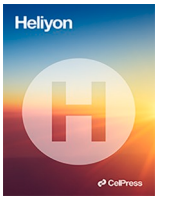
Heliyon 10 (2024) e30007

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The clinical characteristics of cerebral small vessel disease patients with motoric cognitive risk syndrome during single- and dual-task walking

Hongyang Xie [a,1], Nan Zhang [a,1], Cuiqiao Xia [a], Yu Ding [a], Hongyi Zhao [a,b], Yonghua Huang [a,*]

[a] Department of Neurology, Chinese PLA General Hospital, Beijing, China
[b] Department of Neurology, Number 984 Hospital of the PLA, Beijing, China

ARTICLE INFO

Keywords:
Cerebral small vessel diseases
Dual-task walking
Aging
White matter hyperintensities

ABSTRACT

Objective: We aimed to (1) identify neuroimaging biomarkers of distinguishing motoric cognitive risk syndrome (MCRS) risk among older Chinese adults with cerebral small vessel disease (CSVD) and (2) detect differences in gait parameters and neuroimaging biomarkers between CSVD individual with and without MCRS, especially during dual-task walking (DTW).
Methods: We enrolled 126 inpatients with CSVD who were divided into two groups according to MCRS status. Data on basic parameters, variability, asymmetry, and coordination were collected during single-task walking (STW) and DTW. Neuroimaging features (white matter hyperintensities, lacunes, and microbleeds) and total disease burden were calculated. Analysis of variance and logistic regression analyses were applied to assess the role of STW, DTW, and neuroimaging biomarkers in MCRS.
Results: In total, 126 consecutive inpatients with CSVD were included (84 and 42 patients were classified as MCRS-negative and MCRS-positive, respectively). The MCRS-positive group showed poorer performance for nearly all gait parameters compared with the MCRS-negative group during cognitive DTW. Meanwhile, all gait parameters except asymmetry were assessed in participants with MCRS for significant deterioration during cognitive DTW compared with that during STW. However, only basic parameters differed between STW and cognitive DTW in participants without MCRS. A significant independent association between total CSVD scores and MCRS was also detected.
Conclusions: For CSVD patients, with higher total CSVD burden rather than any single neuroimaging marker, was linked to a greater risk of MCRS. In addition, CSVD individuals with MCRS had higher variability and phase coordination index (PCI), especially in cognitive DTW. Thus, they should concentrate more on their gait variability or coordination and reduce secondary task loads while walking in daily life, especially in cognitive secondary tasks.

* Corresponding author. Ph.D. Department of Neurology, Chinese PLA General Hospital. 5 Nanmencang, Dongsi Shitiao, Dongcheng District, Beijing, 100010 China.
E-mail address: huangyh@163.com (Y. Huang).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e30007
Received 15 January 2024; Received in revised form 10 April 2024; Accepted 18 April 2024
Available online 30 April 2024

Abbreviations

CSVD	cerebral small vessel disease
WMHs	white matter hyperintensities
LIs	lacunar infarctions
CMBs	cerebral microbleeds
DTW	Dual-task walking
STW	single-task walking
MCRS	motoric cognitive risk syndrome
MRI	magnetic resonance imaging
MMSE	Mini-Mental State Examination
PCI	phase coordination index
CV	coefficient of variation
GA	Gait asymmetry
SD	standard deviation
GEE	generalized estimation equations

1. Main points

Neuroimaging biomarkers of motoric cognitive risk syndrome (MCRS) among older Chinese adults with cerebral small vessel disease (CSVD) and differences in gait parameters between CSVD individual with and without MCRS, especially during dual-task walking (DTW) haven't been reported yet.

For CSVD patients, with higher total CSVD burden rather than any single neuroimaging marker, was linked to a greater risk of MCRS.

CSVD individuals with MCRS had higher variability and phase coordination index (PCI), especially in cognitive DTW. Thus, they should concentrate more on their gait variability or coordination and reduce secondary task loads while walking in daily life, especially in cognitive secondary tasks.

2. Introduction

The neuroimaging biomarkers of cerebral small vessel disease (CSVD) include recent small subcortical infarcts, white matter hyperintensities (WMHs), lacunar infarctions (LIs), enlarged perivascular spaces, cerebral microbleeds (CMBs), and atrophy [1]. Movement disorders and cognitive impairment are the main clinical features of this disease [1]. Meanwhile, lacunar syndromes due to acute lacunar stroke are another significant symptomatic clinical presentation of CSVD [2]. Therefore, indicators for assessing lacunar infarcts, motor deficits, and cognitive deficits are important for the diagnosis of CVSD. However, these symptoms are usually not obvious in individuals with CSVD; therefore, they are difficult to detect using traditional methods [3]. Dual-task walking (DTW) helps to evaluate the gait characteristics of individuals with CSVD comprehensively and precisely. It provides vital information for detecting changes in gait. DTW is defined as walking while carrying out another assignment, which includes cognitive tasks (cognitive DTW) and motor tasks (motor DTW) [4,5]. Walking and secondary tasks compete for similar neural resources. Therefore, completing walking and secondary tasks perfectly simultaneously [6] is difficult for individuals with CSVD.

CSVD is an independent disease which could cause deterioration of cognition and motion. If cognitive or motor function were detected separately, we cannot show panorama of the lesion. A growing body of research shows that cognition and movement are a unity. Recently, a series of concepts such as "brain muscle circuit", " motoric cognitive risk syndrome (MCRS) ", and "cognitive decline" have been proposed and confirmed, which provides favorable conditions for assessing CSVD more holistically. While the most important notion is MCRS.

MCRS is a predementia syndrome characterized by the simultaneous presence of subjective cognitive complaints and slow gait in older individuals without dementia or mobility disabilities [7]. MCRS is often considered a transition state between normal aging and mild cognitive impairment [7]. The syndrome can be assessed simply and rapidly, making diagnosis easy and feasible in primary care settings worldwide [1]. A relationship exists between MCRS and an increased risk of vicious health events, such as cognitive decline and dementia[1] falls [8].

Some studies have indicated that cerebrovascular pathologies such as CSVD, primarily in the cognitive control (or motor planning) pathway of human locomotion, contribute to MCRS [9]. In addition, MCRS and CSVD could share common risk factors such as age, hypertension, diabetes, and clinical symptoms [10]. In order to understand disease comprehensively, it is very important to find out the clinical manifestation and imaging features of CSVD patients with MCRS.

A previous study reported that regional LIs, not WMHs and cortical CMBs, may be useful markers for MCRS in patients with CSVD [10,11]. A recent study also reported that MCRS are associated with WMH pathologies in older Chinese adults [5]. These data indicate that specific types of CSVD biomarkers might contribute to the development of MCRS. However, choosing which biomarkers to investigate in CSVD older adults with MCRS remains controversial, especially in Chinese adults. Thus, in this study, we first aimed to identify neuroimaging biomarkers of distinguishing MCRS risk in older Chinese adults with CSVD.

In addition, previous studies mainly evaluated relationships between MCRS and cognitive function or dementia; however, research on the characteristics of gait disorders in MCRS is rare [12,13]. In particular, no study has assessed the gait characteristics of individuals with MCRS among patients with CSVD. We want to explore the change of other gait parameters expect speed. Moreover, although DTW is widely used in CSVD research, gait changes during DTW for CSVD individuals with MCRS remains unclear. Therefore, our second aim was to assess the differences in gait parameters between MCRS-negative and MCRS-positive groups among individuals with CSVD during STW and DTW conditions and to detect the reason of high risk of falls and mortality in CSVD individuals with MCRS.

3. Materials and methods

3.1. Participants

This clinical study was designed and performed in accordance with the Declaration of Helsinki and approved by the Academic Ethics Committee of the Biological Sciences Division of the Seventh Medical Center of the PLA General Hospital (2020-106). All the participants provided written informed consent.

A total of 126 individuals with CSVD admitted to the Seventh Medical Center of the PLA General Hospital between September 1, 2020, and September 1, 2021, participated in this study. All the participants were classified into two groups: MCRS-positive and MCRS-negative. Most of our participants had strong will of MRI scan, with complaints about mild dizziness, mild headache, mood disturbances, cognitive disorders, motor dysfunction, etc. The inclusion criteria were as follows: (1) ability to independently ambulate without a tray in the hands for 30 steps, (2) sufficient ability to comprehend and implement commands, and (3) at least one of the following CSVD imaging manifestations: WMHs, LIs, or CMBs (Significantly, if grad of WMHs is 1, the patients should have at least one vascular risk factor, such as hypertension, diabetes, hyperlipemia and so on). The exclusion criteria were as follows: (1) inability to independently walk 30 steps with or without a tray in their hands, (2) lack of receptive language ability to understand and follow commands, (3) diagnosis of mild cognitive impairment or dementia (4) acute cerebral ischemic or bleeding episodes, leukoencephalopathy with demyelinating or genetic causes, major psychiatric diseases, gait disorders caused by nonvascular factors, and magnetic resonance imaging (MRI) contraindications.

Personal information was collected, including age, sex, and education level, comorbid conditions. Mini-Mental State Examination (MMSE) results were also collected through interviews for all participants.

3.2. MRI measurements and CSVD biomarkers

Neuroimaging of the participants was performed using a 3.0 T MRI scanner (Siemens AG, Munich, Germany). All participants underwent the following sequences: T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, and susceptibility-weighted imaging. Images were captured by two neurologists blinded to the participants' personal information. In cases of differing opinions between two neurologists, disagreements were resolved through consensus with a third expert.

WMHs were graded according to the Fazekas scale, which divides the participants into grades 1, 2, and 3 [14]. The Fazekas scale is a simple and widely accepted method used in research on CSVD and Alzheimer disease. We also recorded the numbers of LIs and CMBs. The total CSVD burden score was computed with the intent to capture the overall damage caused by CSVD more effectively than any single neuroimaging biomarker. However, we did not record WMHs, LIs, and CMBs by brain region because we wanted to identify a simple biomarker that could predict the risk of MCRS.

The total number of CSVD biomarkers, such as LIs, CMBs, and WMHs, were counted to obtain the total CSVD burden score [15].

Individuals with three or more LIs, any CMBs, or Fazekas scores of 2–3 points had one point added to their total score for each of these features (scale range: 0–3). When LIs or CMBs were calculated independently, the presence of LIs or CMBs was defined as two or more LIs and any CMBs. Based on the total CSVD burden score, the individuals were divided into three groups: severe (2 and 3), moderate (1), and mild (0).

3.3. STW and DTW protocols

The gait characteristics of all participants were collected under three conditions: (1) walking without any additional task, (2) walking while performing three serial subtractions from a randomly selected starting number (90, 95, 100, or 105; cognitive DTW), and (3) walking while holding a tray with four empty glasses placed on the corners (motor DTW).

As stated earlier, patients were required to walk 30 strides during STW and DTW. They needed to implement two types of tasks without prioritizing either activity. Twenty-five strides in the middle part of the study were collected to avoid the influence of acceleration and deceleration.

3.4. The gait parameters of participants with CSVD

All data related to gait were collected using the MiniSun Intelligent Device for Energy Expenditure and Activity System (MiniSun, Fresno, CA, USA). The average values of basic gait parameters, such as velocity, cadence, stride length, and stride time, were recorded. Interlimb bilateral coordination was determined using the phase coordination index (PCI %, equations (1)–(3)) [15]. Briefly, the gait cycle was modeled as 360° with a step (i.e., heel strike to toe off on the same foot) equating to a phase (φ) within the cycle. The addition of φCoV (coefficients variation of φ) and φABS (mean absolute difference between φ) is used to calculate the PCI (1), and a PCI value

closer to zero indicates better coordination [16].

The PCI was calculated as follows:

$$PCI(\%) = \varphi CoV + \varphi ABS \tag{1}$$

$$\varphi ABS = \frac{mean|\varphi - 180\circ|}{180\circ} \times 100\% \tag{2}$$

$$\varphi CoV = \frac{\mathrm{stdev}(\varphi)}{mean(\varphi)} \times 100\% \tag{3}$$

Gait variability (%) was determined as the common expression of coefficient of variation (CV), calculated by stride time [17]. Moreover, because the ratio of bilateral legs was related, we calculated the CV for each side as follows:

$$\text{stride } CV = \frac{\mathrm{stdev}(stride)}{mean(stride)} \times 100\%$$

Gait asymmetry [GA (%)] was determined using the following formula [18]:

$$GA = |\ln(\text{R\_STP} / \text{L\_STP}) \times 100|\%$$

where R_STP or L_STP represents the average number of bilateral swing times separately.

The PCI, CV and GA is defined as reanalysis generated parameters, because they are calculated by basic parameters.

3.5. Motoric cognitive risk syndrome diagnosis

MCRS is the presence of subjective cognitive complaints and slow gait in older individuals without dementia or mobility disability [7]. Subjective cognitive complaints were noted by recorders based on positive responses for either of the following problems: 1) "How would you rate your memory currently?" Individuals answered the question as excellent, very good, good, fair, or poor. We defined the answer "fair" and "poor" as positive responses. 2) "Compared with a year ago, would you think your memory is better, the same, or worse now?" The answer "worse" was considered a positive response. 3) "In the past month, how often do memory problems disturb your daily activities." The answers "not at all," "slightly," "somewhat," "a lot," and "everyday" were recorded as positive responses. Low velocity was defined as a gait speed of 1 standard deviation (SD) or more below age- and sex-specific means [19]. Individuals had different cutoff scores in several age groups. Slow walking speed was defined as 1.11, 1.08, 0.98, and 0.88 m/s in men and 1.08, 1.03, 0.94, and 0.77 m/s in women for the ≤64, 65–69, 70–74, and ≥75 years age groups, respectively [20,21], according to Chinese and Asian data.

3.6. Statistical analysis

The Shapiro–Wilk test was used to determine the statistical indicators of normality. Factors expressed as the mean ± SD were used for normally distributed variables and the median with interquartile range for skewed distributions. Categorical variables were presented as frequencies. The *t*-test and nonparametric Mann–Whitney *U* test was applied for normal and skewed distributions,

Table 1
Demographic and clinical characteristics and neuroimaging biomarkers of the study participants.

		MCRS- (84)	MCRS+ (42)	Statistic	P-value
Sex, n	Female	30	18	0.780	0.377
Education, years (range)		12 (9.12)	12 (9,12)	−0.198	0.843
Age, years (Mean ± SD)		63.7 ± 8.0	68.5 ± 8.6	0.232	0.631
MMSE, points (range)		29 (27,30)	28 (27.75,30)	−0.760	0.446
Hypertension, n		57	32	0.937	0.333
Stenocardia, n		9	3	0.414	0.749
Myocardial infarct, n		8	3	0.199	0.750
Hyperlipidemia, n		64	34	0.367	0.544
Diabetes, n		22	16	1.884	0.170
CSVD Total score	0	25	5	−4.227	**<0.001**
	1	30	4		
	2	29	33		
WMHs	0	14	6	−1.699	0.089
	1	31	8		
	2	22	16		
	3	17	12		
CMBs		35	25	−1.884	0.060
LIs		45	35	−3.258	**0.001**

MCRS, motoric cognitive risk syndrome; MMSE, Mini-Mental State Examination; WMHs, white matter hyperintensities; CMBs, cerebral microbleeds; LIs, lacunar infarctions; SD, standard deviation.

respectively. Categorical variable data were analyzed using the chi-squared test. The differences in gait variance were detected by generalized estimation equations (GEE) when performed in condition (STW and DTW) and group (two types of MCRS states). If interaction between condition and group were discovered, the Post-hoc comparisons will be performed. Post-hoc comparisons were corrected using Bonferroni's method. Logistic regression models were also used to assess the independent relationship between neuroimaging CSVD biomarkers and MCRS risk. And the logistic regression analysis was also adjusted for age, gender, and education level. The data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA), and statistical significance was established at $P < 0.05$.

4. Results

4.1. Participants' characteristics

The demographic and clinical parameters of the study participants are presented in Table 1. A total of 126 consecutive patients with CSVD were included (mean age 66.1 ± 8.3 years, 38.1 % female), of which 84 (mean age 63.7 ± 8.0 years, 35.7 % female) and 42 (mean age 68.5 ± 8.6 years, 42.9 % female) were classified as MCRS-negative and MCRS-positive patients, respectively. There was no difference between the groups in terms of age, sex, education, or comorbidities ($P > 0.05$).

4.2. The gait characteristics of patients with motoric cognitive risk syndrome in different walking conditions

The mean and SD of the direct parameters of the gait cycle during the different walking methods are reported in Tables 2 and 3. Discrepancies between MCRS (group) and walking (condition) were also detected simultaneously. The results of GEE are presented in Table 4. The main effects and interactions between the groups and conditions were detected in all the parameters. Post-hoc analysis of between group (MCRS + vs. MCRS-) differences showed that, in the cognitive DTW condition, the MCRS positive group showed poor performance for all direct parameters than the MCRS negative group ($P \leq 0.001$). Only gait speed was different in the STW ($P = 0.004$) and motor DTW ($P = 0.011$) conditions.

Post-hoc analysis of condition (STW vs. DTW) differences was also performed to detect discrepancies between the three walking methods. Participants in the MCRS positive group showed lower cadence, slower speed, longer stride time, and stride length during cognitive DTW than during STW ($P < 0.001$). A similar conclusion was obtained for the MCRS negative group ($P < 0.010$).

Tables 5 and 6 shows the reanalysis-generated parameters of gait, and each group of statistics is indicated as medians and quartiles. The outcomes of the GEE are displayed in Table 7. The analysis revealed that the interaction between condition and group were discovered in all reanalysis-generated parameters, except GA. Therefore, post-hoc analysis was performed. Post-hoc analysis demonstrated that, MCRS group exhibited a higher variability in the all directs gait parameters and higher PCI during the cognitive DTW when compared to non-MCRS group($P < 0.05$); however, there were no differences during motor DTW and STW. In addition, for MCRS group, a higher variability in the all directs gait parameters and higher PCI in cognitive DTW compared to those values in STW ($P < 0.05$). We not detected any difference in above parameters among the three walking conditions in CSVD patients without MCRS.

4.3. The neuroimaging biomarkers of motoric cognitive risk syndrome

We investigated the neuroimaging biomarkers of CSVD, and the results are presented in Table 1. There were significant discrepancies in the total CSVD score and presence of LIs between the two groups with or without MCRS; however, the presence or absence of

Table 2
Mean (SD) of direct gait parameters in single and dual-task conditions for the MCRS and non-MCRS groups.

	Group	
	MCRS- (84)	MCRS+ (42)
STW		
Stride length (m)	0.981 ± 0.188	0.919 ± 0.153
Stride time (s)	1.120 ± 0.126	1.152 ± 0.112
Candence (step/min)	107.593 ± 12.328	105.468 ± 10.342
Velocity (m/s)	0.897 ± 0.225	0.813 ± 0.151**
Cognitive DTW		
Stride length (m)	0.943 ± 0.172	0.846 ± 0.140**
Stride time (s)	1.172 ± 0.121	1.302 ± 0.210**
Candence (step/min)	103.019 ± 11.113	94.495 ± 15.165**
Velocity (m/s)	0.818 ± 0.194	0.665 ± 0.155**
Motor DTW		
Stride length (m)	0.952 ± 0.179	0.893 ± 0.162
Stride time (s)	1.124 ± 0.142	1.171 ± 0.146
Candence (step/min)	107.343 ± 13.087	103.616 ± 11.903
Velocity (m/s)	0.865 ± 0.224	0.778 ± 0.160*

SD, standard deviation; MCRS, motoric cognitive risk syndrome; STW, single-task walking; DTW, dual-task walking; *$P < 0.05$, **$P < 0.01$.

Table 3
Mean (SD) of direct gait parameters in MCRS and non-MCRS population for the single and dual-task conditions.

	STW	Cognitive DTW
MCRS-		
Stride length (m)	0.981 ± 0.188	0.943 ± 0.172**
Stride time (s)	1.120 ± 0.126	1.172 ± 0.121**
Candence (step/min)	107.593 ± 12.328	103.019 ± 11.113**
Velocity (m/s)	0.897 ± 0.225	0.818 ± 0.194**
MCRS+		
Stride length (m)	0.919 ± 0.153	0.846 ± 0.140**
Stride time (s)	1.152 ± 0.112	1.302 ± 0.210**
Candence (step/min)	105.468 ± 10.342	94.495 ± 15.165**
Velocity (m/s)	0.813 ± 0.151	0.665 ± 0.155**

SD, standard deviation; MCRS, motoric cognitive risk syndrome; STW, single-task walking; DTW, dual-task walking; *P < 0.05, **P < 0.01.

Table 4
Summary of generalized estimation equations for direct gait parameters: χ^2 and P-values by variable (If there is interaction according to generalized estimation equations, post-hoc analysis would be performed).

		Velocity	Stride length	Candence	Stride time
Main effect					
Group (MCRS)	χ^2	13.163	6.269	5.064	7.648
	P	**<0.001**	**0.012**	**0.024**	**0.006**
Condition (STW vs. DTW)	χ^2	99.225	42.999	65.734	67.484
	P	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Interaction					
Group × condition	χ^2	10.201	6.522	11.325	15.917
	P	**0.006**	**0.038**	**0.003**	**<0.001**

MCRS, motoric cognitive risk syndrome.

Table 5
Medians and quartiles of reanalysis-generated parameters of gait in single and dual-task conditions for the MCRS and non-MCRS groups.

	Group	
	MCRS- (84)	MCRS+ (42)
STW		
Stride length CV (%)	6.050 (4.350, 9.300)	6.650 (4.800, 9.850)
Stride time CV (%)	2.778 (1.947, 3.695)	2.778 (1.933, 4.103)
Candence CV (%)	4.048 (3.163, 6.152)	3.968 (3.076, 6.433)
Velocity CV (%)	8.233 (5.753, 13.585)	8.959 (7.044, 13.751)
GA (%)	1.128 (0.000, 2.602)	1.086 (0.929, 2.186)
PCI (%)	4.463 (3.002, 7.266)	4.655 (3.284, 9.573)
Cognitive DTW		
Stride length CV (%)	6.704 (5.107, 8.530)	8.866 (6.277, 11.566) **
Stride time CV (%)	2.983 (2.500, 4.464)	4.772 (2.804, 9.137) *
Candence CV (%)	4.925 (3.625, 6.252)	6.741 (3.989, 9.566) **
Velocity CV (%)	9.339 (6.410, 12.375)	13.519 (8.440, 20.674) **
GA (%)	1.174 (0.955, 3.141)	1.516 (0.929, 2.242)
PCI (%)	5.486 (3.426, 7.742)	6.820 (4.547, 9.693) *
Motor DTW		
Stride length CV (%)	7.386 (5.229, 9.040)	7.575 (5.249, 8.866)
Stride time CV (%)	2.916 (2.405, 4.196)	3.019 (2.598, 4.934)
Candence CV (%)	4.308 (3.400, 5.168)	4.858 (3.140, 7.162)
Velocity CV (%)	9.040 (6.818, 12.131)	11.069 (8.649, 13.495)
GA (%)	1.247 (0.960, 3.300)	1.269 (0.976, 2.313)
PCI (%)	4.623 (3.154, 8.010)	4.404 (3.918, 7.156)

MCRS, motoric cognitive risk syndrome; STW, single-task walking; DTW, dual-task walking; CV, coefficient of variation; GA, gait asymmetry; PCI, phase coordination index; *P < 0.05, **P < 0.01.

WMHs and CMBs did not differ in the univariate analysis. Therefore, a logistic regression analysis was performed considering the total CSVD score and presence of LIs. The outcome, presented in Table 8, indicated a significant independent association between the total CSVD scores and MCRS. Specifically, MCRS incidence increased significantly with CSVD severity. The correlations were not eliminated after adjusting for all confounding factors. The presence of LIs showed no relationship with MCRS, However, after adjusting for other

Table 6
Medians and quartiles of reanalysis-generated parameters of gait in the MCRS and non-MCRS population for the single and dual-task conditions.

	STW	Cognitive DTW
MCRS-		
Stride length CV (%)	6.050 (4.350, 9.300)	6.704 (5.107, 8.530)
Stride time CV (%)	2.778 (1.947, 3.695)	2.983 (2.500, 4.464)
Candence CV (%)	4.048 (3.163, 6.152)	4.925 (3.625, 6.252)
Velocity CV (%)	8.233 (5.753, 13.585)	9.339 (6.410, 12.375)
GA (%)	1.128 (0.000, 2.602)	1.174 (0.955, 3.141)
PCI (%)	4.463 (3.002, 7.266)	5.486 (3.426, 7.742)
MCRS+		
Stride length CV (%)	6.650 (4.800, 9.850)	8.866 (6.277, 11.566) **
Stride time CV (%)	2.778 (1.933, 4.103)	4.772 (2.804, 9.137) *
Candence CV (%)	3.968 (3.076, 6.433)	6.741 (3.989, 9.566) **
Velocity CV (%)	8.959 (7.044, 13.751)	13.519 (8.440, 20.674) **
GA (%)	1.086 (0.929, 2.186)	1.516 (0.929, 2.242)
PCI (%)	4.655 (3.284, 9.573)	6.820 (4.547, 9.693) **

MCRS, motoric cognitive risk syndrome; STW, single-task walking; DTW, dual-task walking; CV, coefficient of variation; GA, gait asymmetry; PCI, phase coordination index; *P < 0.05, **P < 0.01.

Table 7
Summary of generalized estimation equations for reanalysis-generated parameters of gait: χ^2 and P-values by variable (If there is interaction according to generalized estimation equations, post-hoc analysis would be performed).

		GA	PCI	Velocity CV	Stride length CV	Candence CV	Stride time CV
Main effect							
Group (MCRS)	χ^2	0.191	2.564	4.342	0.408	2.114	5.666
	P	0.662	0.109	**0.037**	0.523	0.146	**0.017**
Condition (STW vs. DTW)	χ^2	2.030	11.323	6.779	10.697	9.120	27.725
	P	0.362	**0.003**	**0.034**	**0.005**	**0.010**	**<0.001**
Interaction							
Group × condition	χ^2	3.536	6.098	9.514	14.193	7.391	17.049
	P	0.171	**0.047**	**0.009**	**0.001**	**0.025**	**<0.001**

CV, coefficient of variation; GA, gait asymmetry; MCRS, motoric cognitive risk syndrome; PCI, phase coordination index.

Table 8
Logistic regressions showing the association between the different neuroimaging signatures of cerebral small vessel disease and the risk of MCRS (as the dependent variable).

		Model 1					Model 2				
		B	OR	95%CI		P	B	OR	95%CI		P
Total score	1	−1.480	0.228	0.074	0.697	**0.010**	−1.436	0.238	0.069	0.817	**0.023**
	2	−1.872	0.154	0.047	0.506	**0.002**	−2.234	0.107	0.027	0.433	**0.002**
	3	0	1				0	1			
LI	negative	−0.919	0.399	0.174	1.083	0.071	−1.258	0.284	0.082	0.982	**0.047**
	positive	0	1				0	1			

Model 2 was adjusted for all confounding factors, including age, sex, and education level.
LIs, lacunar infarctions; MCRS, motoric cognitive risk syndrome.

factors, a marginally significant relationship was discovered.

5. Discussion

We measured the differences in basic gait parameters and CV, GA, and PCI between MCRS negative and positive groups during DTW and STW conditions for patients with CSVD. We identified lower velocity or cadence, shorter stride length, longer stride time, greater variability, and poorer coordination in CSVD individuals with MCRS, especially during cognitive DTW conditions. In addition, we detected significant deterioration in all gait parameters except GA during cognitive DTW compared with STW for participants with MCRS. However, only basic parameters differed between cognitive DTW and STW in individuals without MCRS. We also examined the relationship between MCRS and neuroimaging biomarkers in patients with CSVD. As predicted, the independent risk factor of MCRS was the total CSVD burden. The preceding conclusion remains valid even after adjusting for age and other confounding factors.

5.1. Motoric cognitive risk syndrome prevalence in patients with cerebral small vessel disease

According to previous literature, the prevalence of MCRS in other countries apart from China varies from 2.6 % to 14.3 % [22–24]. Participants recruited from memory clinics may have had a higher prevalence than community-based respondents. In addition, the incidence of MCRS in China was approximately 7.3–12.7 % [20,25,26], similar to that in other countries. However, the morbidity associated with MCRS has increased significantly in patients with CSVD. The Kerala-Einstein Study based on older Indians with CSVD reported that MCRS prevalence was 27.3 % [11]. Another study also reached a similar conclusion; they reported that MCRS incidence was approximately 20.7 % in volunteers with WMHs [23]. Another study based on older Chinese patients with CSVD reported an MCRS incidence of approximately 28.35 % [7]. The morbidity recorded in our study was only slightly higher than that of a previous study (approximately 33.3 %). These discrepancies might be due to the definition of subjective cognitive complaints or low gait speed, and health disparities in different counties.

5.2. The neuroimaging biomarkers of motoric cognitive risk syndrome in patients with cerebral small vessel disease

A recent study discovered that WMHs might confer an increased risk of MCRS [27]. Gomez et al. performed a diffusion tensor imaging examination which measured the white matter microstructure and observed that an MCRS-positive status was associated with increased mean diffusivity, and projection and commissural white matter tracts [28]. In addition, Zhào et al. and Doi et al. reported that more moderate and severe WMHs were present in MCRS-positive individuals [7,29]. Recently, other studies have reported that participants with MCRS had lower cortical thickness and volume but not lower white matter volume than participants without MCRS [8,26,27]. Progressive gray matter brain atrophy is known to be a new feature of CSVD [30]. And, elderly patients had varying degrees of brain atrophy in this study. Therefore, we did not evaluate in detail the characterization of gray matter atrophy in MRCS.

Similarly, Mergeche et al. reported that the association between regional WMHs and MCRS was not statistically significant in their study sample [10]. Another study of patients with CSVD reached a similar conclusion. They reported that the overall amount of WMHs was not associated with MCRS, while regional LIs may play an important role in MCRS development [11].

Our study results were partly consistent with those of previous studies; however, we still did not detect any relationship between MCRS and the scale of WMHs or the presence of CMBs or LIs. A marginally significant correlation between the presence of LIs and MCRS was discovered upon controlling for confounding factors. Surprisingly, the total CSVD burden was an independent risk factor for MCRS; even after adjusting for all confounding factors, the correlation was not eliminated.

CSVD is caused by various pathophysiological mechanisms, while the total CSVD burden score is a better representation of the overall damage caused by CSVD. According to a previous study, the presence of LIs is a more specific marker than WMHs or CMBs for MCRS when present in specific regions, such as the frontal lobe [11]. This may be because WMH is a less specific form of cerebrovascular injury [11] and only a few CMBs can be detected in each individual. LIs in the frontal lobe may disturb the frontal neural networks of memory and gait functions, which is an important pathway for MCRS [31]. However, in our study, the relationship between MCRS and LIs was not strong. The total CSVD burden may appear to be a more appropriate index for evaluating MCRS, possibly because single neuroimaging biomarkers are a less comprehensive form of evaluating cerebrovascular injury than the total CSVD burden. We did not evaluate LIs and WMHs by brain region in this study. Thus, the overall vascular mechanisms of the brain other than single neuroimaging biomarkers may contribute to the pathophysiology of MCRS.

In a word, deterioration of single neuroimaging marker could not increase risk of MCRS, however, total CSVD burden had a close relationship with MCRS. Therefore, for CSVD patients, with higher total CSVD burden rather than any single neuroimaging marker, was linked to a greater risk of MCRS. They should pay more attention to their change of gait in case falls happened in our daily life.

5.3. The gait characteristics of cerebral small vessel disease patients with motoric cognitive risk syndrome

Allali et al. first proposed a gait disorder, except slow speed, in community-dwelling adults with MCRS. The MCRS subtypes were defined as the existence of low velocity with short stride length, long swing time, and high variability of stride length or swing time. They verified that changes in spatiotemporal gait parameters were common in individuals with MCRS [12]. Recently, another study analyzed the clinical characteristics of the MCRS subtypes. The changes in stride length, swing time, and variability were also significant in participants with MCRS [13]. In our study, we could only detect deterioration in gait speed during STW conditions. However, the discrepancy in other gait parameters was not significant in the patients with MCRS compared with that in patients without MCRS participants during STW.

Our results are inconsistent with those of previous studies, possibly due to differences in the enrolled participants. Previous research has mainly focused on community-dwelling adults, whereas we largely focused on individuals with CSVD. As stated in the previous paragraph, symptoms are usually not evident in individuals with CSVD. Therefore, it was necessary to introduce DTW to detect gait disorders in CSVD patients with MCRS.

Only a few studies have applied cognitive DTW conditions. Ward et al. first investigated the associations between dual-task costs and cognitive performance in community-based adults with MCRS and verified the discrepancy in dual-task costs between the two groups [32]. However, recently, Udina et al. [33] reported that the MCRS group did not show differences in dual-task costs compared with the negative group, whereas individuals with MCRS showed slower speed during cognitive DTW conditions. Similarly, Zhào et al. verified that MCRS negatively correlated with cognitive DTW speed in older adults with CSVD [5]. However, other gait characteristics during DTW were not considered in this study.

In our study, the difference between the positive and negative-MCRS groups was observed only in speed during motor DTW, similar

to STW. However, the MCRS-positive group showed poor performance for almost all parameters except GA than the MCRS-negative group during cognitive DTW conditions.

Walking without performing a secondary task might be a semi-automatic action and does not require additional cognitive recourse of the brain. A mild decline in brain reserve in CSVD patients with MCRS did not affect gait characteristics. In addition, although motor DTW requires more cognition recourse, vision might help individuals with CSVD maintain track stability to utilize more attention resources to maintain normal gait patterns [34]. An additional secondary task influences only parts of the brain and does not activate more neural resources. However, there is little opportunity to use compensatory mechanisms during cognitive DTW. Compared with the MCRS-negative group, the cognitive reserve in MCRS-positive individuals was significantly decreased [35], and the remaining neural reserve could not satisfy the requirement of normal walking. Therefore, CSVD individuals with MCRS should concentrate more on their gait and reduce secondary task loads while walking in daily life, especially in cognitive secondary tasks, because broader deterioration in gait parameters might increase the risk of falls and the probability of vicious events, which may increase their medical burden.

Previous studies have indicated that gait parameters could be classified into three categories: pace/rhythm, variability, and asymmetry [6,36]. Pace/rhythm factors mainly include gait speed, step time, stride length, and double-support time [37]. However, no study has classified gait parameters in individuals with CSVD. Thus, we divided the variables into three or four classes according to a previous study (including basic parameters, variability, asymmetry, and/or coordination). We discovered discrepancies in basic gait parameters in the MCRS-negative group between cognitive DTW and STW; however, no differences were detected in variability, coordination, and asymmetry. In the MCRS group, almost all gait parameters except asymmetry could be tested for significant deterioration in the cognitive DTW condition compared with STW. Although basic parameters and asymmetry are important gait characteristics [38], they may not be biomarkers of MCRS in patients with CSVD. However, variability and coordination, which comprise the cognitive component [39], were closely associated with MCRS. Therefore, the high risk of falls and mortality in CSVD individuals with MCRS is mainly caused by changes in variability and coordination, but not basic parameters. Hence, in our future clinical work, variability and coordination will be better studied to improve the quality of management and reduce fall risk in CSVD patients with MCRS.

5.4. Limitations

This study has some limitations. First, it was a single-center study, and the sample size was relatively small; therefore, multicenter studies with larger sample sizes are required in the future. Second, other gait characteristics during DTW were not considered in this study. Third, neuroimaging findings were evaluated semi-quantitatively. In future research, neuroimaging characteristics should be measured using an automatic system that could provide a more objective measure and metric information.

5.5. Conclusion

In conclusion, for CSVD patients, with higher total CSVD burden rather than any single neuroimaging marker, was linked to a greater risk of MCRS. Therefore, they should pay more attention to their change of gait in case falls happened in our daily life. In addition, CSVD individuals with MCRS had higher variability and PCI, especially in cognitive DTW. Thus, they should concentrate more on their gait variability or coordination and reduce secondary task loads while walking in daily life, especially in cognitive secondary tasks.

Ethics committee approval

This clinical study was approved by the Academic Ethics Committee of the Biological Sciences Division of the Seventh Medical Center of the PLA General Hospital (Beijing, China) (2020-106).

Informed consent

All the participants provided written informed consent.

Availability of data and materials

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

Funding

This study was supported by the Wu Jieping Medical Foundation (Grant No. 320.6750.18456).

CRediT authorship contribution statement

Hongyang Xie: Writing – original draft, Conceptualization. **Nan Zhang:** Visualization, Methodology. **Cuiqiao Xia:** Formal analysis, Data curation. **Yu Ding:** Software, Resources, Methodology. **Hongyi Zhao:** Writing – review & editing, Supervision.

Yonghua Huang: Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

The authors thank Dr. W Wei for providing magnetic resonance imaging support. We also thank Miss JJ Gao for her assistance with data processing.

References

[1] M Duering, GJ Biessels, A Brodtmann, C Chen, C Cordonnier, FE de Leeuw, et al., Neuroimaging standards for research into small vessel disease-advances since 2013, Lancet Neurol. 22 (7) (2023 Jul) 602–618.
[2] A. Arboix, J. Massons, L. García-Eroles, C. Targa, E. Comes, O. Parra, et al., Nineteen-year trends in risk factors, clinical characteristics and prognosis in lacunar infarcts, Neuroepidemiology 35 (3) (2010) 231–236.
[3] J.M. Wardlaw, S. Debette, H. Jokinen, F.E. De Leeuw, L. Pantoni, H. Chabriat, et al., ESO Guideline on covert cerebral small vessel disease, Eur Stroke J 6 (2) (2021) CXI–CLXII.
[4] C.J. George, J. Verghese, Motoric cognitive risk syndrome in polypharmacy, J. Am. Geriatr. Soc. 24 (2020) 2020.
[5] H. Zhào, W. Wei, H. Xie, Y. Huang, Motoric cognitive risk syndrome among Chinese older adults with white matter lesions: a cross-sectional Observational study, J Alzheimers Dis 91 (3) (2023) 925–931.
[6] T. Ghanavati, M.S. Smitt, S.R. Lord, P. Sachdev, W. Wen, N.A. Kochan, et al., Deep white matter hyperintensities, microstructural integrity and dual task walking in older people, Brain Imaging Behav 12 (5) (2018) 1488–1496.
[7] J. Verghese, C. Annweiler, E. Ayers, N. Barzilai, O. Beauchet, D.A. Bennett, et al., Motoric cognitive risk syndrome: multicountry prevalence and dementia risk, Neurology 83 (8) (2014) 718–726.
[8] H. Shim, M. Kim, C.W. Won, Motoric cognitive risk syndrome using three-item recall test and its associations with fall-related outcomes: the Korean frailty and aging cohort study, Int J Environ Res Public Health 17 (10) (2020) 3364.
[9] H.M. Blumen, E. Schwartz, G. Allali, O. Beauchet, M. Callisaya, T. Doi, et al., Cortical thickness, volume, and surface area in the motoric cognitive risk syndrome, J Alzheimers Dis 81 (2) (2021) 651–665.
[10] J.L. Mergeche, J. Verghese, G. Allali, C. Wang, O. Beauchet, V.G.P. Kumar, et al., White matter hyperintensities in older adults and motoric cognitive risk syndrome, J Neuroimaging Psychiatry Neurol 1 (2) (2016) 73–78.
[11] N. Wang, G. Allali, C. Kesavadas, M.L. Noone, V.G. Pradeep, H.M. Blumen, et al., Cerebral small vessel disease and motoric cognitive risk syndrome: results from the Kerala-einstein study, J Alzheimers Dis 50 (3) (2016) 699–707.
[12] G. Allali, E.I. Ayers, J. Verghese, Motoric cognitive risk syndrome subtypes and cognitive profiles, J Gerontol A Biol Sci Med Sci 71 (3) (2016) 378–384.
[13] E. Ayers, J. Verghese, Gait dysfunction in motoric cognitive risk syndrome, J Alzheimers Dis 71 (s1) (2019) S95–S103.
[14] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (2) (1987) 351–356.
[15] Al Olama A. Amin, J.M.S. Wason, A.M. Tuladhar, E.M.C. van Leijsen, M. Koini, E. Hofer, et al., Simple MRI score aids prediction of dementia in cerebral small vessel disease, Neurology 94 (12) (2020) e1294–e1302.
[16] S.H. Han, C.O. Kim, K.J. Kim, J. Jeon, H. Chang, E.S. Kim, et al., Quantitative analysis of the bilateral coordination and gait asymmetry using inertial measurement unit-based gait analysis, PLoS One 14 (10) (2019) e0222913.
[17] A. Kalron, Gait variability across the disability spectrum in people with multiple sclerosis, J. Neurol. Sci. 361 (2016) 1–6.
[18] C.W. Swanson, B.W. Fling, Associations between gait coordination, variability and motor cortex inhibition in young and older adults, Exp. Gerontol. 113 (2018) 163–172.
[19] J. Verghese, C. Wang, G. Allali, R. Holtzer, E. Ayers, Modifiable risk factors for new-onset slow gait in older adults, J. Am. Med. Dir. Assoc. 17 (5) (2016) 421–425.
[20] L. Zhang, B.L. Feng, C.Y. Wang, Y. Zhang, P. Lin, Y.L. Zhang, et al., Prevalence and factors associated with motoric cognitive risk syndrome in community-dwelling older Chinese: a cross-sectional study, Eur. J. Neurol. 27 (7) (2020) 1137–1145.
[21] L.K. Lau, S.L. Wee, W.J.B. Pang, K.K. Chen, K. Abdul Jabbar, P.L.K. Yap, et al., Reference values of gait speed and gait spatiotemporal parameters for a south east asian population: the yishun study, Clin. Interv. Aging 15 (2020) 1753–1765.
[22] F.J. Maguire, I. Killane, A.P. Creagh, O. Donoghue, R.A. Kenny, R.B. Reilly, Baseline association of motoric cognitive risk syndrome with sustained attention, memory, and global cognition, J. Am. Med. Dir. Assoc. 19 (1) (2018) 53–58.
[23] M. Maggio, F. Lauretani, Prevalence, incidence, and clinical impact of cognitive-motoric risk syndrome in Europe, USA, and Japan: facts and numbers update 2019, J Cachexia Sarcopenia Muscle 10 (5) (2019) 953–955.
[24] O. Beauchet, H. Sekhon, A.M. Schott, Y. Rolland, S. Muir-Hunter, M. Markle-Reid, et al., Motoric cognitive risk syndrome and risk for falls, their recurrence, and postfall fractures: results from a prospective observational population-based cohort study, J. Am. Med. Dir. Assoc. 20 (10) (2019) 1268–1273.
[25] J.K. Chhetri, C. Han, X. Dan, L. Ma, P. Chan, Motoric cognitive risk syndrome in a Chinese older adult population: prevalence and associated factors, J. Am. Med. Dir. Assoc. 21 (1) (2020) 136–137.
[26] A. Bai, W. Xu, Z. Lin, Prevalence and correlates of motoric cognitive risk syndrome in Chinese community-dwelling older adults, Front. Aging 3 (2022) 895138.
[27] A. Yaqub, S.K.L. Darweesh, L.J. Dommershuijsen, M.W. Vernooij, M.K. Ikram, F.J. Wolters, et al., Risk factors, neuroimaging correlates and prognosis of the motoric cognitive risk syndrome: a population-based comparison with mild cognitive impairment, Eur. J. Neurol. 29 (6) (2022) 1587–1599.
[28] G.T. Gomez, R.F. Gottesman, K.P. Gabriel, P. Palta, A.L. Gross, A. Soldan, et al., The association of motoric cognitive risk with incident dementia and neuroimaging characteristics: the Atherosclerosis Risk in Communities Study, Alzheimers Dement 18 (3) (2022) 434–444.
[29] T. Doi, S. Nakakubo, K. Tsutsumimoto, S. Kurita, Y. Kiuchi, K. Nishimoto, et al., The association of white matter hyperintensities with motoric cognitive risk syndrome, Cereb Circ Cogn Behav 3 (2022) 100150.
[30] M. Grau-Olivares, A. Arboix, C. Junqué, E.M. Arenaza-Urquijo, M. Rovira, D. Bartrés-Faz, Progressive gray matter atrophy in lacunar patients with vascular mild cognitive impairment, Cerebrovasc. Dis. 30 (2) (2010) 157–166.
[31] K. Takakusaki, Neurophysiology of gait: from the spinal cord to the frontal lobe, Mov. Disord. 28 (11) (2013) 1483–1491.
[32] N. Ward, A. Menta, S. Peach, S.A. White, S. Jaffe, C. Kowaleski, et al., Cognitive motor dual task costs in older adults with motoric cognitive risk syndrome, J Frailty Aging 10 (4) (2021) 337–342.
[33] C. Udina, E. Ayers, M. Inzitari, J. Verghese, Walking while talking and prefrontal oxygenation in motoric cognitive risk syndrome: clinical and pathophysiological aspects, J Alzheimers Dis 84 (4) (2021) 1585–1596.
[34] J.E. Wittwer, K.E. Webster, K. Hill, The effects of a concurrent motor task on walking in Alzheimer's disease, Gait Posture 39 (1) (2014) 291–296.
[35] H. Sekhon, G. Allali, C.P. Launay, J. Barden, T. Szturm, T. Liu-Ambrose, et al., Motoric cognitive risk syndrome, incident cognitive impairment and morphological brain abnormalities: systematic review and meta-analysis, Maturitas 123 (2019) 45–54.

[36] I. Arcolin, S. Corna, M. Giardini, A. Giordano, A. Nardone, M. Godi, Proposal of a new conceptual gait model for patients with Parkinson's disease based on factor analysis, Biomed. Eng. Online 18 (1) (2019) 70.
[37] M. Godi, I. Arcolin, M. Giardini, S. Corna, M. Schieppati, A pathophysiological model of gait captures the details of the impairment of pace/rhythm, variability and asymmetry in Parkinsonian patients at distinct stages of the disease, Sci. Rep. 11 (1) (2021) 21143.
[38] A. Fasano, C.G. Canning, J.M. Hausdorff, S. Lord, L. Rochester, Falls in Parkinson's disease: a complex and evolving picture, Mov. Disord. 32 (11) (2017) 1524–1536.
[39] K.N. Arya, S. Pandian, Interlimb neural coupling: implications for poststroke hemiparesis, Ann Phys Rehabil Med 57 (9–10) (2014) 696–713.