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Cerebral Small Vessel Disease and Motoric Cognitive Risk Syndrome: Results from the Kerala-Einstein Study

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Abstract

Background—The contribution of cerebral small vessel disease to cognitive decline, especially in non-Caucasian populations, is not well established.

Objective—We examined the relationship between cerebral small vessel disease and motoric cognitive risk syndrome (MCR), a recently described pre-dementia syndrome, in Indian seniors.

Methods—139 participants (mean age 66.6 ± 5.4 y, 33.1% female) participating in the Kerala-Einstein study in Southern India were examined in a cross-sectional study. The presence of cerebral small vessel disease (lacunar infarcts and cerebral microbleeds (CMB)) and white matter hyperintensities on MRI was ascertained by raters blinded to clinical information. MCR was defined by the presence of cognitive complaints and slow gait in older adults without dementia or mobility disability.

Results—Thirty-eight (27.3%) participants met MCR criteria. The overall prevalence of lacunar infarcts and CMB was 49.6% and 9.4%, respectively. Lacunar infarcts in the frontal lobe, but no other brain regions, were associated with MCR even after adjusting for vascular risk factors and presence of white matter hyperintensities (adjusted Odds Ratio (aOR): 4.67, 95% CI: 1.69–12.94). Frontal lacunar infarcts were associated with slow gait (aOR: 3.98, 95% CI: 1.46–10.79) and poor performance on memory test (β : -1.24 , 95% CI: -2.42 to -0.05), but not with cognitive complaints or non-memory tests. No association of CMB was found with MCR, individual MCR criterion or cognitive tests.

Conclusions—Frontal lacunar infarcts are associated with MCR in Indian seniors, perhaps, by contributing to slow gait and poor memory function.

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Keywords

Aging; cerebral small vessel diseases; cognition; frontal lobe; gait; lacunar infarct; magnetic resonance imaging; memory

INTRODUCTION

Motoric cognitive risk (MCR) syndrome is a recently described pre-dementia syndrome characterized by the presence of both cognitive complaints and slow gait in older adults without dementia [1–3]. MCR is common, with a world wide prevalence of 9.7% reported in a recent study involving over 26,000 older adults from 17 countries [3]. Prevalence of MCR in six low- or middle-income countries (including India) ranged from 5.3% to 15.5% [3]. MCR is a strong predictor of cognitive decline and dementia in Western populations [1–3], yet the pathophysiology of MCR has not been established.

Both cerebral large and small vessel disease are linked to the risk of developing cognitive decline in aging [4–6]. Cerebral small vessel disease such as lacunar infarcts and cerebral microbleeds (CMB) contribute independently to cognitive decline in older adults even after accounting for cortical strokes [5]. These relationships, however, have been reported mainly in Caucasian populations [4, 5]. Little is known about the independent contributions of cerebral small vessel disease to dementia in low and middle income countries such as India, where there is a growing epidemic of vascular diseases [7].

To address this knowledge gap and to examine vascular contributions to MCR, we studied the association of lacunar infarcts and CMB with MCR in the Kerala-Einstein study (KES) located in Southern India [8]. A recent study involving over 3,000 older adults reported that stroke, diabetes, hypertension, obesity, and sedentary lifestyle were risk factors for incident MCR [1]. Since these risk factors can act through vascular mechanisms to impair brain function, we hypothesized that the presence of cerebral small vessel disease would be associated with MCR in Indian seniors even after accounting for potential confounders. Establishing this association will provide pathologic insights that may improve diagnosis and treatment of older adults at high risk of developing dementia.

MATERIALS AND METHODS

Study population

We examined the cross-sectional relationship between cerebral small vessel disease and MCR in older adults with neuroimaging from Kozhikode city site of the KES. The KES study design and protocols have been described elsewhere [8]. In brief, the goal of KES is to identify risk factors for dementia in Indian seniors. A neuroimaging sub-study was initiated in 2011 to examine vascular mechanisms of dementia. There was only a 26% overlap between the KES sample reported in the previous study [8] and the more recently recruited sample for this imaging sub-study. Potential participants were identified from patients attending the Neurology clinic at Baby Memorial Hospital, Kozhikode. Reasons for referral to clinic included cognitive complaints or other neurological symptoms such as headache, strokes, or neuropathy. Additional participants were recruited from relatives of clinic

patients (30%) as well as patients attending medical clinics for non-neurological problems (30%). Inclusion criteria were age 60 and older and absence of dementia (see below). Exclusion criteria were presence of severe audiovisual disturbances, any severe medical or neurological diseases, or standard neuroimaging exclusion criteria such as presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin, or body [8]. Of the 157 participants screened between February 2011 and February 2015 in KES, 139 who completed clinical evaluations and neuroimaging studies were included. Reasons for not obtaining neuroimaging included refusal ($n = 3$) and logistical constraints ($n = 15$).

The study was conducted in accord with the ethical standards of the Committee on Human Experimentation of the participating institutions. The study protocol was approved by institutional review boards in India (Baby Memorial Hospital, Kozhikode) and United States (Albert Einstein College of Medicine, NY). Written informed consent was obtained from all participants prior to study enrollment.

MCR diagnosis

As previously reported in the KES [2], MCR was defined as the presence of cognitive complaints and slow gait in older adults without dementia or mobility disability (inability or requiring assistance to ambulate). The MCR definition builds on the mild cognitive impairment syndrome (MCI) criteria [9]. The only difference is that the objective cognitive impairment criterion based on cognitive tests in MCI is substituted by presence of slow gait in MCR. All other criteria remain the same, and MCR diagnosis does not require cognitive tests [2]. Cognitive complaints were assessed with a memory complaint item on the 15-item Geriatric Depression Scale (GDS) [8, 10], and corroborated by reliable informants when available as well as by observations of KES clinicians [2, 3]. The same GDS memory complaint item was used to define subjective cognitive complaints of MCR in eight out of the 22 cohorts in the earlier worldwide MCR prevalence study [3]. Subjective cognitive complaints have been reported to be associated with increased risk of cognitive decline [11]. However, MCR was shown to have improved predictive validity for dementia compared to either subjective cognitive complaints or slow gait alone in multiple cohorts [2, 3]. Gait speed (cm/s) was assessed with a 16-foot computerized walkway (GAIT Rite) [12]. Participants walked for one trial on the walkway at their normal pace without any attached monitors or assistive devices. Slow gait was defined as gait speed one standard deviation or more below age and gender-specific means previously established in the KES sample [2]. Slow gait was objectively defined independent of subjective clinical gait evaluations. Slow gait by itself or as part of the MCR definition was associated with increased risk of dementia irrespective of the underlying neurological or non-neurological etiologies [2]. Participants with dementia were excluded after review of all clinical and neuropsychological data at consensus case conferences as previously described [8].

MRI protocol and assessment

Participants underwent a standard MRI protocol with a 1.5 Tesla MRI system (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany), including T1-weighted (acquisition matrix = 256×256 , FOV = $256 \text{ mm} \times 256 \text{ mm}$, 1 mm resolution, no gap,

TE/TR = 4.9 ms/11 ms), T2-weighted (acquisition matrix = 320×245 , FOV = $195 \text{ mm} \times 230 \text{ mm}$, 5 mm resolution, gap = 2.3 mm, TE/TR = 96 ms/ 4130 ms), Fluid Attenuated Inversion Recovery (FLAIR; acquisition matrix = 256×232 , FOV = $208 \text{ mm} \times 230 \text{ mm}$, 5 mm resolution, gap = 0.8 mm, TE/TR= 93 ms/9000 ms), and susceptibility-weighted image (SWI; acquisition matrix = 320×221 , FOV = $186 \text{ mm} \times 230 \text{ mm}$, 1.6 mm resolution, no gap, TE/TR = 40 ms/49ms) sequences.

CMB were defined as small, focal, round, and hypointense lesions sized 2 to 10 mm in diameter on SWI [13]. We excluded curvilinear lesions in the sub-arachnoid space (cortical vessels) and symmetrical hypointensities in the globi pallidi or dentate nuclei (mineralization) [13, 14]. The validated Microbleed Anatomic Rating Scale (MARS) was used to rate CMB. The MARS assesses CMB in three regions: lobar (frontal, parietal, temporal, occipital), infratentorial (brainstem and cerebellum), and deep brain (basal ganglia, thalamus, capsule, corpus callosum) [13]. The number of CMB in each region was recorded, and summed as a global CMB score [13].

Lacunar infarcts were identified as hyperintense focal lesions $>3\text{mm}$ and $<15\text{mm}$ in diameter on T2-weighted images [6]. Lacunar infarcts in the white matter also had to be hypointense on T1-weighted and FLAIR images to differentiate them from white matter hyperintensities. The number of lacunar infarcts in each brain region was recorded, including frontal, parietal, temporal, occipital, infratentorial (brainstem and cerebellum), and deep brain regions (basal ganglia, thalamus, capsule, corpus callosum). The total number of lacunar infarcts was calculated as a global lacunar infarct score.

White matter hyperintensity burden was rated by the Age-Related White Matter Changes scale (ARWMC) in five regions: frontal, parietal-occipital (parietal and occipital lobes), temporal, infratentorial, and basal ganglia [15]. Scores in all five regions were summed to obtain a global white matter hyperintensity burden score (range 0–30), which was included as a covariate in analyses. Cortical strokes were examined separately, and rated as large infarcts involving cortical and adjacent subcortical tissue or striatocapsular/subcortical lesions $>15\text{mm}$ in diameter [16].

All neuroimaging studies were rated by a consultant neuroradiologist (CK) blinded to MCR status and study assessments. An inter-rater reliability study in a random sample of 20 KES participants was done between readings by the neuroradiologist and a study investigator (NW) trained in rating lesions of cerebral small vessel disease. Inter-rater reliability calculated using weighted κ values was in the substantial agreement range for lacunar infarcts (κ 0.68), CMB on the MARS scale (κ 0.75), and white matter hyperintensity burden on the ARWMC scale (κ 0.71) [17].

Assessment of covariates

All interviews and tests were conducted in the local language (Malayalam) [8]. A study clinician obtained medical history, reviewed medications, recorded vital signs, and conducted a neurological examination. Physician-diagnosed vascular diseases such as myocardial infarction, strokes, diabetes, peripheral vascular disease, and hypertension were recorded [18]. Hypertension was defined as any one of the following: self-reported

hypertension, high blood pressure at study visits (systolic ≥ 150 mm Hg or diastolic ≥ 90 mm Hg) [19], or current antihypertensive medication use. No participant had peripheral vascular disease or strokes. Smoking status was ascertained. Cognitive function was assessed by a clinician with behavioral neurology expertise [8]. For this study, we examined performance on the Mini-Mental State Examination (MMSE) for global cognitive status, Rey auditory verbal learning test (number of words recalled at 20 minutes delay) for memory function, and digit span test (total span) for attention and working memory [8]. The 15-item GDS was used to assess mood [8, 10].

Statistical analysis

All statistical analyses were performed with SPSS version 21.0 (IBM Corp, Armonk). Descriptive statistics were used to compare baseline characteristics of participants with and without MCR. Logistic regression was used to investigate the association of cerebral small vessel disease globally and in brain subregions with MCR. The brain regions were defined as global (lesions in any part of the brain), frontal, parietal, temporal, occipital, basal ganglia, and infratentorial regions (brainstem and cerebellum). Both lacunar infarcts and CMB were entered together in models to assess their statistically independent associations with MCR status. All analyses were adjusted for age, gender, education, GDS score, vascular diseases, smoking status, white matter hyperintensity burden, and cortical strokes. Associations were reported as adjusted odd ratios (aOR) with 95% confidence intervals (CI).

Since MCR includes both cognitive and motor features, we conducted sensitivity analyses with the individual MCR criterion (cognitive complaints and slow gait) using logistic regression. As cognitive complaints may not be sensitive to early pathological stages of dementia, we examined objective cognitive tests of amnesic (Rey auditory verbal learning test) and non-amnesic domains (digit span test) as secondary outcomes using linear regression. We chose digit span test as our primary non-amnesic test, as it assesses attention and working memory processes, which are strongly correlated with gait speed [20]. Both sensitivity analyses were adjusted for the same covariates as in the primary analysis. Associations were reported as unstandardized regression coefficients (β) with 95% CI. We did not adjust for multiple comparisons in our main analyses as our approach was hypothesis driven. Nonetheless, we examined the significant results applying Bonferroni correction (threshold $p < 0.01$).

RESULTS

Baseline characteristics of the study population are presented in Table 1. Among the 139 participants, 38 met MCR criteria (mean age 67.5 ± 4.9 y, 26.3% female) and 101 were non-MCR (mean age 66.3 ± 5.5 y, 35.6% female). Compared to the non-MCR group, the MCR group had lower gait speed ($p = 0.001$). There were no other significant group differences. The MCR group had higher prevalence of lacunar infarcts in the frontal lobe (57.9% versus 29.7%, $p = 0.003$). The prevalence of CMB in the MCR group was non-significantly higher than the non-MCR group (13.2% versus 7.9%, $p = 0.516$).

Cerebral small vessel disease and MCR

Table 2 showed that lacunar infarcts globally were not associated with MCR. Only frontal lacunar infarcts were associated with MCR (aOR: 4.67, 95% CI: 1.69–12.94). The association of frontal lacunar infarcts with MCR survived statistical correction for multiple comparisons (threshold $p = 0.003$).

Global and regional CMB were not associated with MCR (Table 3).

White matter hyperintensities and MCR

The white matter hyperintensity scores on the ARWMC scale were not associated with MCR (aOR: 0.80, 95% CI: 0.29–2.16).

Cortical strokes and MCR

The presence of cortical strokes was not associated with MCR (aOR: 9.06, 95% CI: 0.75–109.56).

Sensitivity analysis

Table 2 showed that frontal lacunar infarcts were associated with slow gait (aOR: 3.98, 95% CI: 1.46–10.79). Global and regional lacunar infarcts were not associated with cognitive complaints. Frontal lacunar infarcts were related to poor performance on the amnesic test (β : -1.24, 95% CI: -2.42 to -0.05). Global and regional lacunar infarcts were not associated with digit span test scores.

Global and regional CMB were not associated with cognitive complaints, slow gait, or cognitive tests (Table 3).

DISCUSSION

We found an association of MRI-defined lacunar infarcts, specifically in the frontal lobe, with MCR in Indian seniors in this cross-sectional study. Despite the growing burden of cardiovascular diseases and dementia in low- and middle-income countries [7, 21], there is a dearth of research in these countries. To our knowledge, this is one of the first and largest clinical imaging studies to link cerebral small vessel disease on MRI to a predementia syndrome such as MCR in India. The association of lacunar infarcts with MCR remained even after accounting for several demographic confounders, vascular risk factors, CMB, white matter hyperintensities, and cortical strokes.

Frontal lacunar infarcts were related to slow gait but not cognitive complaints in our study. Cognitive complaints might be less sensitive to early pathological stages of dementia than objective cognitive tests [22]; though other investigators have suggested that subjective cognitive complaints might be an early marker of cognitive decline in highly educated individuals [11, 23]. Our sensitivity analysis showed that frontal lacunar infarcts were associated with poor memory performance. Frontal lacunar infarcts might lead to MCR by disrupting frontally based neural networks sub-serving memory and gait functions [24,25]. While online investigation of frontal lobe involvement in locomotion is limited, recent

studies using a variety of techniques including functional near infra-red spectroscopy [26], functional MRI studies using imagined walking protocols [27] and correlative studies of brain substrates with quantitative gait parameters all support a role of the frontal lobe, especially the pre-frontal areas, in the cortical control of gait speed [28]. Frontal lobe damage is also associated with a variety of specific memory deficits [29]. While frontally based non-amnesic cognitive processes such as executive function and attention are also linked to gait [30], disruption of these processes by lacunar infarcts does not appear to be prominent in MCR. Our initial validation study showed that MCR predicted vascular dementia [2]. However, in a subsequent study, MCR predicted Alzheimer's disease in over 3,000 individuals from two U.S. based cohorts [1]. The current results suggest that cerebral small vessel disease may initiate amnesic deficits in seniors that could clinically present as early stages of Alzheimer's dementia. Further research is required to assess the influence of combined neurodegenerative and vascular pathologies on the development of MCR and specific dementia subtypes in older adults.

While there are no previous clinicopathological studies of MCR, our findings are supported by studies in Western populations that have examined cognitive and motor correlates of cerebral small vessel disease. A multicenter European study reported that lacunar infarcts were related to steeper decline in executive functions and psychomotor speed [31]. Baune et al. [32] found that lacunar infarcts were strongly associated with cognitive processing speed and weakly associated with memory in older Germans. Silent brain infarcts were related to slower gait and lower supratentorial white matter volume in a large Canadian cohort aged 40 to 75 years [33]. A Netherlands-based study found that frontal lacunar infarcts were associated with slow gait [34]. In contrast, in low- and middle-income countries, very few studies have examined the impact of lacunar infarcts on cognitive and motor functions. A study from China suggested that lacunar infarcts might impair cognitive function by disrupting cerebral network connectivity [35]. The converging evidence from previous studies regarding the associations of lacunar infarcts with cognitive-motor features suggests that our MCR findings may be applicable to other populations, and should be verified in more diverse groups.

No association of CMB with MCR or its components was observed, suggesting that the influence of CMB on dementia risk might be weaker than that of lacunar infarcts in Indian seniors. Previous studies that examined the relationship between CMB and cognitive impairment showed mixed results; with some reporting significant associations [36, 37] and others were not significant [38, 39]. Our sample had a lower prevalence of CMB compared to studies in developed countries (18–38%) [40], which might reflect regional or lifestyle differences that need to be further examined. Besides, most of our participants only had one CMB lesion. Increasing CMB burden has been associated with cognitive impairment in other cohorts, suggesting a threshold effect on dementia risk [41].

Study strengths include the standardized and validated cognitive, gait, and imaging assessments. While our focus was on defining the pathogenesis of MCR, our findings also shed light on the vascular basis of cognitive and gait impairment in this population.

Our study has several potential limitations. The cross-sectional design did not permit causal inferences, which needs to be tested in longitudinal studies. We used a convenience sample mainly recruited patients from neurology clinics, which explains the higher prevalence of vascular lesions and disease burden, and should not be considered representative of the general population. The prevalence of MCR (27.3%) in this convenience sample was higher than previously reported in KES (15.0%) [3]. Both rates were higher than the global prevalence (9.7%), which reflected the clinic-based nature of the KES population [3]. There was only a 26% overlap between the previous and current KES samples. The higher prevalence of MCR might reflect selection bias due to the fact that patients with cognitive or other medical complaints are more likely to volunteer for the MRI substudy. Our sample was predominantly male, reflective of research participation patterns in this region, and needs to be verified in samples with greater female representation.

Adjustment for vascular risk factors in our models did not attenuate the relationship between frontal lesions of cerebral small vessel disease and MCR, suggesting that other non-vascular mechanisms might be involved. However, direct measures of vascular pathology were limited, and needs to be examined. Lipid profiles were not obtained in all participants. There was a very low prevalence of cardiac arrhythmias reported in this study [18]. While we examined white matter hyperintensities, these lesions could result from both vascular and neurodegenerative pathologies [6]. The relatively large sample size with clinical and imaging data from an understudied region is an advantage, but we acknowledge that the lack of associations with some lesions could reflect limited power. The limited number of lacunar infarcts in temporal and occipital regions did not permit examination of these regions, although this vascular damage pattern might reflect pathological distributions in the Indian population. While we adjusted for multiple confounders, residual or unmeasured confounding variables cannot be excluded. For instance, information on important variables such as body mass index and physical activity was lacking. Future studies in larger and heterogeneous samples with quantitative measures of vascular and neurodegenerative pathologies are needed to follow up on our results.

In conclusion, presence of lacunar infarcts in the frontal lobe was associated with MCR in older Indian adults, by contributing to poor performance on memory processes as well as slow gait. Longitudinal follow-up is necessary to build on these findings. A better understanding of the underlying etiologies of MCR can help improve early detection of high-risk dementia population and provide insights into preventive interventions for cognitive decline in older adults.

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Fig. 1. Frontal lacunar infarcts appear hyperintense on T2 image (A, arrow) and hypointense on FLAIR image (B, arrow).

Table 1Baseline characteristics of the study population (*p* values <0.05 are bolded)

Characteristics (<i>n</i> = 139)	Non-MCR (<i>n</i> = 101)	MCR (<i>n</i> = 38)	<i>p</i> value
Demographic characteristics			
Age, y	66.3 ± 5.5	67.5 ± 4.9	0.258
Female, %	35.6	26.3	0.321
Education, y	8.9 ± 3.4	8.7 ± 2.5	0.710
Geriatric depression scale (range 0–15)	4.2 ± 3.4	5.2 ± 2.8	0.108
Hypertension, %	55.4	68.4	0.319
Smoking, %	5.9	5.3	0.999
Diabetes, %	24.8	28.9	0.831
Previous myocardial infarction, %	6.9	2.6	0.437
Gait speed (cm/s)	91.0 ± 16.3	61.9 ± 11.2	0.001
Neuroimaging characteristics			
<i>Lacunar infarcts:</i>	44.6	63.2	0.059
Total, %			
Frontal, %	29.7	57.9	0.003
Parietal, %	15.8	13.2	0.796
Temporal, %	2.0	0.0	0.999
Occipital, %	1.0	0.0	0.999
Basal ganglia, %	10.9	18.4	0.263
Infratentorial, %	1.0	2.6	0.473
<i>Cerebral microbleeds:</i>	7.9	13.2	0.516
Total, %			
Frontal, %	2.0	0.0	0.999
Parietal, %	2.0	5.3	0.311
Temporal, %	3.0	0.0	0.560
Occipital, %	0.0	0.0	0.999
Basal ganglia, %	2.0	2.6	0.999
Infratentorial, %	3.0	2.6	0.999
<i>White matter hyperintensity score:</i>	2.6 ± 3.7	3.0 ± 3.4	0.638
<i>Cortical strokes, %:</i>	2.0	7.9	0.130
Cognition characteristics			
MMSE (range 0–30)	28.1 ± 2.4	27.9 ± 2.5	0.568
Rey auditory verbal learning test	5.1 ± 3.0	4.3 ± 3.2	0.205
Digit span test – total span	10.0 ± 1.9	9.6 ± 1.5	0.394

^aValues are mean ± SD unless otherwise specified.^bMMSE, Mini-Mental State Examination.

Table 2

Association between lacunar infarcts and MCR, individual MCR criterion, and cognitive tests (*p* values <0.05 are bolded)

Location of Lacunar infarcts	MCR		Cognitive complaints		Slow gait		Amnesic test		Non-amnesic test	
	<i>aOR</i>	(95% CI)	<i>aOR</i>	(95% CI)	<i>aOR</i>	(95% CI)	β	(95% CI)	β	(95% CI)
Global	2.43	(0.88–6.68)	1.58	(0.55–4.60)	2.70	(0.99–7.38)	–1.14	(–2.36 to 0.09)	–0.24	(–0.87 to 0.40)
	0.085		0.398		0.053		0.069		0.463	
Frontal	4.67	(1.69–12.94)	2.15	(0.75–6.14)	3.98	(1.46–10.79)	–1.24	(–2.42 to –0.05)	0.28	(–0.33 to 0.89)
	0.003		0.155		0.007		0.041		0.368	
Parietal	0.63	(0.19–2.09)	0.64	(0.18–2.25)	1.27	(0.39–4.06)	–1.02	(–2.55 to 0.51)	–0.21	(–0.98 to 0.56)
	0.447		0.485		0.692		0.189		0.588	
Basal ganglia	2.33	(0.62–8.72)	3.86	(0.69–21.60)	1.43	(0.38–5.44)	–0.71	(–2.57 to 1.14)	0.34	(–0.56 to 1.23)
	0.210		0.124		0.597		0.448		0.459	
Infra-tentorial	1.77	(0.06–49.81)	#		0.90	(0.03–24.16)	–0.89	(–6.77 to 5.00)	–1.55	(–3.91 to 0.80)
	0.738				0.947		0.765		0.194	

^a All associations were adjusted for age, gender, education, GDS score, vascular disease, smoking status, global CMB, white matter hyperintensity burden score and cortical strokes.

^b The amnesic test is Rey auditory verbal learning test, and the non-amnesic test is digit span test.

^c The analysis could not be performed in temporal and occipital regions due to limited number of lacunar infarcts in these regions.

^d #: insufficient data.

Table 3

Association between cerebral microbleeds (CMB) and MCR, individual MCR criterion, and cognitive tests (*p* values <0.05 are bolded)

Location of CMB	MCR <i>aOR</i> (95% CI) <i>p</i> value	Cognitive complaints <i>aOR</i> (95% CI) <i>p</i> value	Slow gait <i>aOR</i> (95% CI) <i>p</i> value	Amnesic test		Non-amnesic test	
				β (95% CI) <i>p</i> value	β (95% CI) <i>p</i> value	β (95% CI) <i>p</i> value	β (95% CI) <i>p</i> value
Global	1.22 (0.32–4.67) 0.774	0.24 (0.05–1.14) 0.072	1.48 (0.38–5.78) 0.569	–1.47 (–3.35 to 0.41) 0.125	–0.55 (–1.49 to 0.39) 0.249		
Frontal	#	0.11 (0.01–4.42) 0.244	#	–1.55 (–5.74 to 2.63) 0.463	–0.46 (–2.73 to 1.80) 0.687		
Parietal	0.88 (0.10–7.83) 0.905	#	0.69 (0.07–6.62) 0.746	–2.49 (–5.45 to 0.47) 0.098	0.31 (–1.31 to 1.93) 0.706		
Temporal	#	0.35 (0.02–6.15) 0.470	#	–0.40 (–6.23 to 5.43) 0.892	0.72 (–1.11 to 2.55) 0.437		
Basal ganglia	1.73 (0.20–14.88) 0.616	0.17 (0.02–1.98) 0.158	4.27 (0.35–52.00) 0.255	0.48 (–2.81 to 3.77) 0.775	0.21 (–1.35 to 1.77) 0.789		
Infra-tentorial	2.01 (0.09–43.73) 0.657	0.12 (0.01–2.89) 0.189	2.35 (0.08–70.17) 0.621	–1.77 (–5.76 to 2.23) 0.383	–1.44 (–3.60 to 0.71) 0.187		

^a All associations were adjusted for age, gender, education, GDS score, vascular disease, smoking status, global lacunar infarcts, white matter hyperintensity burden score and cortical strokes.

^b The amnesic test is Rey auditory verbal learning test, and non-amnesic test is digit span test.

^c The analysis could not be performed in occipital regions due to limited number of CMB in these regions.

^d #: insufficient data.