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Original Research

Impact of Cerebral Microbleeds on Gait, Balance, and Upper Extremities Function in Cerebral Small Vessel Disease

Yutong Hou[1], Shuna Yang[1], Yue Li[1], Wei Qin[1], Lei Yang[1], Wenli Hu[1,*]

[1]Department of Neurology, Beijing Chao-Yang Hospital, Capital Medical University, 100020 Beijing, China
*Correspondence: wenlihu3366@126.com (Wenli Hu)
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Abstract

Background and Purpose: White matter hyperintensites (WMHs) , lacunes and brain atrophy have been demonstrated to be positively related to gait disorder. However, cerebral microbleeds (CMBs) as a manifestation of cerebral small vessel disease (CSVD) is still under-investigated. Therefore, correlations between CMBs and upper extremity, gait and balance performance were investigated in this study. **Methods**: A cross-sectional study of middle-aged to older adults was conducted. CSVD burden was measured with magnetic resonance imaging (MRI) and the location and number of CMBs were analysed. Gait and balance functions were evaluated using a four meter walkway, Tinetti, Timed-Up-and-Go (TUG) and Short Physical Performance Battery (SPPB) tests. Upper extremity function was measured by 10 repeated pronation-supination time, 10 repeated finger tapping time, and 10 repeated opening and closings of the hands. **Results**: A total of 224 participants were included in this study, with a mean age of 60.6 $\pm$ 10.5 years. The prevalence of CMB was 34.8% and most was lobar. Multiple linear regression analysis showed that CMB was associated with lower gait velocity, wider stride width, longer TUG test time, and poor performance on Tinetti and SPPB tests independently of other coexisting CSVD markers and risk factors. These relationships appeared to be explained by CMBs in the frontal, temporal, basal ganglia and infratentorial regions. The motor function of upper extremity also had independent correlations with CMBs especially in frontal, parietal, and temporal areas, and in the basal ganglia. **Conclusions**: CMBs were found to be associated with both gait, balance and upper extremity disturbances. The presence of CMB seems to be another major driving force for CSVD on lower and upper extremity impairment in healthy elderly subjects.

Keywords: cerebral small vessel disease; cerebral microbleed; gait; balance; upper extremities; motor disturbance

1. Introduction

Gait disturbances are a major issue among elderly patients, and related to functional impairment induced by injury such as fall, institutionalization and of the lead to death [1]. Beside increasing age, there are many contributing factors causing gait and balance disturbances. Many studies have reported associations between poorer motor performance and cerebral small vessel disease (CSVD), especially for white matter hyperintensities (WMHs) [2–5], lacunes [6,7], and brain atrophy [8,9]. Cerebral microbleed (CMB), being a manifestation of CSVD, has been confirmed to play a pivotal role in the development of dementia and vascular cognitive impairment. However, the exploration of the relationship between movement disorder and CMB is still rare and conclusions are controversial. Only two studies have found the number of CMBs is related to gait disturbances [10,11] with the majority of studies not finding any influences of CMBs on motor performance [3,12,13].

With the two exceptions just mentioned, the correlation between the spatial distribution of CMB and gait disturbances remains poorly understood. Normal motor function relies on the integration of information from multiple areas of the brain. Several studies have shown that movement disorders are associated with lesions in the frontal lobe and basal ganglia [6,11] and that the caudate nucleus plays a significant role in walking speed [9]. Simultaneously, the pathophysiology of CMBs may differ according to their location, with deep or infratentorial CMBs attributable to hypertension, or a history of stroke and lobar (cortical-subcortical) CMBs to cerebral amyloid angiopathy (CAA) [14]. Consequently, a more comprehensive study to investigate the relationship in between different lesions of CMB and movement disorders, is opportune.

In contrast to walking and balance disturbances, upper extremity functions are still underestimated. With the aging of the population, increasing numbers of older adults may be affected by sensorimotor impairment, which negatively impacts their upper extremity performance and independence [15]. Limited study has found an association between WMH and upper extremity movement disorders [12]. As a marker of CSVD, CMB is closely related to WMH and can cause the required destruction in cortical and subcortical regions. But the relationship between the number and location of CMBs and upper extremity function has not been thoroughly studied.

This study, investigates the association between gait, balance and upper extremity functions as measured by quantitative tests and clinical rating scales and the number and location of CMBs to provide new insights into the importance of CMB in movement disorders.

2. Materials and Methods

2.1 Study Participants and Clinical Data Collection

From February 2019 to October 2019, 224 participants were recruited who presented for routine screening at the department of Neurology in Beijing Chao-Yang Hospital, Capital Medical University. All the included participants aged from 45 to 85 years could completed the movement tests and a brain magnetic resonance imaging (MRI) scan. The participants were excluded from the study if they had at least one of the following conditions: (1) dementia, including Alzheimer's disease, frontotemporal dementia, or dementia with Lewy bodies; Parkinson's disease (PD) or PD-plus syndrome; other neurodegenerative diseases such as multiple sclerosis or amyotrophic lateral sclerosis; (2) a history of severe stroke, large-vessel cerebrovascular diseases or lacunar syndrome within the previous six months; (3) diabetic neuropathy or neuropathies from other causes; peripheral vascular disease causing gait disturbances and/or upper limb motor function impairment; (4) intracranial space occupying lesion, cancer, toxicity, trauma or infections; (5) recent or current use of acetylcholine-esterase inhibitors, neuroleptic agents and L-dopa; (6) inability to finish the tests because of prominent visual, hearing, language impairment, or psychiatric disease; (7) heart failure, atrial fibrillation, myocardial infarction, severe nephrosis/liver diseases; (8) conditions not related to CSVDs affecting motor function (e.g., joint fusion, severe arthritis, rheumatic disease, joint replacement, or lumbar spondylopathy); (9) participants with poor MRI quality. Ethical approval was obtained from the Committee of Beijing Chao-Yang Hospital, Capital Medical University and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed for participation in the study.

2.2 Clinical Assessment

Baseline demographics and laboratory parameters of participants were assessed using structured interviews and laboratory examinations. A comprehensive questionnaire was administered by trained personnel to the patients. Data on demographic profiles (age, sex, height, weight) and a self-reported history of smoking, drinking, hypertension, hyperlipidemia, diabetes mellitus, ischemic stroke, coronary heart disease and medication use were collected and analyzed. Venous blood samples were routinely drawn after an overnight fast. Results of blood tests (white blood cell (WBC), neutrophil, hemoglobin, platelet, triglyceride, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), homocysteine, aspartate aminotransferase (AST); alanine transaminase (ALT); alkaline phosphatase (ALP); fasting blood glucose, glycosylated hemoglobin levels; urea; creatinine; uric acid; sodium; potassium; prothrombin time (PT); international normalized ratio (INR) and d-dimer) were all recorded.

2.3 MRI Acquisition

MRI data were acquired by a 3.0-T MRI scanner (Prisma 2016080316;Siemens AG, Erlangen, Germany) with the following sequences: T1-weighted imaging (repetition time [TR] = 2000.0 ms, echo time [TE] = 9.2 ms, slice thickness = 5 mm, and field of view [FOV] = 220 $\times$ 220 mm^2), T2-weighted imaging (TR = 4500.0 ms, TE = 84.0 ms, slice thickness = 5.0 mm, FOV = 220 $\times$ 220 mm^2), T2-weighted fluid-attenuated inversion recovery (FLAIR) (TR = 8000.0 ms, TE = 86.0 ms, slice thickness = 5.0 mm, FOV = 199 $\times$ 220 mm^2), diffusion-weighted imaging (DWI) (TR = 3300.0 ms, TE = 91.0 ms, slice thickness = 5.0 mm, FOV = 230 $\times$ 230 mm^2, b = 0 and 1000 s/mm^2), and susceptibility-weighted imaging (SWI) (TR = 27.0 ms, TE = 20.0 ms, slice thickness = 3.2 mm, FOV = 172 $\times$ 230 mm^2).

The MRI markers of CSVD including lacunes, WMH, CMB and enlarged perivascular space (EPVS) were rated according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) consensus criteria [16]. The degree of periventricular and deep WMH were evaluated separately and combined as Fazekas scores [17]. Severity of EPVS in areas of the centrum semiovale (CSO) and basal ganglia (BG) were assessed according to the semi-quantitative rating scale developed by the Edinburg group [18]. Brain atrophy was assessed via MRI visual ratings [19]. Brain atrophy and lacunes were divided into present or absent.

CMBs were identified as small, rounded hypointense lesions with clear margins and size ranging from 2 to 10 mm on SWI. The definition and rating of CMBs was determined and modified according to the Microbleed Anatomical Rating Scale [20]. The number of CMBs were recorded. The location of CMBs were categorized anatomically into lobar (frontal, parietal, occipital, and temporal), deep (basal ganglia and thalamus) and infratentorial. Two experienced neurologists who were blinded to all clinical data independently rated WMH, lacunes, CMBs, and PVS independently.

2.4 Assessment of Motor Performance

The quantitative analysis, recorded velocity (m/s), stride length (cm) and cadence (number of steps on a 4-m walkway), stride width (cm) using 4-m walkway and simultaneously measured the duration of the Timed-Up-and-Go (TUG) test. The participants walked twice at self-selected normal gait speed in low-heeled shoes. The stride length was defined as the distance between the heel points of two consecutive footprints and the stride width was the distance between one midpoint of a footprint and the line of progression of the opposite foot.

Table 1. Demographic, clinical and imaging characteristics of participants with CMBs.

Variables	All	CMB (-)	CMB (1–4)	CMB (>4)	*p*
	n = 224	n = 146	n = 65	n = 13	
Age, year	60.6 ± 10.5	59.2 ± 11.4	64.1 ± 7.7	58.6 ± 6.9	0.002
Sex, male, n (%)	144.0 (64.3)	92 (63.0)	42 (64.6)	10 (76.9)	0.603
Height, m	166.6 ± 8.2	166.4 ± 8.1	166.4 ± 8.6	169.7 ± 7.9	0.348
Weight, kg	71.6 ± 10.1	71.8 ± 9.7	70.2 ± 11.4	77.4 ± 6.2	0.036
BMI, kg/m^2	25.8 ± 3.9	26.1 ± 4.1	25.3 ± 2.9	25.5 ± 6.3	0.317
Hypertension, n (%)	142.0 (63.4)	87.0 (59.6)	43 (66.2)	12 (92.3)	0.055
DM, n (%)	85.0 (37.9)	56.0 (38.4)	26.0 (40.0)	3 (23.1	0.510
Hyperlipidemia, n (%)	41.0 (18.3)	25 (17.1)	13 (20.0)	3 (23.1)	0.795
CAD, n (%)	39.0 (17.4)	23 (15.8)	12 (18.5)	4 (30.8)	0.379
TIA, n (%)	26.0 (11.6)	15 (10.3)	8 (12.3)	3 (23.1)	0.377
Smoke, n (%)	107.0 (47.8)	68 (46.6)	31 (47.7)	8 (61.5)	0.585
Alcohol, n (%)	86.0 (38.4)	53 (36.3)	25 (38.5)	8 (61.5)	0.200
WMH, Fazekas score	1.0 (0, 2.0)	1.0 (0, 2.0)	2.0 (1.0, 4.0)	3.0 (2.0, 4.0)	<0.001
BG-EPVS	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	<0.001
CSO-EPVS	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	2.0 (1.0, 4.0)	3.0 (1.0, 4.0)	0.146
Lacunes, n (%)	96.0 (43.0)	48.0 (33.1)	36.0 (55.4)	12.0 (92.3)	<0.001
Brain atrophy, n (%)	116.0 (51.8)	58 (39.7)	47 (72.3)	11 (84.6)	<0.001

Data represent number (percentage), mean ± standard deviation, or median (interquartile range).
CMB, cerebral microbleed; MRI, magnetic resonance imaging; CSVD, cerebral small vessel disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; CAD, coronary artery disease; TIA, transient ischemic attacks; WMH, white matter hyperintensity; BG-EPVS, basal ganglia enlarged perivascular spaces; CSO-EPVS, centrum semiovale enlarged perivascular spaces.

Clinical rating of semi-quantitative scale assessments consisted of the Tinetti test with 17 items (9 for balance and 8 for gait) with a maximum score of 28. The maximum score of 28 indicates normal gait and balance, while the lower the score, the poorer the gait and balance performance. Balance was evaluated by a Short Physical Performance Battery (SPPB) test. The SPPB test was incorporated with standing balance, timed walk, and repeated chair stands. Balance was evaluated over a 10 s period by ability to a maintain side-by-side, semi-tandem, and tandem position standing with closed feet together.

Upper extremity function was assessed by 10-repeat pronation–supination time, 10-repeat finger-tapping time and 10-repeat opening and closing hands time.

2.5 Statistical Analysis

Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Chicago, IL, USA). Continuous variables with a normal distribution were presented as the mean with standard deviation (SD) and variables with a nonnormal distribution were presented as the median with the interquartile range. First, we compared the clinical information and imaging characteristics of the present of CMB were compared using one-way analysis of variance and Kruskal–Wallis tests for continuous data, and chi-square test or Fisher exact tests for categorical data. Second, the relationships between the number of CMB and movement disorders were investigated using single and multiple linear regression analysis adjusted for age, sex, height. Subsequent adjustments were made for WMH assessed by Fazekas score, score of BG-EPVS and CSO-EPVS, the presence of lacunar, brain atrophy, and other risk factors. The relationships between different locations of CMBs and gait, balance, and upper extremities disorder were studied and also adjusted for the covariates mentioned above. Statistical significance was established at $p < 0.05$.

3. Results

3.1 Demographic, Imaging, and Gait Characteristics

Characteristics of the participants are given in Table 1. The mean age was 60.6 ± 10.5 years, and 144 (64.3%) were male. CMBs appeared in 78 (34.8%) participants, 42 (53.8%) exhibited 1 CMB, 16 (20.5%) had 2 CMBs, 4 (5.1%) had 3 CMBs, 3 (3.8%) had 4 and 13 (16.7%) had more than 4 CMBs. For location of CMBs, 41 (18.3%) were located in lobes, 29 (13.0%) in the deep region, and 34 (15.2%) in infratentorial areas. Of the total number of CMBs observed 19 (25.3%) were mixed with lobar and deep/infratentorial location. The distribution of CMBs is given in Table 2. Inter-rater agreement for EPVSs, WMH, CMBs, and lacunes was assessed in a random sample of 50 individuals with a month's interval between the first and second readings. Kappa values for the inter-rater agreements were 0.81–0.89, indicating good reliability.

Table 2. Distributions and proportions of CMBs.

Lobe				Deep		Infratentorial	
41 (18.3)				29 (13.0)		34 (15.2)	
Frontal	Parietal	Occipital	Temporal	Basal ganglia	Thalamus	Brainstem	Cerebellum
11 (4.9)	7 (3.1)	10 (4.5)	19 (8.5)	28 (12.5)	28 (12.5)	23 (10.3)	16 (7.1)

Data given as represent number (percentage).

Participants were divided into three groups based on the number of CMBs 0, 1–4 and >4. Table 1 and **Supplementary Table 1** revealed no differences in demographics or laboratory tests except for age. In terms of other CSVD markers, there were significant different in WMH, BG-EPVS and the presence of lacunes and brain atrophy ($p <$ 0.001).

Table 3. Movement Performance Characteristics of Participants with CMBs.

Variables	All	CMB (-)	CMB (1–4)	CMB (>4)	*p*
	n = 224	n = 146	n = 65	n = 13	
Stride length, cm	63.3 (58.0, 68.0)	66.2 (60.0, 68.0)	60.0 (54.5, 68.0)	60.2 (60.0, 70.0)	0.046
Stride width, cm	10.8 (8.0, 18.0)	10.0 (7.0, 13.0)	13.0 (10.0, 15.0)	14.0 (10.0, 17.0)	<0.001
Cadence, steps	6.3 (5.9, 7.0)	6.2 (5.9, 6.8)	6.6 (5.9, 7.5)	6.1 (5.7, 6.7)	0.210
Gait velocity, m/sec	1.1 (0.9, 1.2)	1.1 (1.0, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.008
Tinetti test (range 0–28)	26.0 (24.3, 28.0)	28.0 (25.0, 28.0)	25.0 (24.0, 28.0)	24.0 (24.0, 25.0)	<0.001
Gait (range 0–12)	12.0 (11.0, 12.0)	12.0 (11.0, 12.0)	11.0 (11.0, 12.0)	11.0 (11.0, 11.0)	<0.001
Body balance (range 0–16)	15.0 (13.0, 16.0)	16.0 (14.0, 16.0)	13.0 (13.0, 14.0)	12.0 (11.0, 12.0)	<0.001
TUG test, sec	9.4 (8.3, 11.0)	8.7 (8.2, 10.6)	10.1 (8.9, 11.8)	10.3 (9.5, 12.2)	0.001
SPPB test (range 0–12)	11.0 (9.0, 12.0)	12.0 (10.0, 12.0)	10.0 (9.0, 12.0)	9.0 (9.0, 11.0)	<0.001
Standing balance (range 0–4)	3.0 (2.0, 4.0)	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	2.0 (2.0, 3.0)	<0.001
Timed walk (range 0–4)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)	0.918
Repeated chair stands (range 0–4)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	4.0 (3.0, 4.0)	3.0 (2.0, 4.0)	0.001
Repeated chair stands, sec	10.2 (9.4, 12.1)	10.0 (9.3, 11.3)	11.2 (9.8, 12.6)	12.4 (10.2, 13.1)	<0.001
Pronation–supination, sec	6.7 (5.3, 7.7)	6.2 (4.9, 7.2)	7.2 (6.3, 8.1)	7.4 (7.3, 8.2)	<0.001
Finger-tapping, sec	4.6 (3.8, 6.1)	4.2 (3.7, 5.7)	5.4 (4.2, 6.8)	5.5 (4.1, 6.2)	<0.001
Opening and closing hands time, sec	4.5 (4.1, 5.7)	4.4 (4.1, 5.2)	5.1 (4.2, 6.1)	4.5 (4.3, 5.9)	0.021

Data represent number (percentage), mean ± standard deviation, or median (interquartile range).

TUG, Timed-Up-and-Go; SPPB, Short Physical Performance Battery.

3.2 Relationship between Lower Extremity Function and CMB

The median gait velocity was 1.1 m/s, stride width 11.0 cm, stride length 63.3 cm and cadence 6.3 steps. The average time for the TUG test was 9.9 seconds. Higher numbers of CMBs had lower gait velocity, wider gait width, shorter gait length, and longer TUG time. As seen in Table 3, they had poor performance in the Tinetti and SPPB tests, as well as significant differences in the balance tests.

Single linear regression analysis showed that a number of CMBs was associated with gait velocity ($\beta = –0.117$; $p < 0.001$), gait width ($\beta = 0.500$, $p < 0.001$), and TUG testing time ($\beta = 0.172$, $p = 0.024$). With additional adjustment for sex, height, age, risk factors and other CSVD markers, the relationships were still significant. In semi-quantitative tests, the correlation between CMBs and Tinetti test scores was evident ($\beta = –0.150$; $p = 0.004$), particularly for balance function ($\beta = –0.160$; $p = 0.001$). The SPPB test was also associated with the number of CMBs ($\beta = –0.153$; $p = 0.002$) the coefficient for standing balance was also significant ($\beta = –0.096$; $p = 0.001$) (Table 4).

Wider stride width and lower gait velocity were associated with CMBs in the frontal ($\beta = 0.111$, –0.816; $p = 0.040$, 0.006, respectively) and temporal lobes ($\beta = 2.172$, –1.226; $p = 0.013$, 0.025, respectively) and the relationships were also significant in basal ganglia and infratentorial areas with stride width ($\beta = 2.052$, 1.584; $p = 0.006$, 0.024, respectively). Meanwhile, stride length had correlations with CMBs in parietal and temporal areas ($\beta = –8.646$, –3.968; $p = 0.002$, 0.002, respectively), given in Table 5. In the semi-quantitative scale measurement, it was found that the Tinetti and SPPB tests more likely had associations with lobe (parietal and temporal) and infratentorial CMBs. Moreover, the gait function measured by the Tinetti test was strictly associated with CMB in temporal areas ($\beta = –0.311$; $p = 0.004$) which was consistent with previous quantitative measurements of gait. Balance function measured by the Tinetti and SPPB tests had relationships with parietal regions ($\beta = –0.968$, –0.786; $p = 0.042$, 0.023, respectively) and infratentorial areas ($\beta = –0.609$, –0.476; $p = 0.011$, 0.005, respectively).

Table 4. Association between number of CMBs and performance of gait, balance and upper extremity.

	CMBs(n)					
	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Stride length, cm	–0.348	0.207	–0.480	0.049	–0.099	0.101
Stride width, cm	0.500	<0.001	0.471	0.000	0.287	0.020
Cadence, steps	0.016	0.295	0.043	0.409	0.062	0.428
Gait velocity, m/sec	–0.117	<0.001	–0.236	0.001	–0.310	0.004
Tinetti test	–0.254	<0.001	–0.249	<0.001	–0.150	0.004
Gait	–0.069	<0.001	–0.068	<0.001	–0.042	0.005
Body balance	–0.185	<0.001	–0.181	<0.001	–0.160	0.001
TUG test, sec	0.172	0.024	0.173	0.015	0.162	0.018
SPPB test	–0.188	0.001	–0.183	0.001	–0.153	0.002
Standing balance	–0.121	<0.001	–0.177	<0.001	–0.096	0.001
Timed walk	–0.004	0.740	–0.031	0.643	–0.041	0.672
repeated chair stands	–0.068	0.001	–0.066	0.002	–0.058	0.005
repeated chair stands time, sec	0.238	0.001	0.232	0.001	0.209	0.001
Pronation-supination time, sec	0.204	0.001	0.213	0.001	0.143	0.018
Finger-tapping time, sec	0.092	0.101	0.124	0.055	0.156	0.071
Opening and closing hands time, sec	0.075	0.130	0.118	0.072	0.155	0.069

β, standardized β coefficient. Model 1 represents the unadjusted relation between CMBs (n) and gait, balance and upper extremity. Model 2 is with adjustment for age, sex and height. Model 3 is with additional adjustment for WMH, EPVS and the present of lacunar and brain atrophy.

Table 5. Association between location of CMB and performance of upper and lower extremity.

N of CMBs					Tinetti test				SPPB test			
	Length, cm	Stride width, cm	Gait velocity, m/sec	Cadence, steps	Total score	Gait	Balance	TUG test, sec	Total score	Standing balance	Repeated chair stands	Pronation–supination
	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)	β (p value)
Lobe	–4.146 (0.001)	1.845 (0.004)	–1.602 (0.001)	0.042 (0.515)	–0.886 (0.001)	–0.351 (<0.001)	–0.536 (0.015)	0.809 (0.011)	–0.712 (0.006)	–0.425 (0.008)	1.128 (0.001)	0.724 (0.005)
Frontal	–0.014 (0.805)	0.111 (0.040)	–0.816 (0.006)	0.032 (0.627)	–0.073 (0.216)	–0.276 (0.030)	–0.044 (0.454)	0.051 (0.433)	–0.042 (0.498)	–0.015 (0.887)	0.136 (0.034)	0.714 (0.005)
Parietal	–8.646 (0.002)	0.097 (0.124)	–0.015 (0.713)	0.084 (0.192)	–1.291 (0.031)	–0.123 (0.056)	–0.968 (0.042)	0.089 (0.114)	–1.608 (0.004)	–0.786 (0.023)	2.073 (0.007)	1.930 (0.005)
Occipital	–0.035 (0.533)	0.018 (0.774)	–0.007 (0.665)	0.014 (0.527)	–0.090 (0.122)	–0.100 (0.096)	–0.049 (0.381)	0.011 (0.852)	–0.008 (0.892)	–0.098 (0.112)	–0.001 (0.998)	0.089 (0.171)
Temporal	–3.968 (0.002)	2.172 (0.013)	–1.226 (0.025)	0.013 (0.838)	–0.871 (0.021)	–0.311 (0.004)	–0.102 (0.071)	0.062 (0.291)	–0.878 (0.012)	–0.581 (0.017)	–0.117 (0.022)	0.181 (0.002)
Deep	–0.027 (0.660)	1.860 (0.013)	–0.011 (0.065)	0.031 (0.638)	–0.084 (0.194	–0.076 (0.192)	–0.100 (0.084)	0.045 (0.461)	–0.005 (0.092)	–0.016 (0.728)	–0.049 (0.450)	1.215 (0.001)
Basal ganglia	–0.019 (0.743)	2.052 (0.006)	–0.023 (0.125)	0.017 (0.792)	–0.096 (0.094)	–0.104 (0.098)	–0.112 (0.048)	0.064 (0.278)	–0.013 (0.832)	–0.008 (0.798)	–0.040 (0.538)	1.219 (0.001)
Thalamus	–0.031 (0.591)	0.036 (0.561)	–0.006 (0.718)	0.096 (0.142)	–0.015 (0.798)	–0.014 (0.816)	–0.033 (0.568)	0.005 (0.924)	–0.060 (0.315)	–0.095 (0.114)	–0.039 (0.541)	0.041 (0.513)
Infratentorial	–0.091 (0.116)	1.584 (0.024)	–0.002 (0.213)	0.009 (0.884)	–0.748 (0.013)	–0.101 (0.105)	–0.609 (0.011)	0.892 (0.021)	–0.706 (0.011)	–0.476 (0.005)	–1.007 (0.008)	0.093 (0.148)
Brainstem	–0.066 (0.290)	1.604 (0.049)	–0.001 (0.334)	0.036 (0.569)	–0.088 (0.121)	–0.080 (0.189)	–0.071 (0.214)	0.083 (0.164)	–0.108 (0.069)	–0.483 (0.017)	–0.109 (0.089)	0.025 (0.695)
Cerebellum	–0.077 (0.172)	0.089 (0.157)	–0.006 (0.516)	0.066 (0.299)	–0.107 (0.065)	–0.357 (0.359)	–0.660 (0.047)	1.101 (0.038)	–0.071 (0.236)	–0.091 (0.132)	–0.085 (0.190)	0.103 (0.106)

β, standardized β coefficient.

Adjusted for age, sex, height, WMH, EPVS and the present of lacunar and brain atrophy.

3.3 Relationship between Upper Extremity Function and CMB

Pronation-supination, finger-tapping and opening and closing of hands were performed giving medians of 6.7, 4.6 and 4.5 sec, respectively, with a significant difference between CMB and 10 repeated pronation–supination, finger-tapping and opening and closing hands time, $p < 0.05$.

Multiple linear regression analysis showed a significant correlation between the time of 10-repeat pronation–supinations ($\beta = 0.143$; $p = 0.018$) and the number of CMBs. But this relationship did not apply to the 10-repeat finger-tapping and the 10-repeat opening and closing hands time. In the analysis of the different distributions of CMBs, lesions located in frontal, parietal, and temporal areas and the basal ganglia ($\beta = 0.714$, 1.930, 0.181, 1.219; $p = 0.005$, 0.005, 0.002, 0.001, respectively) were associated with impairments of upper extremity function.

4. Discussion

In this study, we reported that CMBs, particularly located in the frontal and temporal lobes, basal ganglia and infratentorial areas, were associated with gait dysfunction and balance problems, regardless of the presence of other CSVD categories. A novel finding was that CMBs located in the lobes (frontal, parietal and temporal) and basal ganglia correlated with motor disorder of the upper extremity. This indicates that CMB can impair gait, balance and upper extremity function and the analysis of different regions reveals the possible pathogenesis of CMBs. This type of CSVD needs to be identified and managed appropriately in the treatment of movement disorders.

In previous studies, the relationships between individual CSVD imaging markers and gait performance remained controversial [3,8,12,21]. The association between WMH and lacunes and gait has consistently been reported [12,22–25]. However, just a few studies have shown that the presence of CMB magnifies the effects of the volume of WMH on gait but not on postural stability [25]. In studies focusing specifically on CMBs and movement disorders, it was observed that the presence of CMBs were associated with a slower walking speed [26], and a longer stride time and stance phase [27]. According to another study, a higher number of CMBs, measured by T2*-weighted gradient-echo (GRE) sequences, was associated with shorter stride length and worse performance on Tinetti and TUG tests [11]. In the current research, it was discovered that the number of CMBs had correlations with both gait and balance disorders. To examine the specific reasons for this, previous studies were reviewed and several differences identified that need to be addressed. First, the incidence of CMBs in previous studies was lower than in this study, which may affect the research about the location of CMBs. Second, some studies detected CMBs using GRE, which is not as sensitive in terms of number and distribution as SWI. Third, CMBs in most patients are not severe enough to have a functional impact, so just examining general gait parameters is not sufficient for the detection of early changes in gait performance for people with CMBs. During this study, gait function was measured with both quantitative and semi-quantitative methods which were more comprehensive for the detection of gait disorders. The effect of increased number of CMB on motor function was explored and significant differences were found. Furthermore, the SPPB test measured gait and balance, providing more validity, reliability and responsiveness to assess physical function, increasing accuracy of any relationship between CMBs and motor function [28].

When compared to the lower extremity, the association between CMBs and upper extremity has not been investigated. In this study, it was demonstrated that CMBs in the frontal, parietal, temporal and basal ganglia, were associated with the function of pronation-supination. Many studies have concluded that people with mild cognitive impairment have a greater reduction in finger dexterity [29]. A further study from the Rehabilitative Impairment Study of the Elderly (RISE) study indicated participants with mild cognition impairment had significantly affected reaction on reactions times and pronation-supination of the hands [30]. As one important cause of cognitive impairment, CSVD may also have an important impact on hand function. Currently investigations between the upper extremity and CSVD are still uncommon. One of the studies involving 30 individuals from the Austrian Stroke Prevention Study, Purdue's Pegboard Test was used to assess upper extremity function. The results showed a positive correlation between finger movement and increasing WMH in the frontal lobe, but the correlation was not significant [2]. Another study found that WMH was associated with motor deficits in pronation–supination, as well as brain atrophy associated with both pronation–supination and finger-tapping, but other types of CSVD were not adjusted [8,13]. In this study, we examined the relationship between CMB and upper extremity function independently and the sample size appropriately expanded.

CMBs seem to play an important role in motor function, but the mechanisms are still not to be fully elucidated. The direct damage of CMB lesions on brain tissues may cause myelin loss, neuronal loss, variable extent of gliosis, and lead to disordered brain function [31]. The products derived from blood extravasations, especially ions, can also lead to a series of secondary brain injuries, such as blood brain barrier (BBB) breakdown and inflammatory activation associated with other categories of CSVD and neurodegenerative pathologies [32]. Additional to direct damage to brain, CMBs are also found to have associations with the disruption of white matter and impairment of brain networks, including longer path length, and less global efficiency with diffusion tensor imaging (DTI) and ^{11}C-Pittsburgh Compound-B positron emission tomography (PIB PET) [33,34]. A study from Campo *et al.* [35]

has found that increased Aβ deposition in motor related regions, including posterior and anterior putamen, occipital cortex, precuneus, and anterior cingulate, have association with decreased gait speed and De Laat's study [11] found CMBs, especially those located in the frontal lobe and basal ganglia (and thalamus), interfered with gait function. This was consistent with the results reported here. A further study in patients with CAA also declared that brain network impairment worsened from posterior to frontal connections (observed by fractional anisotropy) with increasing disease severity [36]. With that exception, this study also found that lesions in the temporal lobe and infratentorial were correlated with gait and balance disturbances. It was found that the temporal lobe has many neuronal networks which connect visual and vestibular signals and control gait performance and maintain balance [37]. Simultaneously, it is known that the cerebellum and brainstem are also important regions in the control of balance in the body. So, CMB in temporal and infratentorial areas should also be taken seriously.

Takakusaki [38] has pointed out that the upper extremity had sophisticated abilities depending on integrated visual, somatosensory, and action systems of motor cortex, as well as its subcortical connections with brainstem and cerebellum. The process of pronation–supination involves hand movements with visuospatial and coordination components, strength, and speed, and may require the overall function of an intact nervous system. In agreement with the findings reported here, CMBs involved multiple brain regions that controlled motor, sensory, and visual functions associated with hand movements.

The strength of this study includes the use of high-resolution MRI, evaluating both the number and location of CMBs and improved accuracy of imaging markers of CMBs. Another strength was the exploring of relationships between CMBs and motor performances in gait, balance and upper extremity which are rarely discussed. There are limitations to this study. First, its cross-sectional design precluded assumptions of causality. Longitudinal studies are needed to further explore this and to obtain a better insight into optimal timing with respect to prevention and disease progression. Second, although more accurate MRI was employed, visual ratings of CSVD imaging might have introduced errors which could not be overruled, better imaging equipment and software packages are needed to assess CSVD quantitatively so as to explore the correlations more rigorously. Third, the measuring equipment was not accurate enough which might induce error of movement data and more advanced equipment should be used. Fourth, considering lobar CMBs indicate CAA are associated with Alzheimer's disease and vascular cognitive impairment. Therefore, in exploring the relationship between CMB and movement disorder, cognitive impairment should be considered and the influence of cognitive function should be ruled out in future research. Finally, only one hospital provided patients which limited the generalizability of the results.

5. Conclusions

The present study indicated that CMBs, particularly in the frontal lobe, temporal lobe, basal ganglia and infratentorial areas, were associated with gait and balance dysfunction independent of other coexisting markers of CSVD. It is also the first study to demonstrate that CMBs contribute to upper extremity disorder. The influence of CMBs on movement impairment should be confirmed in future explorations and these factors should be considered during the development of new interventions.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author Contributions

Y-TH drafted the manuscript and conducted the statistical analyses. W-LH managed the database and provided additional statistical expertise. Y-TH, S-NY, Y-L, W-Q and L-Y contributed to the conception and design of the study and interpretation of the data. Y-L provided expertise on brain imaging analysis. W-LH was the principal investigator of the study and was responsible for the study conception and interpretation of data and had final responsibility for the decision to submit for publication. All authors contributed to editorial changes in the manuscript. All authors provided final approval for the version of the manuscript submitted for publication and agree to be accountable for the work.

Ethics Approval and Consent to Participate

Ethical approval (2020-3-27-1) was obtained from the Committee of Beijing Chao-Yang Hospital, Capital Medical University. All methods were carried out in accordance with the Declaration of Helsinki and informed consent was obtained from all the study participants or their legal guardians for participation in the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2204082.

References

[1] van der Holst HM, van Uden IWM, Tuladhar AM, de Laat KF, van Norden AGW, Norris DG, *et al*. Factors Associated With 8-Year Mortality in Older Patients With Cerebral Small Vessel Disease: The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) Study. JAMA Neurology. 2016; 73: 402–409.

[2] Linortner P, Fazekas F, Schmidt R, Ropele S, Pendl B, Petrovic K, *et al*. White matter hyperintensities alter functional organization of the motor system. Neurobiology of Aging. 2012; 33: 197.e1–9.

[3] Kim YJ, Kwon HK, Lee JM, Cho H, Kim HJ, Park HK, *et al*. Gray and white matter changes linking cerebral small vessel disease to gait disturbances. Neurology. 2016; 86: 1199–1207.

[4] Pasi M, van Uden IWM, Tuladhar AM, de Leeuw FE, Pantoni L. White Matter Microstructural Damage on Diffusion Tensor Imaging in Cerebral Small Vessel Disease: Clinical Consequences. Stroke. 2016; 47: 1679–1684.

[5] van der Holst HM, Tuladhar AM, Zerbi V, van Uden IWM, de Laat KF, van Leijsen EMC, *et al*. White matter changes and gait decline in cerebral small vessel disease. NeuroImage. Clinical. 2017; 17: 731–738.

[6] de Laat KF, van Norden AGW, Gons RAR, van Oudheusden LJB, van Uden IWM, Bloem BR, *et al*. Gait in elderly with cerebral small vessel disease. Stroke. 2010; 41: 1652–1658.

[7] Smith EE, O'Donnell M, Dagenais G, Lear SA, Wielgosz A, Sharma M, *et al*. Early cerebral small vessel disease and brain volume, cognition, and gait. Annals of Neurology. 2015; 77: 251–261.

[8] Su N, Liang X, Zhai FF, Zhou LX, Ni J, Yao M, *et al*. The consequence of cerebral small vessel disease: Linking brain atrophy to motor impairment in the elderly. Human Brain Mapping. 2018; 39: 4452–4461.

[9] Dumurgier J, Crivello F, Mazoyer B, Ahmed I, Tavernier B, Grabli D, *et al*. MRI atrophy of the caudate nucleus and slower walking speed in the elderly. NeuroImage. 2012; 60: 871–878.

[10] Chiu WT, Chan L, Wu D, Ko TH, Chen DYT, Hong CT. Cerebral Microbleeds are Associated with Postural Instability and Gait Disturbance Subtype in People with Parkinson's Disease. European Neurology. 2018; 80: 335–340.

[11] de Laat KF, van den Berg HAC, van Norden AGW, Gons RAR, Olde Rikkert MGM, de Leeuw FE. Microbleeds are independently related to gait disturbances in elderly individuals with cerebral small vessel disease. Stroke. 2011; 42: 494–497.

[12] Pinter D, Ritchie SJ, Doubal F, Gattringer T, Morris Z, Bastin ME, *et al*. Impact of small vessel disease in the brain on gait and balance. Scientific Reports. 2017; 7: 41637.

[13] Su N, Zhai FF, Zhou LX, Ni J, Yao M, Li ML, *et al*. Cerebral Small Vessel Disease Burden Is Associated with Motor Performance of Lower and Upper Extremities in Community-Dwelling Populations. Frontiers in Aging Neuroscience. 2017; 9: 313.

[14] Ding J, Sigurdsson S, Garcia M, Phillips CL, Eiriksdottir G, Gudnason V, *et al*. Risk Factors Associated With Incident Cerebral Microbleeds According to Location in Older People: The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. JAMA Neurology. 2015; 72: 682–688.

[15] Lawrence EL, Dayanidhi S, Fassola I, Requejo P, Leclercq C, Winstein CJ, *et al*. Outcome measures for hand function naturally reveal three latent domains in older adults: strength, coordinated upper extremity function, and sensorimotor processing. Frontiers in Aging Neuroscience. 2015; 7: 108.

[16] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet. Neurology. 2013; 12: 822–838.

[17] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR. American Journal of Roentgenology. 1987; 149: 351–356.

[18] Zhu YC, Tzourio C, Soumaré A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. Stroke. 2010; 41: 2483–2490.

[19] Rhodius-Meester HFM, Benedictus MR, Wattjes MP, Barkhof F, Scheltens P, Muller M, *et al*. MRI Visual Ratings of Brain Atrophy and White Matter Hyperintensities across the Spectrum of Cognitive Decline Are Differently Affected by Age and Diagnosis. Frontiers in Aging Neuroscience. 2017; 9: 117.

[20] Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, *et al*. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology. 2009; 73: 1759–1766.

[21] Rosario BL, Rosso AL, Aizenstein HJ, Harris T, Newman AB, Satterfield S, *et al*. Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2016; 71: 968–973.

[22] Shen DC, Wu SL, Shi YZ, Wang S, Zhang YM, Wang CX. The correlation between white matter hyperintensity and balance disorder and fall risk: An observational, prospective cohort study. Chronic Diseases and Translational Medicine. 2016; 2: 173–180.

[23] Moniruzzaman M, Kadota A, Segawa H, Kondo K, Torii S, Miyagawa N, *et al*. Relationship Between Step Counts and Cerebral Small Vessel Disease in Japanese Men. Stroke. 2020; 51: 3584–3591.

[24] de Laat KF, Tuladhar AM, van Norden AGW, Norris DG, Zwiers MP, de Leeuw FE. Loss of white matter integrity is associated with gait disorders in cerebral small vessel disease. Brain: a Journal of Neurology. 2011; 134: 73–83.

[25] Choi P, Ren M, Phan TG, Callisaya M, Ly JV, Beare R, *et al*. Silent infarcts and cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study. Stroke. 2012; 43: 1505–1510.

[26] Stijntjes M, de Craen AJM, van der Grond J, Meskers CGM, Slagboom PE, Maier AB. Cerebral Microbleeds and Lacunar Infarcts Are Associated with Walking Speed Independent of Cognitive Performance in Middle-Aged to Older Adults. Gerontology. 2016; 62: 500–507.

[27] Li P, Wang Y, Jiang Y, Zhang K, Yang Q, Yuan Z, *et al*. Cerebral small vessel disease is associated with gait disturbance among community-dwelling elderly individuals: the Taizhou imaging study. Aging. 2020; 12: 2814–2824.

[28] Treacy D, Hassett L. The Short Physical Performance Battery. Journal of Physiotherapy. 2018; 64: 61.

[29] Suzumura S, Osawa A, Maeda N, Sano Y, Kandori A, Mizuguchi T, *et al*. Differences among patients with Alzheimer's disease, older adults with mild cognitive impairment and healthy older adults in finger dexterity. Geriatrics & Gerontology International. 2018; 18: 907–914.

[30] Rycroft SS, Quach LT, Ward RE, Pedersen MM, Grande L, Bean JF. The Relationship Between Cognitive Impairment and Upper Extremity Function in Older Primary Care Patients. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2019; 74: 568–574.

[31] Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. Nature Reviews. Neurology. 2018; 14: 387–398.

[32] Fisher M. Cerebral microbleeds: where are we now? Neurology. 2014; 83: 1304–1305.

[33] Heringa SM, Reijmer YD, Leemans A, Koek HL, Kappelle LJ, Biessels GJ, *et al*. Multiple microbleeds are related to cerebral network disruptions in patients with early Alzheimer's disease. Journal of Alzheimer's Disease: JAD. 2014; 38: 211–221.

[34] Reijmer YD, Fotiadis P, Martinez-Ramirez S, Salat DH, Schultz A, Shoamanesh A, *et al*. Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. Brain: a Journal of Neurology. 2015; 138: 179–188.

[35] Del Campo N, Payoux P, Djilali A, Delrieu J, Hoogendijk EO, Rolland Y, *et al*. Relationship of regional brain β-amyloid to gait speed. Neurology. 2016; 86: 36–43.

[36] Reijmer YD, Fotiadis P, Riley GA, Xiong L, Charidimou A, Boulouis G, *et al*. Progression of Brain Network Alterations in Cerebral Amyloid Angiopathy. Stroke. 2016; 47: 2470–2475.

[37] Annweiler C, Montero-Odasso M, Bartha R, Drozd J, Hachinski V, Beauchet O. Association between gait variability and brain ventricle attributes: a brain mapping study. Experimental Gerontology. 2014; 57: 256–263.

[38] Takakusaki K. Functional Neuroanatomy for Posture and Gait Control. Journal of Movement Disorders. 2017; 10: 1–17.