

Microstructural damage of normal-appearing white matter in subcortical ischemic vascular dementia is associated with Montreal Cognitive Assessment scores

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Abstract

Objectives: This study was performed to determine whether multimodal biomarkers are more strongly associated with the Montreal Cognitive Assessment (MoCA) scores compared with the Mini-Mental State Examination (MMSE) scores, and whether they are correlated with the Clinical Dementia Rating (CDR) in patients with subcortical ischemic vascular dementia (SIVD).

Methods: Patients diagnosed with SIVD were enrolled. Peripheral blood hypersensitive C-reactive protein, white matter lesion volume (WMLV), fractional anisotropy (FA)/mean diffusivity (MD) of whole brain white matter (WBWM), and normal-appearing white matter (NAWM) were measured and correlated with MMSE, MoCA, and CDR scores.

Results: Bivariate analyses of data from 48 included patients revealed that both MoCA and MMSE were significantly associated with age, education, and FA of NAWM. Only MD of NAWM was correlated with MoCA scores. In partial correlation analysis adjusted for demographic and neuroimaging variables, MD/FA of NAWM and the MoCA scores were significantly correlated. FA/MD of NAWM had a modest trend toward a correlation with the CDR, but it was not significant.

Conclusions: In the patients with SIVD, FA/MD of NAWM were more strongly related to MoCA scores compared with MMSE scores.

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Keywords

Cerebral small vessel disease, subcortical ischemic vascular dementia, cognition, diffusion tensor imaging, psychological assessment, multimodal biomarker, Clinical Dementia Rating, Mini-mental state Examination

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Introduction

Vascular dementia is the second most common dementia, and subcortical ischemic vascular dementia (SIVD) is its most frequent subtype.¹ The main risk factors of SIVD are hypertension and/or diabetes mellitus, and the pathology is fibrosis of small arteries, arterioles, venules, and capillaries of the brain.² Deep white matter regions are the most vulnerable to pathological insults to the vasculature system because of reduced blood flow. A cascade of events is triggered as a consequence of reduced blood flow and hypoxia, ending in neuroinflammation.³ This chronic situation leads to detectable changes in cognition and several serological and magnetic resonance (MR) imaging markers related to SIVD, including hypersensitive C-reactive protein (hs-CRP), white matter lesion volumes (WMLV), fractional anisotropy (FA), and mean diffusivity (MD) of diffusion tensor MR imaging.^{4,5}

Neuropsychological testing of suspected SIVD patients reveals primarily executive dysfunction, and memory and language problems can also be present. The Mini-Mental Status Examination (MMSE) is widely used, but it is insensitive to vascular cognitive impairment because of a lack of prefrontal-executive tasks. The Montreal Cognitive Assessment (MoCA) picks up more cognitive deficits than the MMSE in patients with cerebral vascular disease, including executive, attention, and abstraction tasks.⁶ Compared with the MMSE,

the MoCA appears to be more sensitive for detecting impairments in executive function.⁷ Thus, the MoCA, rather than the MMSE, has been proposed as a tool to screen for vascular cognitive impairment.⁸

Studies suggested that the MoCA-detected impairment was independently associated with the white matter lesions in the frontal anterior regions and with lower FA in all white matter tracts.⁹ Both the total MoCA score and subtest scores of MoCA (visuoexecutive function, attention, language, and delayed recall scores) were positively correlated with the regional cerebral blood flow (rCBF) in the prefrontal cortex, which corresponded to the essential components of the prefrontal-subcortical circuits and played an important role in cognitive function. However, the total MMSE score did not correlate significantly with any of the rCBF measures. Even in the normal-appearing white matter (NAWM), rCBF may be reduced, thereby affecting the integrity of cortico-cortical or cortico-subcortical connections and cognitive function.¹⁰ A previous study showed that MoCA scores are more relevant to changes in FA/MD of whole brain white matter (WBWM) than MMSE scores in patients with SIVD.¹¹ It is unclear whether there is a difference between the WBWM and NAWM in the MoCA-detected impairment. The present study further assessed whether hs-CRP, WMLV, FA/MD of WBWM, and NAWM are more strongly associated with MoCA scores, and whether

they correlate with the Clinical Dementia Rating (CDR).

Methods

Study population

Patients diagnosed as SIVD were enrolled from an ongoing study entitled, the Remote Ischemic Preconditioning for Subcortical Vascular Dementia study. This study is registered in the NIH Clinical Trial Registration website at <http://www.clinicaltrials.gov> (unique identifier: NCT 03022149). Our inclusion criteria were based on those described previously:¹² (1) 50 to 85 years old; (2) complaint of cognitive impairment lasting at least 3 months; (3) vascular dementia diagnosis conforming to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), with MMSE score of 10 to 26; MoCA score of 10 to 26; and CDR of 0.5 to 2. Additionally, their brain MRI findings had to meet the diagnostic criteria for SIVD, as described by the following:¹³ (1) multiple (≥ 3) small infarcts (3–20 mm in diameter) in supratentorial white matter; or moderate to severe white matter lesions (WML) (score ≥ 2 , based on the Fazekas rating scale¹⁴) or strategically localized small infarcts in the thalamus; (2) no cortical or watershed infarcts, hemorrhages, or hydrocephalus, or no WML resulting from specific causes (e.g., multiple sclerosis). Exclusion criteria were as follows: severe aphasia, presence of physical disabilities, or any other reason preventing complete neuropsychological testing; a Hamilton depression scale score of >17 ; new strokes within the last 3 months; and hereditary or inflammatory small vessel disease. This study was approved by the hospital ethics committee of Tianjin Medical University General Hospital (IRB6-YX-042), and written informed consent was obtained from all participants.

Neuropsychological testing

The MMSE is the most widely used instrument for cognitive screening. Compared with the MMSE, the MoCA includes more comprehensive assessment of major cognitive domains (executive function, short-term memory, language abilities, and visuospatial processing). We used the CDR scale to assess the severity of dementia, which combines inquiries about both cognitive and functional performances in life. Other cognitive domains were also assessed. Immediate memory, delayed memory, and recognition memory were assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R).¹⁵ We assessed language ability by measuring the category fluency using the Controlled Oral Word Association Test (COWAT).¹⁶ Measures of attention and executive function were assessed using the Trail Making Test A and B (TMT-A and TMT-B).¹⁷ Visual-spatial processing was examined by the Symbol Digit Modalities Test (SDMT) and the Judgment of Line Orientation (JLO).^{18,19} All the neuropsychiatric scales were Chinese versions except the JLO, which is almost not influenced by language.

Measurements of the inflammatory factor Hs-CRP

Hs-CRP was detected in the plasma using a commercially available turbidimetric immunoassay ELISA kit, in accordance with the manufacturer's instructions (MedicalSystem Biotechnology Co., Ltd., Ningbo, China).

MRI scanning protocol

MRI was performed using a 3.0T whole-body system (Discovery MR750; General Electric, Milwaukee, WI, USA) with an eight-channel phased array head coil. Head scans were acquired. Cube FLAIR parameters (156 slices; repetition time [TR],

6000 ms; echo time [TE], 144 ms; echo train length, 200; slice thickness, 1.2 mm; and in-plane resolution, 1 mm²) were used for lesion detection. Three-dimensional (3D) T1-weighted images were constructed using a brain volume (BRAVO) sequence (156 slices; TR, 8.14 ms; TE, 3.17 ms; inversion time [TI], 450 ms; flip angle, 12°; slice thickness, 1.2 mm; in-plane resolution, 1 mm²); these images were used for brain volume measurements. To detect micro-structural damage, diffusion tensor images (DTIs) were acquired (48 slices; TR, 5000 ms; TE, 60.6 ms; slice thickness, 3 mm; in-plane resolution, 2 mm²; 50 non-collinear diffusion gradients [$b = 1000 \text{ s/mm}^2$]).

Image analysis

Analysis of WML. Marking and measuring WMLV on cube FLAIR images were performed manually using MRIcro software (<http://www.mccauslandcenter.sc.edu/crnl/mricro>).

DTI analysis. The mean diffusion indices of the WBWM, WML, and NAWM (WBWM minus lesion regions) were extracted, and DTI data were processed using the FMRIB Software Library (FSL) 5.0 (Analysis Group, FMRIB, Oxford, UK). First, an affine transformation on the raw diffusion data was used to correct image distortion by eddy current. Second, voxels outside brain tissue were filtered out by the brain extract toolbox (BET). Then, a linear least-square fitting algorithm was used to fit the tensor, and three eigenvalues, MD, and FA were calculated from the tensor.

WML were manually separated from the T2 FLAIR images and saved as a binary mask for each subject. The 3D T1-weighted images (T1WI) were segmented into gray matter, white matter, and cerebrospinal fluid using SPM8 software routines (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Then, the white matter

was binarized, and a whole white matter mask was created using a threshold of 50%. The T1WI were co-registered to the b0 images (diffusion images without exerting gradient field), T2 FLAIR images were registered to the T1 images, and the two transformations were combined to obtain a transformation from Flair to b0, and then applied to the lesion masks. The NAWM mask was obtained by subtracting the WML mask from the WBWM mask. Finally, by averaging the values of all voxels with the mask, the FA and MD of each mask were calculated for each subject.

Statistical analysis

The independent *t*-test or chi-squared analysis was used to assess the characteristics of the study population. The statistical association between demographic values, hs-CRP values, WMLV values, FA/MD of DTI values, and neuropsychological testing scores were evaluated using the independent *t*-test, bivariate analysis or partial correlation analysis (adjusting for all demographic and neuroimaging variables). Analysis of variance (ANOVA) was used to test the difference of the hs-CRP, WMLV, and FA/MD in the three groups (CDR = 0.5, CDR = 1, CDR = 2).

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp., Armonk, NY, USA). All hypothesis tests were two-tailed, and *P* values <0.05 were considered significant.

Results

Characteristics of SIVD patients

Between January 2016 and September 2016, 48 patients satisfied our inclusion criteria and were enrolled. Demographic, clinical neuropsychological, and neuroimaging characteristics are shown in Table 1. The mean age of the participants was

Table 1. Characteristics of the study population (n = 48).

Characteristic	Mean \pm SD or Percentage (%)
Age (years)	68.8 \pm 7.7
Education (years)	9.8 \pm 3.3
Gender	
Female	41.7
Male	58.3
Medical history	
Hypertension	85.4
Hyperlipidemia	22.9
Diabetes mellitus	43.8
Neuropsychological test scores	
HAMD	5.9 \pm 3.7
MMSE	22.7 \pm 3.8
MoCA	17.9 \pm 4.3
CDR	1.1 \pm 0.6
HVLТ	
HVLТ1	12.7 \pm 4.6
HVLТ2	2.4 \pm 2.5
HVLТ3	6.4 \pm 2.2
COWAT	4.7 \pm 3.3
TMT-A	145.5 \pm 90.6
TMT-B	265.7 \pm 117.4
SDMT	21.0 \pm 12.6
JLO	18.3 \pm 6.3
Inflammatory factor	
Hs-CRP (mg/L)	2.9 \pm 4.8
WMLV (mL)	69.4 \pm 37.6
WBWM	
FA	0.31 \pm 0.02
MD ($\times 10^{-4}$)	9.02 \pm 0.59
NAWM	
FA	0.31 \pm 0.02
MD ($\times 10^{-4}$)	8.7 \pm 0.47

CDR, Clinical Dementia Rating; COWAT, Controlled Oral Word Association Test (outcome was the sum of correct words from the both parts); FA, fractional anisotropy; HAMD, Hamilton Depression Scale; hs-CRP, high-sensitivity C-reactive protein; HVLТ1, Hopkins Verbal Learning Test-Revised (HVLТ-R), immediate memory; HVLТ2, delayed memory; HVLТ3, recognition memory; JLO, Judgment of Line Orientation; MD, mean diffusivity; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NAWM, normal-appearing white matter; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; WBWM, whole-brain white matter; WMLV, white matter lesion volume; SD, standard deviation.

68.8 years (standard deviation [SD] 7.7), and 58.3% were male. The mean WMLV was 69.4 mL (SD 37.6). Most patients had a medical history of hypertension and diabetes (85.4% and 43.8%, respectively).

Association between demographic characteristics, multimodal markers, and MMSE and MoCA scores

Table 2 summarizes the main statistical relationships. Other than participant age and education, FA of NAWM was significantly correlated with the MoCA and MMSE scores. MD of NAWM was correlated only with MoCA scores (MD, $r = -0.54$, $P = 0.031$). After adjusting for all demographic and neuroimaging variables in partial correlation analyses, only MD and FA of NAWM were associated with MoCA scores (FA, $r = 0.565$, $P = 0.044$; MD, $r = -0.614$, $P = 0.026$). No associations were found between participant gender, comorbidities, hs-CRP values, WMLV, or FA/MD of WBWM.

Association between hs-CRP values, WMLV, FA/MD values, and CDR scores

No significant correlations were observed between hs-CRP values, WMLV values, or FA/MD of DTI and CDR scores. There was a modest, but non-significant, trend for FA/MD of NAWM to be correlated with the severity of dementia, as measured by CDR (Table 3).

Discussion

SIVD is the most common type of vascular dementia, and it is caused by small artery disease and hypoperfusion and characterized by executive function impairment.² Consistent with a previous report,²⁰ the clinical profiles of the patients in this study were highly consistent with a diagnosis of SIVD, as evidenced by high rates of

Table 2. Analysis of clinical values, MR imaging variables, and MMSE/MoCA scores.

	MMSE	P Values	MoCA	P Values
Age	-0.313	0.034*	-0.295	0.047*
Education	0.463	0.002*	0.395	0.009*
Sex				
Female	22.8 ± 3.8	0.933 [†]	17.3 ± 4.3	0.469 [†]
Male	22.7 ± 4.0		18.3 ± 4.3	
Hypertension				
Yes	22.7 ± 4.0	0.762 [†]	17.8 ± 4.4	0.512 [†]
No	23.2 ± 3.2		19.0 ± 3.5	
DM				
Yes	22.2 ± 4.2	0.385 [†]	17.3 ± 4.6	0.402 [†]
No	23.2 ± 3.5		18.4 ± 4.0	
Hyperlipidemia				
Yes	24.1 ± 3.1	0.201 [†]	18.1 ± 3.9	0.878 [†]
No	22.3 ± 4.0		17.9 ± 4.4	
hs-CRP	0.158	0.366*	0.179	0.302*
WMLV	0.067	0.797*	0.086	0.744*
WBWM				
FA	0.08	0.767*	0.205	0.447*
MD	-0.297	0.264*	-0.409	0.116*
NAWM				
FA	0.507	0.045*	0.595	0.015*
MD	-0.392	0.133*	-0.54	0.031*

*Pearson correlation coefficient (*r*).

[†]Student's *t*-test.

MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; WBWM, whole-brain white matter; WMLV, white matter lesion volume; FA, fractional anisotropy; MD, mean diffusivity; NAWM, normal-appearing white matter.

In partial correlation analyses, only MD and FA of NAWM were associated with MoCA (FA, $r = 0.565$, $P = 0.044$; MD, $r = -0.614$, $P = 0.026$).

Table 3. Comparison of hs-CRP, WMLV, and FA/MD across the CDR groups.

	CDR=0.5	CDR=1	CDR=2	P
Hs-CRP	4.0 ± 5.4	3.0 ± 5.4	1.1 ± 1.0	0.453
WMLV	80.1 ± 85.2	72.9 ± 30.8	63.1 ± 20.1	0.817
WBWM				
FA	0.32 ± 0.03	0.31 ± 0.02	0.31 ± 0.03	0.543
MD ($\times 10^{-4}$)	8.6 ± 0.78	9.0 ± 0.38	9.3 ± 0.78	0.342
NAWM				
FA	0.33 ± 0.02	0.31 ± 0.02	0.29 ± 0.02	0.062
MD ($\times 10^{-4}$)	8.2 ± 0.29	8.7 ± 0.30	8.9 ± 0.61	0.069

hs-CRP, high-sensitivity C-reactive protein; WBWM, whole-brain white matter; WMLV, white matter lesion volume; FA, fractional anisotropy; MD, mean diffusivity; CDR, Clinical Dementia Rating; NAWM, normal-appearing white matter. These results were analyzed using an ANOVA.

hypertension and diabetes mellitus (85.4% and 43.8%, respectively). As with previous reports,¹¹ we also observed correlations of both age and education level with MMSE and MoCA.

Disruption of white matter pathways plays an important role in the genesis of dementia in SIVD.²⁰ DTI is an MRI technique that can detect white matter microstructural damage with the characteristics of reduced FA and increased MD. Compared with conventional MRI, whole-brain DTI is more reliable and sensitive to detect cognitive impairment of SIVD patients.²¹ The Montreal Cognitive Assessment (MoCA) is sufficiently sensitive to detect executive function that is impairment in SIVD, and the previous study showed that MoCA scores are more relevant to changes in FA/MD of WBWM than are MMSE scores.^{9,11} Our study indicates that the FA and MD of NAWM were significantly correlated with MoCA scores but not with MMSE scores, and no correlation was found with WBWM values, which was different from a previous study.¹¹ One possibility to explain the difference is that our study lacked statistical power to detect such changes, having only 48 patients. Second, the rCBF may be reduced in the normal appearing white matter in patients with vascular cognitive impairment, which affected the integrity of the white matter connections between areas that support cognitive function.^{10,22} Therefore, the microstructure damage of the NAWM may play an important role in SIVD pathogenesis.

Some studies suggested that certain serological or radiographic markers are correlated with cognitive impairment. For example, high levels of hs-CRP indicated a high risk of vascular dementia, and white matter lesion load is reported to be inversely associated with cognitive performance.^{23–25} In the present study, we observed no significant correlations between hs-CRP values,

WMLV, and MMSE and MoCA scores. However, we did observe a modest trend that FA/MD of NAWM maybe correlated with CDR, which reflects the severity of dementia (Table 3).

One limitation of our work reported here is that the study population included both patients with vascular cognitive impairment but no detectable signs of dementia and others with mild to moderate dementia (CDR scores of 0.5–2), excluding severe dementia. Thus, the correlation between DTI metrics and severe SIVD is not clear. The relatively small sample size adds variance, suggesting that studies with a larger sample size are warranted to determine if our findings here are robust.

Conclusions

The present study suggests that FA and MD of NAWM are more strongly related to MoCA scores compared with MMSE scores in patients with SIVD. Further research is expected to explore the role of NAWM in the pathogenesis of SIVD.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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