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Original Article

Risk factors, clinical characteristics and MRI features of cerebral small vessel disease

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Abstract: Objective: To investigate the risk factors, clinical characteristics and MRI features associated with cerebral small-vessel disease (CSVD). Methods: Patients diagnosed and hospitalized with CSVD between March 2013 and August 2015 were collected. After screening, 100 males and 56 females were selected. Their ages ranged from 62 to 91 years and the mean was 72.7 ± 8.1 years. Medical histories were gathered. The relationships between risk factors, clinical signs and symptoms, CSVD-associated lesions and the pathological severity were analyzed via logistic regression. Results: Hypertension and high alcohol consumption were independent risk factors for white matter lesions, while hypertension, diabetes, hyperlipidemia and age were independent risk factors for lacunar infarcts (LIs). Palsy was mainly associated with LI number in the brain stem and cerebellum, while periventricular white matter hyperintensity (PVH) and deep white matter hyperintensity (DWMH) were significantly correlated with cognitive dysfunction. Gait disorders were weakly correlated with PVH and LI number in the basal ganglia, and urinary incontinence was significantly correlated with DWMH and subcortical LI number. Cognitive dysfunction was significantly correlated with palsy, gait disorder, limb weakness and incontinence. Conclusions: Age and hypertension were major risk factors for CSVD. The distribution and severity of lesions was consistent with the clinical signs and symptoms. Palsy, urinary incontinence and gait disorders were correlated with the number of LIs in the brainstem/cerebellum, the subcortex and the basal ganglia, respectively. This data should further our understanding of the risk factors and clinical manifestations of CSVD, thereby improving diagnosis, prevention and treatment.

Keywords: Cerebral small-vessel disease, lacunar infarction, leukoaraiosis

Introduction

Cerebral small-vessel disease (CSVD) is a syndrome encompassing clinical, cognitive, radiological and pathological features that result from lesions in and around small blood vessels in the brain; capillaries, venules, arterioles and small arteries up to 200 μm in diameter [1]. CSVD accounts for the etiology of 1/4 of acute ischemic strokes [2, 3] and it has been recognized as serious disease for the past 15 years [4]. Despite this, its basic causes and risk factors remain somewhat unclear. Diabetes, hyperlipoidemia, hypertension and old age, which are major risk factors for cerebrovascular disease [5-8] in general, could also be factors for CSVD; particularly, age and hypertension are thought to be important for CSVD. Khan *et al.* [9] studied the vascular risk factors for CSVD and its subtypes, finding that hypertension was more commonly associated with subcortical ischemic vascular dementia (SIVD) when it was due to small-vessel disease, while hyperlipidemia, smoking, myocardial infarction and peripheral vascular disease were more frequent in SIVD patients with large-vessel disease. Furthermore, the risks for different subtypes were also different: specifically, a history of hypertension was associated with lacunar infarction in combination with white matter lesions (WMLs), whereas hyperlipidemia, diabetes and myocardial infarction were associated with WMLs unaccompanied by lacunar infarcts.

The main features of CSVD-associated cognitive dysfunction are delayed memory, impaired attention and executive function, reduced information processing speed, and neurological dis-

orders such as impaired balance, urinary incontinence and affective disorders, amongst others [10, 11]. The presence of multiple lacunar infarcts (LIs) and subcortical ischemic WMLs (leukoaraiosis), expansion of vascular space (EPVS) and damage to the blood-brain barrier are among the major characteristic features of CSVD pathology [12]. LIs and WMLs are most commonly used to identify the disease since they are easily imaged, especially via magnetic resonance imagining (MRI) [13]. A study based on patients who suffered from stroke or transient cerebral ischemia for 3-6 months found that cognitive impairment was associated with deep WMLs, but not with the number and volume of cerebral infarctions [14]. Some researchers have suggested that cerebral WMLs have less effect on cognitive dysfunction than LIs, when small-vessel lesions are the cause of the dysfunction [15], or that cognitive dysfunction due to small-vessel lesions was not correlated at all with cerebral white matter lesions [16]. In contrast, Sabri et al. found that impaired cognition was associated with both cerebral WMLs and LIs [17]. The discrepancy may be due to differences in the study designs, methodologies and evaluation criteria.

This work examined CSVD in terms of risk factors, MRI imaging features and cognitive and neurological dysfunction in order to establish its clinical and radiological characteristics, and to guide development of unified and operable diagnostic criteria, which would allow for improved diagnosis and treatment.

Materials and methods

Subjects

Patients diagnosed with CSVD and admitted to the neurology department of Inner Mongolia Autonomous Region People's Hospital, from March 2013 to August 2015, were collected and screened. Of the selected patients, 100 were male and 56 were female. Their ages ranged from 62 to 91 years and the mean age was 72.7 ± 8.1 years. All selected patients cooperated with the study and agreed to magnetic resonance imaging (MRI) and other appropriate laboratory examinations. Complete relevant medical histories and laboratory results were collected and standard MRI scans were performed in our hospital.

Inclusion criteria

Inclusion criteria included radiologically confirmed patients with CSVD, with imaging investigations showing at least one of the following: LIs, WMLs, cerebral microbleeds (CMBs) or EPVS. Furthermore, there were no cortical or watershed infarctions, and no subcortical lesions larger than 15 mm in diameter. Written informed consent was obtained from all participants.

Exclusion criteria

(1) Closed craniocerebral injury, brain tumors, multiple sclerosis or other diseases involving the central nervous system; (2) severe liver, kidney or other systemic disease affecting cognitive functions; (3) abusers of alcohol or other psychoactive drugs; (4) obvious vision or hearing impairment, making them unable to complete the relevant neuropsychological examinations; (5) combination with other disease which might lead to cognitive dysfunction; (6) contraindications for MRI or other reasons that patients cannot undergo MRI; (7) presence of other intracranial diseases, such as cerebral hemorrhage and subarachnoid hemorrhage, according to imaging examinations; (8) patients or their families unwilling to participate in the study.

*Examination procedures (**Figure 1**)*

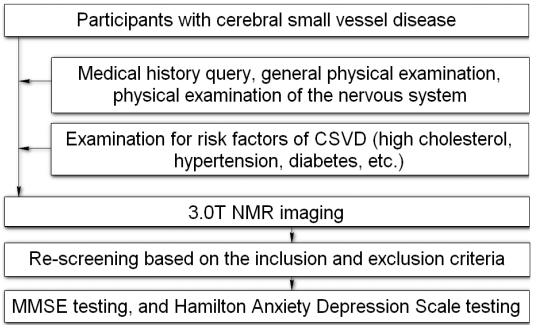

Figure 1. Outline of study procedures.

Study details and methods

Clinical data including sex, age, time in education (years), current medical history, smoking and drinking history, past medical history (hypertension, diabetes, hyperlipidemia, transient ischemic attack [TIA] or stroke), family history, spirituality drugs and hormone history for the selected participants were conventionally recorded.

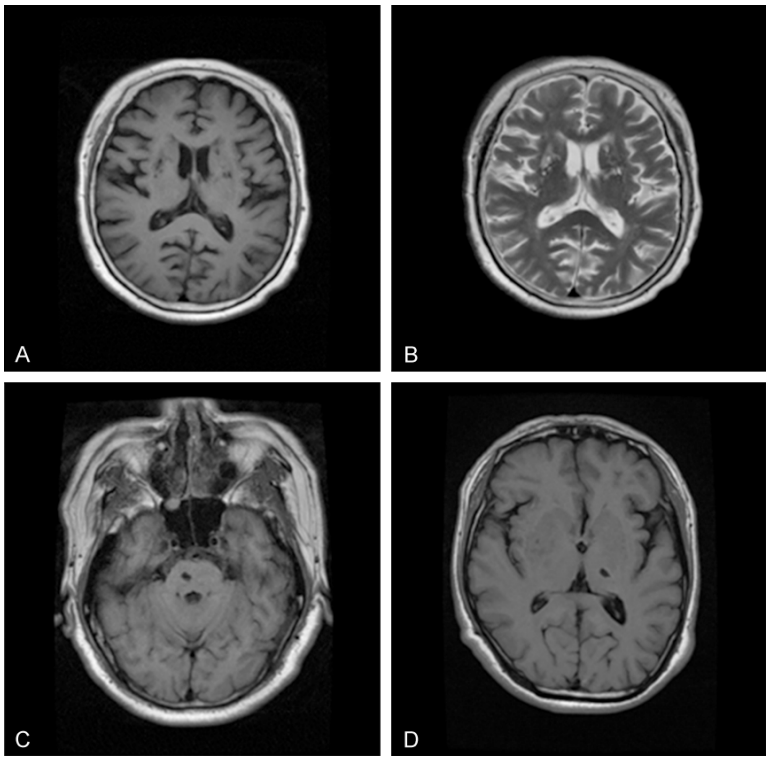

Figure 2. Representative MRI images showing lacunar infarcts (LIs) and white matter lesions. A. LIs in the basal ganglia (T1WI). B. LIs and WMLs in the basal ganglia (T2WI). C. LI in the thalamus (T1WI). D. LI in the pons (T1WI).

Diagnostic criteria for cerebrovascular disease and relevant risk factors included:

Hypertension: previous diagnosis of hypertension or currently taking antihypertensive drugs, or if not using antihypertensives, systolic pressure ≥140 mm Hg and/or a diastolic pressure ≥90 mm Hg.

Diabetes: fasting blood glucose ≥7.0 mmol/L or postprandial glucose ≥11.1 mmol/L or on hypoglycemic medication or previous diagnosis of diabetes; at least one of these criteria was required.

Hyperlipidemia: (1) triglycerides, cholesterol or LDL cholesterol increased; (2) receiving lipid-lowering drug; (3) previous history of hyperlipidemia.

Smoking: current number of cigarettes per day ≥10, which has been sustained for over 6 months.

High alcohol consumption: average daily alcohol consumption >2 U for men and >1 U for women.

Previous stroke or TIA: previous stroke producing the standard continuous stroke-related symptoms of the National Institute of Neurological Disorders and Stroke (NINDS), and confirmed by videography; TIA was also based on the NINDS standard, namely showing stroke-related symptoms within 24 h, but without abnormal imaging results.

Clinical symptoms and signs

The following were the main clinical symptoms and signs that were recorded: limb weakness, gait disorders, dysarthria, drinking cough, urinary incontinence, pathological laughing and crying, and cognitive dysfunction. Assessment of cognitive function and mood was based on mini-mental status examination (MMSE) and the Hamilton Anxiety and Depression Scale; illiteracy < 17 points, primary < 20 points, secondary and higher < 24 points. A gait disorder was defined as difficulty walking, awkward gait, and impaired balance when walking or turning without cerebellar ataxia and deep sensory impairment. Urinary incontinence was defined as impaired control of urination and involuntary urine flow; non-central incontinence was excluded by careful examination of the patient's medical history.

NMR imaging

All admitted patients underwent brain MRI examination using a 3.0 T superconducting MRI scanner (GE, Signa-HDx, USA). Serial axial T2-weighted, T1-weighted, fluid attenuated inversion recovery (FLAIR) and diffusion weighted pulse sequences were used. Layer spacing was 1.5 mm for all sequences.

Evaluation of lacunar infarction

An LI was defined as a brain lesion present during hospitalization that had a long T1 and T2 (similar to cerebrospinal fluid) and measured between 3 and 20 mm in diameter [18]; The LI severity was graded according to the number of

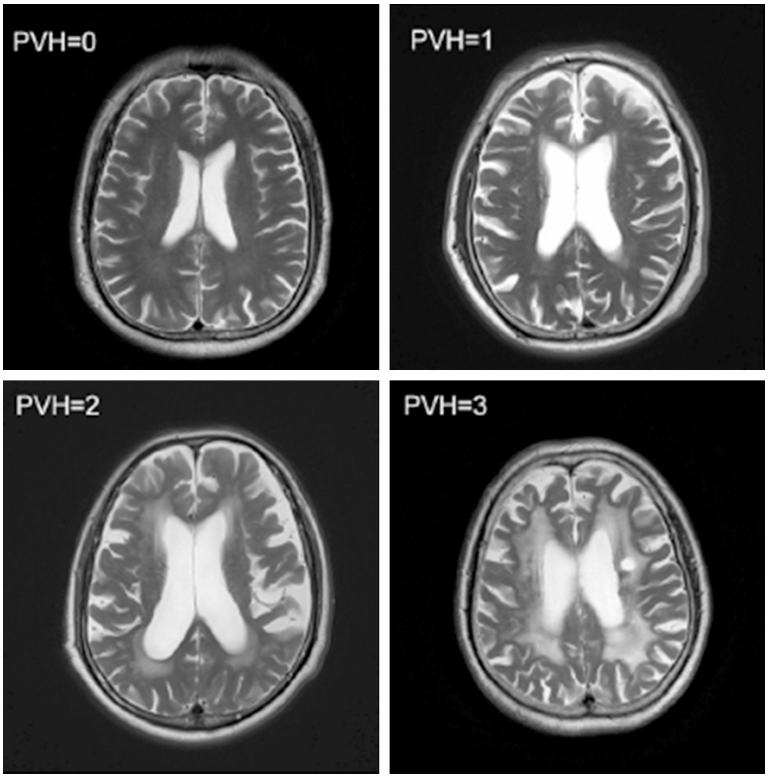

Figure 3. Representative MRI images showing periventricular hyperintensity signals (PVH; graded 0 to 3).

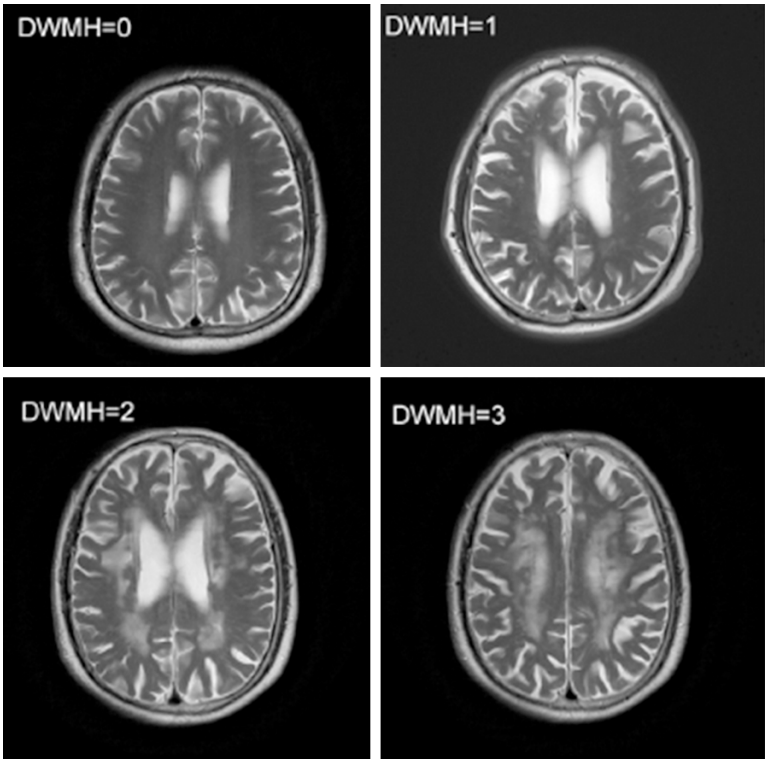

Figure 4. Representative MRI images showing deep white matter hyperintensity signals (DWMH; graded 0 to 3).

LIs: 0 = no LIs, 1 = 1 to 4 LIs, 2 = 5 to 10 LIs, 3 = over 10 LIs. Images were divided into a number of regions representing the cortex/subcortex (including lobes and centrum semiovale), basal ganglia (including internal capsule and thalamus), brainstem and cerebellum (**Figure 2**).

WML grading

T2WI or FLAIR sequences showed hyperintensity lesions with diameters of >5 mm in the periventricular and subcortical white matter. Periventricular and deep WMLs were independently graded according to the methodology of Fazekas [19] and the modified rating scale (0-3) of Scheltens [20]. Periventricular hyperintensity (PVH) signals were scored as 0 for no lesions, 1 for cap or pencil-like thin lesions, 2 for smooth halo-like lesions and 3 for irregular PVH signals extending into the deep white matter (**Figure 3**). Deep white matter hyperintensity (DWMH) signals were graded as 0 for no lesions, 1 for dot-like lesions; 2 for moderately fused lesions and 3 for widely fused lesions (**Figure 4**). The higher value was used when discrepancy existed between the periventricular and deep white matter grades. Interpretation of MRI imaging results was carried out by two physicians and one neurologist; the latter was unfamiliar with the patient's medical history and the final assessment required consensus, which could necessitate re-evaluation and/or compliance with the majority opinion.

Statistical methods

Descriptive statistics were used to provide sample char-

Table 1. Patient Characteristics

Characteristic	Result
Age (mean ± SD)	78 ± 5.6 years
Male	100 cases (64.1%)
Female	56 cases (35.9%)
Smoking	53 cases (34%)
High alcohol consumption	27 cases (17.3%)
Hypertension	105 cases (67.3%)
Previous TIA or stroke	68 cases (43.6%)
Hyperlipidemia	80 cases (51.3%)
Type-2 diabetes	60 cases (38.5%)
Cognitive dysfunction	71 cases (45.5%)
Affective disorder	22 cases (14.1%)
Supranuclear paralysis	27 cases (17.3%)
Walking disorders	64 cases (41.0%)
Urinary incontinence	56 cases (35.9%)
Weak limbs	31 cases (19.9%)
White-matter lesion	
1 point	34 cases (21.8%)
2 points	86 cases (55.1%)
3 points	36 cases (23.1%)
Lacunar infarction	
1 grade	57 cases (37.2%)
2 grade	69 cases (44.2%)
3 grade	29 cases (18.6%)

acteristics. Firstly, we used a multivariate ordered logistic regression analysis to determine associations between CSVD risk factors and the severity of white matter lesions. Variables included in this model were as follows: age (normally distributed continuous variables were organized into quartiles), sex (female = 0; male = 1), smoking (no = 0; yes = 1), high alcohol consumption (no = 0; yes = 1), hypertension (no = 0; yes = 1), previous TIA or stroke (no = 0; yes = 1), hyperlipidemia (no = 0; yes = 1), type 2 diabetes (no = 0; yes = 1). Results are displayed as odds ratios (OR) and 95% confidence intervals (CI). The same approach was used to examine the relationships between CSVD risk factors and the number of lacunar infarcts. For the correlation between the incidence of cognitive dysfunction, affective disorders, supranuclear paralysis, gait disorders, limb weakness and urinary incontinence with lesions in the subcortex, basal ganglia, brainstem and cerebellum, we used Spearman rank correlation test analysis, with *p*-values < 0.05 being considered statistically significant. All analyses were performed using SPSS Version 20.0.

Results

Patient characteristics

Of the 156 CSVD patients studied, 53 (34.0%) and 27 (17.3%) had a history of smoking and high alcohol consumption, respectively. There were 105 cases (67.3%) of hypertension, 80 (51.3%) of hyperlipidemia and 60 (38.5%) of diabetes. A history of TIA or stroke was found for 68 patients (43.6%). These CSVD risk factors are described, along with patient symptoms and signs, in **Table 1**.

Risk factors associated with the severity of WMLs

Multivariate logistic regression analysis, using WML grade as the dependent variable and the above CSVD risk factors as independent variables, found that age, hypertension and high alcohol consumption were significantly associated with the severity (grade) of the WMLs (**Table 2**). However, sex, smoking, diabetes, hyperlipoidemia, TIA and stroke showed no significant association with WML severity.

Risk factors associated with the number of LIs

Multivariate logistic regression analysis, using LI number as the dependent variable and the above CSVD risk factors as independent variables, found that age, hypertension and high alcohol consumption were significantly associated with the severity (grade) of the WMLs (**Table 3**). Sex, smoking, TIA and stroke showed no significant association with LI number.

Correlation of WMLs and LIs with clinical symptoms and signs of CSVD

Analysis of the correlation of PVH, DWMH grade and LI number at different brain sites with cognitive dysfunction, affective disorders, palsy, gait disorders, limb weakness and incontinences presented in **Table 4**. Supranuclear paralysis was mostly strongly correlated with LI number in the brainstem and cerebellum ($r = 0.238$, $P < 0.005$). PVH and DWMH grade were correlated with cognitive dysfunction ($r = 0.205$ and 0.215, respectively; $P < 0.005$). Gait disorders were weakly correlated with PVH grade and LI number in the basal ganglia ($r = 0.169$ and 0.164, respectively; $P < 0.005$), while limb weakness was more strongly correlated with LI number in this region ($r = 0.189$, $P < 0.005$). Urinary incontinence was correlated with DW-

Table 2. Multivariate logistic regression analysis of CSVD risk factors associated with the severity of white matter lesions

Varies	OR	95% CI	P
Age*	0.089	0.011-0.729	0.024
Sex	1.999	0.601-6.649	0.259
Smoking	0.935	0.276-3.166	0.914
High alcohol consumption	0.049	0.007-0.351	0.003
Hypertension	0.066	0.020-0.219	0.000
Previous TIA or stroke	1.195	0.420-3.40	0.738
Hyperlipoidemia	0.675	0.183-2.491	0.556
Type-2 diabetes	1.662	0.448-6.164	0.448

*Normally distributed continuous variables were organized into quartiles and each was then compared to the one directly below it; 4th to 3rd, 3rd to 2nd and 2nd to 1st.

Table 3. Multivariate logistic regression analysis of CSVD risk factors associated with number of lacunar infarcts

Varies	OR	95% CI	P
Age*	0.78	0.013-0.469	0.005
Sex	1.294	0.304-5.519	0.727
Smoking	0.356	0.131-2.802	0.356
High alcohol consumption	0.557	0.101-3.063	0.501
Hypertension	0.35	0.004-0.336	0.004
Previous TIA or stroke	0.818	0.238-2.818	0.751
Hyperlipoidemia	0.250	0.067-0.924	0.038
Type-2 diabetes	0.144	0.41-0.515	0.003

*Normally distributed continuous variables were organized into quartiles and each was then compared to the one directly below it; 4th to 3rd, 3rd to 2nd and 2nd to 1st.

MH grade and subcortical LI number (r = 0.184 and 0.203, respectively; P < 0.005). Cognitive dysfunction was correlated with palsy, gait disorders, limb weakness and incontinence (P < 0.005), and DWMH grade was weakly correlated with subcortical LI number (r = 0.169, P < 0.005).

Discussion

Age and hypertension are thought to be the most important risk factors for CSVD. Development of arteriosclerosis with age causes decreased blood flow to the white matter, and this would provide a potential mechanism for explaining the relationship between old age and leukoaraiosis, one of the key signs of CSVD [21]. Hypertension is the most important risk factor for occurrence and development of leukoaraiosis [22]; it plays important role in hyaline degeneration of fatty tissue and necrosis of muscle fibers in small perforating arteries, which can in turn lead to chronic cerebral ischemia and blood-brain barrier damage, eventually producing leukoaraiosis [23, 24]. In addition, long-term high blood pressure may cause hyaline degeneration of small blood vessels, which can lead to reduced lumen diameter and vascular-wall fragility, thereby generating ischemic or hemorrhagic changes.

Our logistic regression results support to the above, indicating that age, hypertension and high alcohol consumption were independent risk factors for WML severity (grade). Of these, age showed the strongest association. Notably, our analysis found high alcohol consumption to be an independent factor; the reason may be that our subjects were mostly fromthehigh-altitudeInnerMongoliaAutonomous Region, where drinking is particularly popular (especially for the Mongolians).

Diabetes was also confirmed as an independent risk factor for CSVD, and therefore CSVD may be another serious complication of diabetes. Some researchers have proposed that the mechanism linking the two is the substitution of the vascular medial smooth muscle with hyaline substances, leading to stenosis or occlusion of the vessel lumen, followed by decreased cerebral blood flow. Others believe that hyperglycemia-induced neurotoxicity and oxidative stress could lead to changes in the cerebral hemodynamics, causing cerebral ischemia and neurodegeneration. Hyperlipidemia can lead to intimal thickening of small blood vessels, and thus local plaques are formed and the distribution of small vessels in the ischemic area changes. Age, hypertension, hyperlipidemia and diabetes were the risk factors associated with LI number and the strength of the association was in that order. Smoking, sex and a previous stroke were not significantly associated with CSVD; among other reasons, it is possible that this was due to the small sample size or the ethnicity or diet of the subjects. A larger multi-center, multi-ethnic study may be needed to confirm our findings.

Table 4. Analysis of the correlation between PVH, DWMH grade and LI number at different brain sites with cognitive dysfunction, affective disorders, palsy, gait disorders, limb weakness and incontinence

	DWMH										
DWMH	1.000	PVH									
PVH	0.734 (0.000)	1.000	Subcortical white matter								
Subcortex	0.169 (0.035)	0.109 (0.176)	1.000	Basal ganglia							
Basal ganglia	-0.005 (0.952)	0.008 (0.920)	-0.170 (0.054)	1.000	Brainstem and cerebellum						
Brainstem and cerebellum	0.138 (0.086)	0.041 (0.609)	-0.148 (0.064)	-0.283 (0.056)	1.000	Cognitive dysfunction					
Cognitive dysfunction	0.215 (0.007)	0.205 (0.010)	0.153 (0.056)	0.156 (0.052)	0.125 (0.119)	1.000	Affective disorders				
Affective disorders	0.056 (0.487)	0.014 (0.862)	0.048 (0.554)	-0.023 (0.772)	0.052 (0.515)	0.000 (0.995)	1.000	Palsy			
Palsy	0.105 (0.191)	0.143 (0.076)	0.093 (0.248)	0.190 (0.018)	0.238 (0.003)	0.228 (0.004)	0.009 (0.908)	1.000	Gait disorders		
Gait disorders	0.157 (0.051)	0.169 (0.035)	0.004 (0.957)	0.164 (0.040)	0.032 (0.691)	0.232 (0.004)	0.074 (0.359)	0.204 (0.011)	1.000	Limb weakness	
Limb weakness	0.137 (0.088)	0.117 (0.146)	0.141 (0.078)	0.189 (0.018)	0.132 (0.101)	0.255 (0.001)	0.167 (0.037)	0.239 (0.003)	-0.121 (0.131)	1.000	Incontinence
Incontinence	0.184 (0.021)	0.134 (0.095)	0.203 (0.011)	0.114 (0.157	0.095 (0.237)	0.269 (0.001)	0.043 (0.592)	0.165 (0.040)	0.306 (0.000)	0.113 (0.160)	1.000

Importantly, CSVD does not only cause disorders of affect [25] and movement [26, 27], it also induces cognitive dysfunction [28] with a severity comparable to the effects of a main-artery atherosclerotic thromboembolism. Lacunar infarcts and white matter lesions were once regarded as merely typical imaging features of CSVD; however, their clinical significance, especially their relationship to cognitive function, remains unclear. A cross-sectional survey found that both were correlated with palsy, cognitive and emotional abnormalities, and problems with walking and urination [29]; while longitudinal surveys indicated that they were involved in dementia and the decline of cognitive function [30]. Studies of clinical symptoms and risk factors in patients with cerebral microvascular disease showed that frontal WMLs or LIs more frequently cause progressive cognitive decline, gait disorders, stroke and TIA-related symptoms, dizziness and urinary incontinence. Parieto-occipital WMLs and LIs may facilitate the occurrence of TIA, seizures and incontinence, while those in the basal ganglia have been associated with gait disorders, dizziness and urinary incontinence [31]. The results of the present study indicate that palsy was most strongly correlated to LI number in the brain stem and cerebellum, while the severity of periventricular white matter and deep white matter lesions was significantly associated with cognitive dysfunction. Gait disorders were weakly associated with PVH grade and LI number in the basal ganglia. Limb weakness was correlated with LI number in the basal ganglia, while urinary incontinence was associated with DWMH and LI number in the subcortical white matter; this is in accord with the literature.

The clinical signs and symptoms associated with CSVD are similar to other degenerative brain diseases, and include problems with gait, mood, behavior and cognition. Development of CSVD-associated cognitive dysfunction is a gradual process, progressing from normal cognition to significant dementia [32]. The symptoms may be mild and not closely related in the early stage of the disease, whereas patients in the last stage meet the diagnostic criteria for dementia; including significant cognitive dysfunction and functional impairment in daily living. For many patients, gait is seriously affected, so that they can hardly walk and often stumble, and they can become depressed or indifferent, with some suffering from urinary incontinence. These signs of brain dysfunction are, to some degree, consistent with the anatomical and physiological changes shown by imaging [33, 34], which suggests avenues for future research into therapeutic targets [35]. The results of our study indicated that palsy, gait disorders, limb weakness and urinary incontinence were all significantly correlated with cognitive dysfunction, which was consistent with previous studies; however, cognitive dysfunction was not correlated with affective disorders, which may be due to the small sample size and limited time period covered in this study. Further follow-up studies of the long-term cognitive changes and prognosis should be performed.

All its clinical signs, symptoms and complications should be identified and elucidated [36]. Once diagnosed, appropriate antihypertensive therapy can help to delay brain damage, and thus relieve the clinical symptoms; however, 35% of brain-injury patients with hypertension are asymptomatic, and therefore early diagnosis via MRI is also very important. The perindopril protection against recurrent stroke study (PROGRESS) has shown that active antihypertensive treatment could prevent or delay the WML progression in CSVD patients, and prevent development of minor parenchymal damage into much more serious lesions and clinical manifestations [37].

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Disclosure of conflict of interest

None.

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