke, and thus, CMCT could be a predictor of motor function recovery in the rehabilitation period.[8] However, it remains unclear

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whether the silent cerebral lesions often found in CSVD influence the indictors of MEP, including CMCT. The aim of this study was to investigate the association between each type of CSVD and CMCT, one of the objective markers of the function of the pyramidal tract.

Methods and Materials

Participants

This study is a sub-study of Tokyo Women's Medical University for Cerebrovascular Disease prospective registry (UMIN000026671). Ethics approval was obtained from the institutional review board in our hospital and written informed consent was obtained from all patients. We enrolled 350 patients with vascular risk factors or a history of cerebrovascular events, who showed signs of CSVD in the magnetic resonance imaging (MRI) performed within a year, in Tokyo Women's Medical University for Cerebrovascular Disease registry, from April 2015 to March 2017 (Fig 1). Among them, 151 patients agreed to the TMS evaluation. However, 15 people were excluded due to insufficient measurement of MEP. Therefore, 138 patients, accounting for 276 hemispheres, were included in this study.

We classified these hemispheres into symptomatic and asymptomatic. Symptomatic hemispheres were defined by the presence of pyramidal tract signs, such as motor weakness and pathological reflex, at TMS examination, or previously reported as the stroke index and transient ischemic attack. Asymptomatic hemisphere was defined by absence of pyramidal tract signs. The flow chart of patient recruitment is shown in Figure 1.

Patients' Background

Regarding the vascular risk factors, the following generally defined criteria were used. Hypertension was defined as systolic blood pressure less than equal to 140 mmHg, diastolic blood pressure less than 90 mmHg, or oral antihypertensive medication. Dyslipidemia was defined as low density lipoprotein cholesterol less than equal to 140 mg/dL, high density lipoprotein cholesterol more than 40 mg/dL, triglyceride less than equal to 150 mg/dL, or use of lipid-lowering drugs. Diabetes was defined as fasting blood glucose less than equal to 126 mg/dL, occasional blood glucose less than equal to 200 mg/dL, HbA1c less than equal to 6.5%, or the use of hypoglycemic drugs or insulin. Chronic kidney disease was defined as estimated glomerular filtration rate of more than 60 ml/min/1.73 m^2, or proteinemia.[9]

At the time of TWMUCVD registration, cognitive function was evaluated using mini-mental state examination and Montreal Cognitive Assessment for Japan.[10,11] In addition, clinical motor function at MEP examination was evaluated using Movement Disorder Society Unified Parkinson'sDisease Rating Scale part III.[12] A neurologist performed neurological evaluation to assess the presence of pyramidal tract signs at the time of MEP.

Brain MRI Acquisition and MRI Rating

All participants were scanned using a 1.5T MRI scanner (Philips Ingenia 1.5T, Siemens Magnetom Avanto fit 1.5T). For this study, we used axial T2, T2*, fluid-attenuated inversion recovery, T1-weighted sequences, diffusion-weighted imaging, and MR angiography. Images were rated by 2 certified and registered neurologists (M.K., K.K.) for the presence of LI, WMH, CMBs, and EPVS. The rating protocol, using validated visual scales, has been published.[2,13,14] The WMH were defined as hyperintense signal abnormalities surrounding the ventricles on FLAIR images. Periventricular hyperintensity (PVH) and deep WMH (DWMH) were rated on the Fazekas scale (0-3 for each hemisphere). The LI were defined as focal lesions less than 3 mm and more than 15 mm, with a hypointense rim on FLAIR images, when located supratentorially, according to the corresponding hyper- and hypointensity on T2 and T1-weighted images, respectively. The CMBs were small (generally 2-5 mm in diameter, but occasionally up to 10 mm) areas devoid of signal, with associated blooming seen on T2*-weighted MRI. The LI and CMBs were defined as: degree 0, none; degree 1, 1 LI or CMB; degree 2, more than 2 LI or CMBs. The EPVS were identified on T1-weighted images, and defined as round, ovoid, or linear structures, with cerebrospinal fluid-like signal, no larger than 2 mm in diameter, and located in territories supplied by perforating arteries (Fig 2).[15] The numbers of EPVS were counted at the site of basal ganglia (BG), white matter (WM), and the sum of those of BG and WM (Total).

TMS and MEP

The TMS of the motor cortex was performed using a magnetic stimulator (SMN1200, Nihon Koden, Tokyo, Japan). During the examination, the patient was seated comfortably in an armchair, and the examiner used a magnetic 14 cm circular coil (YM122B) to magnetically stimulate the primary motor cortex (C3, C4) and the C7 cervical vertebrae from the back of the patient. Upon stimulation, CMCT, RMT, and SP were evaluated from electromyogram (EMG) waveform obtained from the abductor pollicis brevis (APB) (Fig 3).

The RMT was defined as the lowest TMS intensity required to induce motor response of an amplitude (peak to peak) less than 50 μV in the relaxed contralateral target muscle, in at least 5 out of 10 consecutive trials. Stimuli were applied with increasing intensities, ranging from 50% to 100% (in steps of 5% increments) of the maximum stimulator output. The different stimulus intensities were applied in a random order.

The CMCT was defined as the difference between the latency at primary motor cortex stimulation and the latency at C7 cervical spine stimulation, with the test

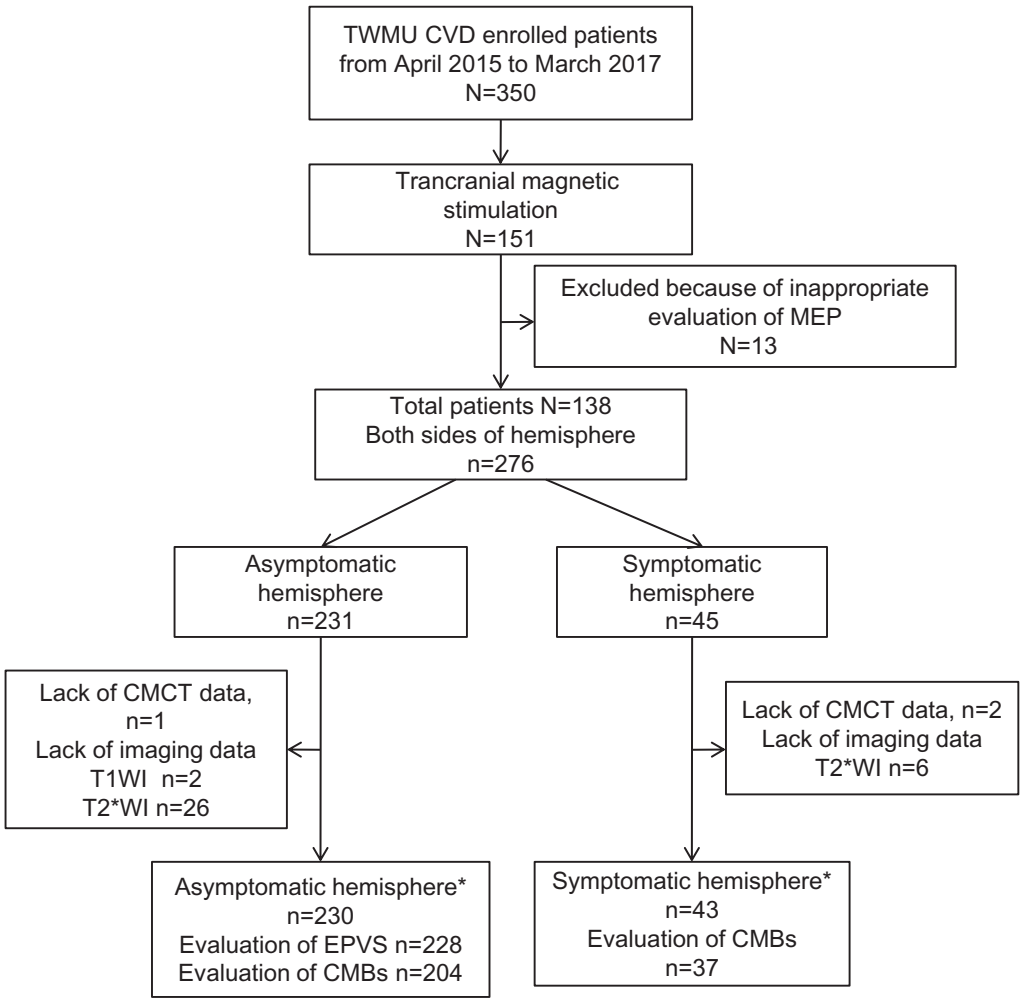

Figure 1. *Flowchart of patient recruitment for this study. We enrolled 350 patients who were registered in the Tokyo Women's Medical University for Cerebrovascular Disease between 2015 and March 2017. Among them, 151 patients agreed with the evaluation of transcranial magnetic stimulation. Fifteen people were excluded due to insufficient measurement of motor evoked potential. The remaining 138 patients, accounting for 276 hemispheres, were included in this study. The 276 hemispheres were divided into 45 symptomatic hemispheres with a history of pyramidal tract signs and 231 without it.*

muscle weakly contracting (Fig 3). First, the C7 cervical spine stimulation was performed, and the waveform was drawn at the time when the stimulus reached the maximum intensity. Thereafter, the stimulation was performed again with the same output, and the reproducibility of the waveform was confirmed. In primary motor cortex stimulation, the output corresponding to the maximum stimulus intensity, in the resting/sitting position, was identified, and the cortical latency was visualized, with weakly contracting APB, using the same output. Regarding the state in which the APB was weakly contracted, the patient was instructed to maximally voluntarily contract the APB, monitored using the EMG, and the maximum amplitude of the waveform was confirmed. Thereafter, while exercising power on the APB to amplitude of 10%-20% of the EMG waveform, the evoked waveform was recorded at least 5 times, while the examiner performed the cortical stimulation. Cortical latency was identified as the mean value of the 5 recordings (Fig 3).

The SP was defined as the time from the magnetic stimulation of primary motor field to the start of the muscle action potential due to voluntary contraction at an output of 120% of RMT, with the subject muscle contracting by 10%-20%.[16]

Statistical Analysis

All values were expressed as mean ±SD, median and interquartile range, or counts and percentage. For group comparisons between hemispheres with and without pyramidal tract signs, we used χ^2 tests for categorical variables and Student's t tests for continuous variables. The relationships between MEP parameters and the grades of PVH, DWMH, LI, and CMB were examined using nonparametric analysis. The relationship between MEP parameters and the number of EPVC were examined using Pearson correlation analysis. All analyses were performed using JMP Pro 12.0 software (SAS Institute Inc.,

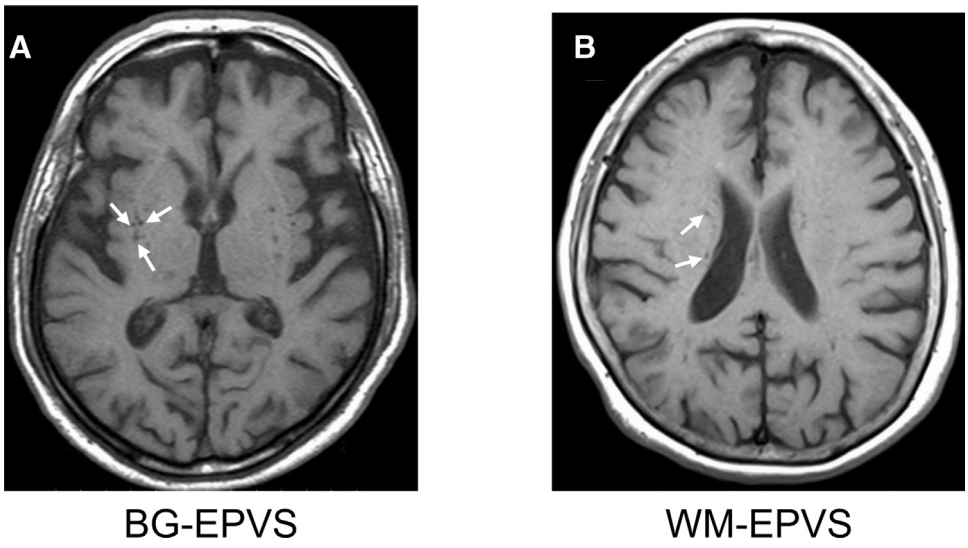

Figure 2. *Axial T1 magnetic resonance imaging scans. (A) Enlarged perivascular spaces (EPVS) in the basal ganglia (BG-EPVS). (B) EPVS in the white matter (WM-EPVS). We counted the radiologic appearance of EPVS (small white arrows).*

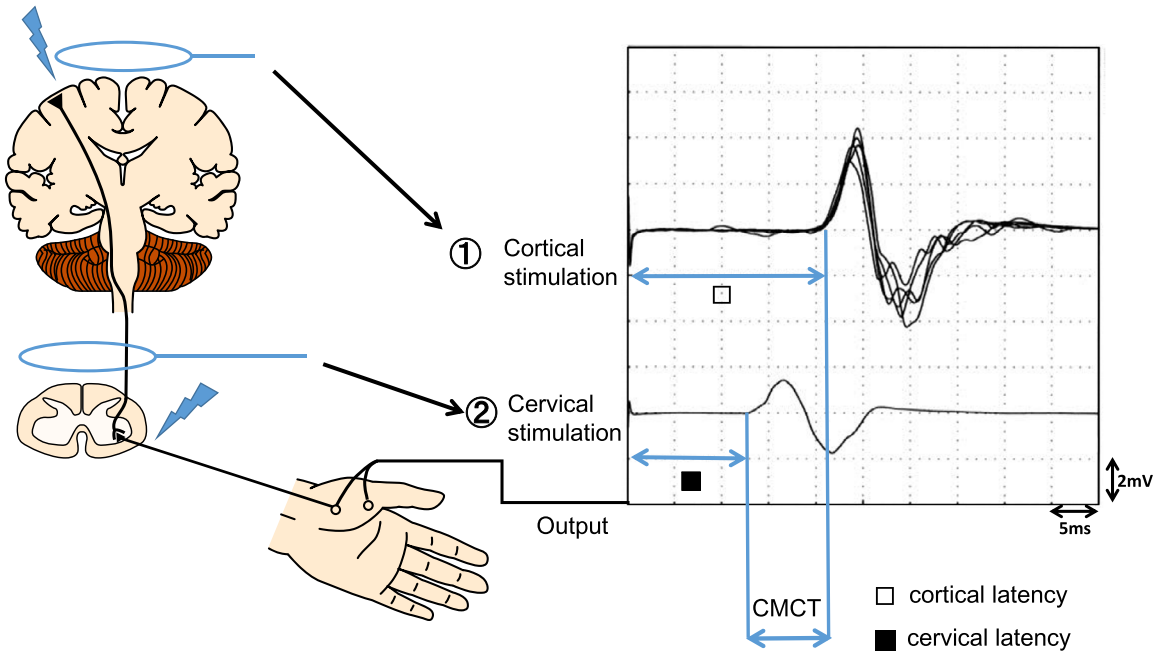

Figure 3. *Transcranial magnetic stimulation. The patient was stimulated at the primary motor cortex (C3, C4) (①) and the C7 cervical vertebrae (②). Each waveform was recorded in the electromyogram. The central motor conduction time was indicated by the difference between cortical latency and cervical latency. (Color version of figure is available online.)*

Cary, NC). All statistical tests were 2-tailed, and $p < .05$ was considered significant.

Results

Patients characteristics are shown in Table 1. Out of the 138 patients, 77 (56%) had a history of stroke. The prevalence of vascular risk factors, such as hypertension, dyslipidemia, diabetes, chronic kidney disease, and atrial fibrillation were 69%, 48%, 22%, 8%, and 12%, respectively. Regarding motor function, 45 patients (33%) exhibited hemiparesis upon TMS examination or had a history of pyramidal tract signs in the past. Thus, the 45 hemispheres from these patients were defined as symptomatic. The characteristics of these symptomatic hemispheres are shown in Table 2. Muscle weakness was observed in 8 patients (18%), enhanced deep tendon reflex was observed in 12 patients (27%), and pathological reflex was observed in 11 patients (25%). Infarction was observed in the vicinity of the pyramidal tract in 37 patients (82%), including cortical infarct in 15 cases, infarct in corona radiate in 10 cases, infarct in internal

Table 1. *Baseline patient characteristics (N = 138)*

Age, yr	70.5 ± 10.3
Male, N (%)	89 (65%)
BMI, kg/m^2	23.9 ± 4.2
Hypertension, %	95 (69%)
Systolic blood pressure, mmHg	132.3 ± 16.7
Diastolic blood pressure, mmHg	72.7 ± 11.6
Dyslipidemia, %	66 (48%)
LDL cholesterol, mmolL	2.83 ± 0.82
HDL cholesterol, mmol/L	1.62 ± 0.48
TG, mmol/L	2.99 ± 1.51
Diabetes, %	30 (22%)
FBS, mg/dL	118.8 ± 45.5
HbA1c, %	6.28 ± 0.9
Chronic kidney disease, %	11 (8%)
Creatinine, mg/dL	0.94 ± 0.40
eGFR, ml/min/1.73 m^2	60.2 ± 15.1
Proteinuria	12 (9.3%)
Atrial fibrillation, %	16 (12%)
Smoking, %	78 (57%)
Drinking, %	41 (30%)
History of stroke, %	77 (56%)
Ischemic stroke	65 (47%)
Cerebral hemorrhage	4 (3%)
Transient ischemic attack	8 (6%)
Presence of hemiparesis	45 (33%)
Current	4 (3%)
Past	41 (30%)
MDS UPDRS Part3	5.9 ± 7.7
MMSE	27.9 ± 2.2
MoCA-J	23.5 ± 3.7

Abbreviations: BMI, indicates body mass Index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, Triglyceride; FBS, fasting blood sugar; HbA1c, Hemoglobin A1c; eGFR, estimated glomerular filtration rate, MDS UPDRS; Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA-J; Japanese version of Montreal Cognitive Assessment.

capsule in 11 cases, and pontine infarct in 4 cases. Of the 45 symptomatic and 231 asymptomatic hemispheres, 2 cases and 1 case, respectively, were excluded due to the insufficient evaluation of CMCT (Fig 1).

Table 2. *Characteristics of symptomatic hemisphere (n = 45)*

MMT 5	37 (82%)
4	7 (16%)
3	1 (2%)
Enhanced tendon reflexes	12 (27%)
Pathological reflex	11 (25%)
Infarction in the vicinity of pyramidal tract	37 (82%)
Infarction site	Cortical and subcortical 15 (37%)
	Corona radiata 10 (24%)
	Internal capsule 11 (27%)
	Pons 4 (10%)

MMT indicates Manual Muscle testing.

The findings from the head MRI for symptomatic and asymptomatic hemispheres are shown in Table 3. Severity of WMH, either as PVH or DWMH, and CMB was similar between asymptomatic and symptomatic hemispheres, while the grade of LI was significantly severer in symptomatic hemispheres than in asymptomatic hemispheres. The number of EPVS was significantly higher in the symptomatic hemispheres than in asymptomatic hemispheres, although the difference in the number of EPVS in the BG and WM was not significant.

For the MEP results, the average CMCT was 7.68 ± 1.45 ms. The CMCT for symptomatic hemispheres (8.21 ± 1.62 ms) was significantly slower than that for the asymptomatic hemispheres (7.58 ± 1.40 ms). The average RMT was 69.8 ± 16.3%. The RMT for symptomatic hemispheres (74.4 ± 16.9%) was significantly higher than that for asymptomatic hemispheres (68.9 ± 16.0%). The average SP was 115.85 ± 37.36 ms. The SP was similar between symptomatic and asymptomatic hemispheres (Table 4).

There was no relationship between CMCT and PVH in asymptomatic ($R^2 = 0.009$, $p = .545$) and symptomatic hemispheres ($R^2 = 0.030$, $p = .756$), between CMCT and DWMH in asymptomatic ($R^2 = 0.025$, $p = .122$) and symptomatic hemispheres, ($R^2 = 0.038$, $p = .673$). No association was found between CMCT and the number of LI in asymptomatic ($R^2 = 0.011$, $p = .300$) and symptomatic hemispheres ($R^2 = 0.007$, $p = .861$), between CMCT and CMB in asymptomatic ($R^2 = 0.006$, $p = .532$) and symptomatic hemispheres ($R^2 = 0.043$, $p = .472$). In terms of EPVS, there are no association between CMCT and the number of EPVS in asymptomatic hemispheres, but modest association was observed between CMCT and the number of EPVS in WM ($R^2 = 0.201$, $p < .01$). Again, modest association was found between CMCT and the number of EPVS within the pyramidal tract only in symptomatic hemisphere ($R^2 = 0.113$, $p = .028$) (Fig 4.)

Discussion

We examined the relationship between CSVD signs and CMCT in MEP, and observed modest association between CMCT and the number of WM-EPVS in symptomatic hemisphere. The perivascular spaces (PVS) are fluid-filled cavities that surround small, penetrating cerebral arterioles and venules, and are commonly considered to play an important role in forming a network of drainage channels for the elimination of metabolic waste and fluid from the brain.[17] When the caliber and the number of normally microscopic PVS increase with advancing age, the PVS appear on T2-weighted MRI as round or tubular hyperintensities in the BG and WM.[18] Pathologic dilatation of the Virchow-Robin space is most commonly associated with arteriolar abnormalities that arise due to aging, diabetes, hypercholesterolemia, smoking, hypertension, and other vascular risk factors.[19] There are several studies showing the effect of EPVS on cognitive function. Moreover, PVS

Table 3. *MRI findings in each hemisphere (Total, Asymptomatic, and Symptomatic hemispheres)*

		Total (n = 276)	Asymptomatic (n = 231)	Symptomatic (n = 45)	*p* value
PVH	0	11 (40%)	10 (4%)	1 (2%)	.680
	1	202 (73%)	170 (74%)	32 (71%)	
	2	53 (19%)	42 (18%)	11 (24%)	
	3	10 (4%)	9 (4%)	1 (2%)	
DWMH	0	23 (8%)	21 (9%)	2 (4%)	.612
	1	163 (59%)	137 (59%)	26 (58%)	
	2	58 (21%)	46 (20%)	12 (27%)	
	3	32 (12%)	27 (12%)	5 (11%)	
Lacunar infarction	0	150 (54%)	135 (58%)	15 (33%)	.006
	1	70 (25%)	55 (24%)	15 (33%)	
	≥2	56 (20%)	41 (18%)	15 (33%)	
Cerebral microbleeds	0	172 (70%)	146 (71%)	26 (67%)	.327
	1	39 (16%)	32 (16%)	7 (18%)	
	≥2	33 (14%)	27 (13%)	6 (15%)	
EPVS	Total	2 (0-4)	1 (0-4)	2 (1-5)	.023
	Basal ganglia (BG)	1 (0-3)	1 (0-3)	1 (0-4)	.145
	White matter (WM)	0 (0-1)	0 (0-1)	0 (0-3)	.057

Abbreviations: PVH indicates periventricularhyperintensity; DWMH, deep white matter hyperintensity; EPVS, enlarged perivascular space.

Table 4. *Motor evoked potentials in each hemisphere (Total, Asymptomatic and Symptomatic hemispheres)*

	Total (n = 276)	Asymptomatic (n = 231)	Symptomatic (n = 45)	*p* value
CMCT, ms	7.68 ± 1.45	7.58 ± 1.40	8.21 ± 1.62	.008
Cervical Latency, ms	13.44 ± 1.45	13.44 ± 1.48	13.44 ± 1.28	
Cortical Latency, ms	21.13 ± 1.89	21.05 ± 1.80	21.55 ± 2.28	
RMT, %	69.8 ± 16.3	68.9 ± 16.0	74.4 ± 16.9	.038
SP, ms	115.9 ± 37.4	114.5 ± 37.3	122.9 ± 37.3	.155

Abbreviations: CMCT indicates central motor conduction time; RMT, resting motor threshold; SP, silent period.

were shown to be associated with the increased risk of dementia, cognitive impairment, and hypertension.[20-22] A higher EPVS burden was also observed in patients with Alzheimer's disease and mild cognitive impairment than controls. The EPVS burden in vascular dementia appears to be greater than that in other forms of dementia, such as frontotemporal dementia and Alzheimer's disease.[23] Previous studies have examined the relationship between movement disorders and CSVD. Among the CSVD markers, WMH score or volume were additional significant and independent predictors of gait speed in the regression model.[24] Further, WMH, LI, and CMB were shown to be associated with mild Parkinsonism.[25] However, the involvement of EPVS in movement disorders or vascular Parkinsonism has not yet been investigated.

In this study, the number of EPVS in WM was associated with the CMCT delay for symptomatic hemispheres. However, no association was observed between other CSVD signs and CMCT. Although the exact mechanisms underlying these finding remain unclear, we propose the following hypothesis (Fig 5).The EPVS, a vessel lumen enlargement due to vascular tortuosity, might mechanically pressurize the nerve bundle traveling around it (Fig 5D). It is well-known that the nerve conduction velocity is easily delayed by mechanical stress in peripheral nerve disorders, such as carpal tunnel syndrome and peroneal neuropathy.[26,27] It is likely that the pyramidal tract fiber, already subjected to subtle damage in symptomatic hemispheres, is easily affected by the mechanical compression due to EPVS. In multiple sclerosis, CMCT is prolonged, together with WMH. The WMH observed in multiple sclerosis is ascribed to severe damage of axon fibers, myelin, and blood brain barrier, accompanied by an inflammatory reaction, but the WMH in CSVD (Fig 5A) are caused by enhanced permeability due to the subclinical inflammation. The preservation of WM structure in CSVD may explain the lack of association between CMCT and PVH or DWMH. The LI and CMB (Fig 5B and C, respectively) may influence motor function when located exactly in the pyramidal tract. However, this scenario is unlikely, leading to their lack of association with CMCT. These speculations need to be validated by further investigation.

There are several limitations in this study. First, we used 1.5T MRI, not 3T; therefore, the association between cortical microinfarctand CMCT could not be investigated.

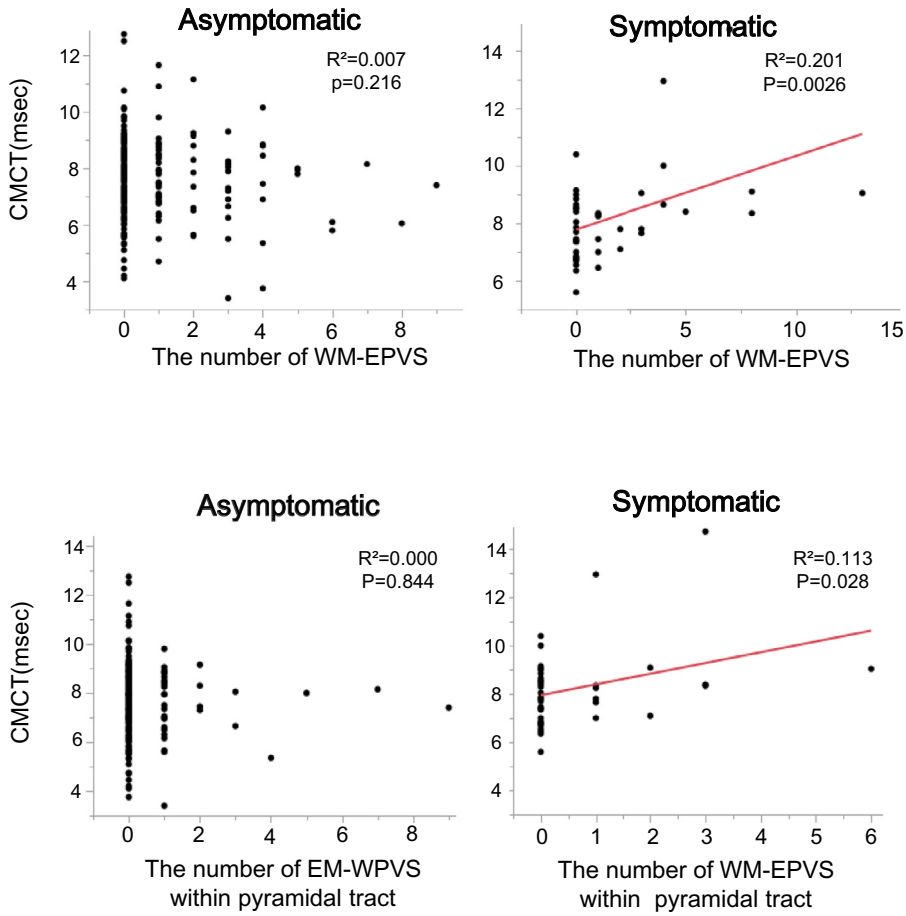

Figure 4. *Association between enlarged perivascular spaces (EPVS) in the white matter and central motor conduction time (CMCT). In the symptomatic hemisphere, the number of EPVS in the white matter was significantly associated with CMCT ($R^2 = 0.201$, $p < .01$). Also, in the symptomatic hemisphere, the number of EPVS in the white matter within pyramidal tract was significantly associated with CMCT ($R^2 = 0.131$, $p = .028$). However, no association was observed between the number of EPVS in asymptomatic hemispheres and CMCT. (Color version of figure is available online.)*

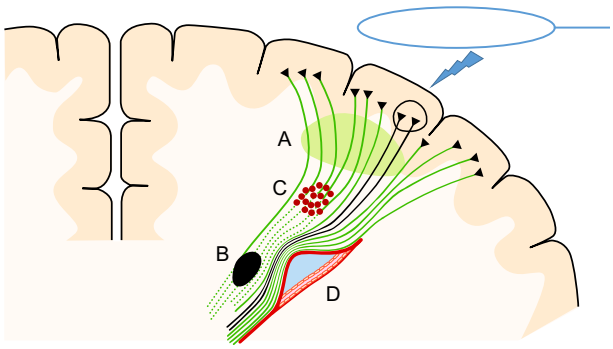

Figure 5. *Hypothesis underlying central motor conduction time (CMCT) extension due to enlarged perivascular spaces (EPVS). White matter hyperintensity (WMH) (A), lacunar infarcts (LI) (B), cerebral microbleeds (CMB) (C), and EPVS (D) are indicated by green oval, black oval, red dots, and blue liquid shapes, respectively. The WMH observed in cerebral small vessel disease is caused by enhanced permeability due to the subclinical inflammation, and neither LI nor CMB would influence CMCT unless they are located on the pyramidal tract. However, EPVS might mechanically pressurize the nerve bundle traveling around it, leading to extension of CMCT, as often seen in peripheral nerve neuropathy. (Color version of figure is available online.)*

Second, this study is a cross-sectional survey; thus, we could not establish the causal relationship between EPVS and CMCT. Longitudinal studies are needed to examine the relationship between EPVS and CMCT. Third, the number of cases with multiple LI or CMB was small. Therefore, we could not draw conclusions regarding the effect of LI and CMB on CMCT in this study. Since a significant association was observed between EPVS in the WM and CMCT, the effect of lobar CMB, a common occurrence in cerebral amyloid angiopathy, on CMCT needs to be investigated. Fourth, since we did not study F waves in the patients, there is a possibility that patients with subclinical cervical myelopathy were included in this study. The CMCT is prolonged in these patients due to the deleterious effect on the anterior horn of the spinal cord and the anterior root.

Summary

To summarize, CMCT is associated with the numbers of EPVS in the WM in symptomatic hemispheres. The

EPVS in the WM may be involved in the motor disturbance observed in CSVD. The clinical significance of EPVS may be more than previously expected, and needs further investigation.

Conflict of Interest

There are no conflicts of interest to declare.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.05.030.

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