Original Research

Neuropsychological and neuroimaging assessments of early cognitive impairment in patients after mild ischemic stroke and transient ischemic attack

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This study aimed to identify markers of early cognitive impairment after acute mild ischemic cerebrovascular disease. To further explore the relationship between neuroimaging markers of vascular and neurodegenerative injuries and post-stroke cognitive impairment, 86 patients with transient ischemic attack/acute mild ischemic stroke were recruited. Demographic information, clinical data, stroke scale scores (Modified Rankin Scale, National Institutes of Health Stroke Scale), and neuroimaging parameters (medial temporal lobe atrophy, global cortical atrophy, white matter hyperintensities, location and number of acute infarcts) were collected. All participants underwent neuropsychological evaluation at the time of discharge. The neurocognitive assessment was conducted using the Montreal Cognitive Assessment-Basic and Trail-Making Test A. It was found that low Montreal Cognitive Assessment-Basic scores were associated with global cortical atrophy and lower education levels. The completion time on the Trail-Making Test A was significantly correlated with medial temporal lobe atrophy and less education. It is concluded that global cortical atrophy and lower education levels can be used as rapid indicators of early cognitive impairment in patients after a transient ischemic attack and acute mild ischemic stroke. Medial temporal lobe atrophy also appears to be associated with mental processing speed in patients after a transient ischemic attack and acute mild ischemic stroke.

Keywords

Neuropsychological assessment; cognitive impairment; post-stroke; global cortical atrophy; medial temporal lobe atrophy; Montreal Cognitive Assessment-Basic; Trail-Making Test A

1. Introduction

Stroke is not only a cause of physical disability but also a cause of cognitive impairment. Post-stroke cognitive impairment (PSCI) generally refers to cognitive impairment occurring within six months of stroke onset. It encompasses a multi-domain impairment of executive/attention, memory, language, and visuospatial functions, with the executive function being the predominantly affected domain (Gorelick et al., 2011). As PSCI is closely related to poor function prognosis and early death (Melkas et al., 2014), timely diagnosis and early intervention are necessary.

Determining the pathogenesis of PSCI will help develop targeted interventions. However, the mechanisms of PSCI are complex as they may result from acute stroke or underlying chronic brain injury (Gottesman and Hillis, 2010). Vascular lesions, global cortical atrophy (GCA), medial temporal lobe atrophy (MTA), and white matter hyperintensities (WMH) are associated with post-stroke dementia (PSD) (for a review see Leys et al. (2005)). Moreover, the characteristics of stroke and multiple strokes are strongly associated with PSD (Pendlebury and Rothwell, 2009). However, some recent studies suggest that chronic brain injuries such as GCA (Chen et al., 2016; Yatawara et al., 2018), MTA (Arba et al., 2017; Yang et al., 2015) and WMH (Yang et al., 2015; Yatawara et al., 2018) are significantly correlated with PSCI. Therefore, the exact contribution of cerebrovascular and neurodegenerative pathology to cognitive impairment after stroke is as yet undetermined.

Acute mild ischemic stroke and transient ischemic attack (TIA) do not usually lead to long-term physical disability but do increase the risk of long-term dementia (Sachdev et al., 2014). In acute stroke treatment, due to a lack of resources and an overwhelming work burden, clinicians often fail to perform cognitive function tests. The detection of cognitive impairment in the acute phase of stroke provides clinicians with valuable information on early cognitive rehabilitation (Pasi et al., 2012). Therefore patients with acute mild ischemic stroke and TIA were recruited to conduct cognitive assessments and collect demographic information, clinical data and neuroimaging indicators to both find an indicator of cognitive impairment in the early acute phase after acute mild stroke/TIA and further explore the relationship between vascular and neurodegenerative injury and PSCI.

2. Methods

2.1 Subjects

Patients diagnosed as acute mild ischemic stroke or TIA were enrolled in the stroke center of the Second Affiliated Hospital of Fujian Medical University from December 2018 to June 2019.

Subjects included in the study: Met the diagnostic criteria for acute ischemic stroke or TIA; had a National Institute of Health stroke scale (NIHSS) score $\leq$ 8 (defined as mild ischemic stroke, Muchada et al. (2014)); had a time from onset to hospital stay $\leq$ 7 days; were aged 35 to 80 years and provided consent and cooperation with the neuropsychological assessment.

Exclusion criteria included: Known history of cognitive impairment before stroke; hemiparesis affecting the hand used for writing; delirious symptoms on admission; aphasia; severe visual or hearing impairment; marked dysarthria; major depression or mental disorder; combined severe heart, liver, or kidney failure; Modified Rankin Scale (MRS) score > 1 before onset and incomplete neuropsychological assessment.

All subjects were informed in detail about the procedure and possible risks and provided informed consent.

The research was approved by the Medical Research Ethics Committee of the Second Affiliated Hospital of Fujian Medical University.

2.2 Clinical data

Clinical data of subjects were collected from demographic information, medical histories, laboratory data, and stroke scale scores. Demographic information included age, sex, education years, body mass index (BMI, $\geq$ 24 defined as overweight); medical histories included history of the previous stroke, hypertension, diabetes, smoking (defined as smoking one or more cigarettes per day, continuous or cumulative for more than six months), excessive alcohol drinking (defined as drinking > 100 ml per day or > 500 ml per week); stroke scale scores included the NIHSS score on admission, NIHSS score at discharge, MRS score at discharge; laboratory data included hypercholesterolemia (defined as total cholesterol > 5.20 mmol/L), hypertriglyceridemia (defined as triglyceride > 1.8 mmol/L), hyperhomocysteinemia (Hhcy) (defined as homocysteine > 15 μmol/L), hyperuricemia (defined as uric acid > 420 μmol/L), hyperglycated hemoglobin (HhbA1C) (defined as glycosylated hemoglobin > 6.5%), and high neuron-specific enolase (Hnse) (defined as neuron-specific enolase > 16.3 ng/ml). The laboratory data were routine examinations required for patients to be admitted to the hospital. All blood samples were collected within 24 hours of hospital admission and were tested in the hospital laboratory department.

2.3 Neuropsychological assessment

The neuropsychological status of each subject was assessed at the time of discharge by neurologists who had completed cognitive assessment training programs. The Chinese version of the Montreal Cognitive Assessment Scale-Basic (MoCA-B) was implemented to assess global cognitive function, and the Trail-Making test A (TMT-A) was implemented to supplement the assessment of mental processing speed and attention. MoCA-B is a modified version of the original MoCA suited to assess illiterate and little-educated subjects. The MoCA-B score ranges from 0 to 30. It evaluates the cognitive domain including executive functioning (simplified alternating trail making, word similarity, problem-solving), language (fruit fluency, animal naming), orientation (time and place), memory (five-word delayed recall), visual perception (superimposed objects) and attention (modified digit Stroop), which is similar to the original MoCA. The Trail Making Test (TMT) consists of two parts, part A and part B. It was challenging to conduct TMT-B due to the low education of most of the subjects included in the trial. Thus, only TMT-A was performed. Subjects with MoCA-B scale scores $\leq$ 21 were considered cognitively impaired, whereas scores > 21 were taken to indicate no significant cognitive impairment (Saleh et al., 2019). The variable of interest in TMT-A testing was the completion time, and where it was $\geq$ 77.5 s, it was considered to indicate an impaired mental processing speed (Wei et al., 2018).

2.4 Neuroimaging assessment

The imaging variables collected included: WMH, GCA, MTA, location, and the number of new infarctions. All subjects underwent brain magnetic resonance imaging on a 1.5 T (General Electric, Milwaukee, USA) or 3.0 T (Pillips, Ingenia, the Netherlands) scanner, including axial T1- and T2-weighted imaging, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery (FLAIR) imaging (slice thickness and spacing 6 mm and 3 mm, respectively). WMH were visually rated on T2-weighted and FLAIR images using the Fazekas scale (Fazekas et al., 1987), which was divided into two parts: periventricular hyperintensity scale (Fazekas PVH) and deep white matter hyperintense scale (Fazekas DWMH). Each part of the scale was graded from zero (normal) to three (severe). GCA was assessed by the Global Cortical Atrophy scale (Pasquier et al., 1996), which was graded on a scale of zero (normal) to three (severe). Due to time constraints, scans did not routinely employ coronal T1-weighted imaging sequences.

A T1-weighted axial visual rating scale (TIW-axial VRS) was employed to semi-quantitatively assess MTA (Kim et al., 2014). The TIW-axial VRS was graded on a scale of zero (normal) to four (severe atrophy). The left and right MTA were separately assessed, and if the degree of atrophy on either side was inconsistent, the score for the more severely atrophied side was preferentially analyzed. An acute infarction was defined as a hyperintensity lesion with a corresponding diffusion limitation on DWI (Van Everdingen et al., 1998). Acute ischemic characteristics were assessed for infarct location and number. Lesion locations were classified as either supratentorial or infratentorial, while lesions were classified as absent, single or multiple. Evaluation of imaging variables was independently performed by two experienced neurologists with inconsistent results confirmed by consultation.

2.5 Statistical methods

Descriptive statistics were calculated for demographic, clinical, and neuroimaging variables. Continuous variables are expressed as the mean $\pm$ standard deviation (X $\pm$ s). In the univariate analysis, continuous variables were tested using the independent-sample t-test or Mann--Whitney U test and categorical variables were determined by the χ^2 test or Fisher's exact test. Multivariate analysis was performed using multivariate logistic regression analysis or multiple linear regression analysis. The variables with a P-value < 0.1 in the univariate analysis were selected for further multivariate regression analysis. Pearson, correlation coefficient analysis, was used to assess correlations between neuroimaging variables and the results of neuropsychological tests. All data analyses were performed in SPSS version 20, and P < 0.05 was assumed to indicate statistical significance.

Table 1. Clinical characteristics comparing patients with high and low MoCA-B scores after TIA/stroke.

Characteristics	Total (n = 86)	MoCA-B ≤ 21 (n = 54)	MoCA-B > 21 (n = 32)	P-value
Demography				
Age (years)[a]	57.5 ± 11.0	60.9 ± 10.3	51.6 ± 9.8	< 0.001
Males (%)[b]	58 (67.4)	35 (64.8)	23 (71.9)	0.635
Education (years)[a]	6.3 ± 4.3	5.0 ± 4.2	8.4 ± 3.8	< 0.001
Body mass index (kg/m^2)[a]	23.9 ± 2.9	23.5 ± 2.8	24.6 ± 3.0	0.093
Clinical features				
Hypertension (%)[b]	57 (66.3)	38 (70.4)	19 (59.4)	0.349
Diabetes mellitus (%)[b]	24 (27.9)	12 (22.2)	12 (37.5)	0.143
Previous stroke history (%)[c]	11 (12.8)	10 (18.5)	1 (3.1)	0.048
Smoking history (%)[b]	42 (48.8)	27 (50.0)	15 (46.9)	0.826
Excessive drinking (%)[b]	19 (22.1)	13 (24.1)	6 (18.8)	0.604
Hypercholesteremia (%)[b]	19 (22.1)	11 (20.4)	8 (25.0)	0.789
Hypertriglyceridemia (%)[b]	22 (25.6)	11 (20.4)	11 (34.4)	0.202
Hhcy (%)[b]	20 (23.3)	13 (24.1)	7 (21.9)	1
Hyperuricemia (%)[c]	12 (14.0)	6 (11.1)	6 (18.8)	0.35
HhbA1c (%)[b]	20 (23.3)	11 (20.4)	9 (28.1)	1
Hnse (%)[c]	13 (15.1)	11 (20.4)	2 (6.3)	0.119
Stroke scale scores				
NIHSS on admission[d]	2 (5)	3 (4)	1.5 (5)	0.978
NIHSS at discharge[d]	1 (3)	1 (3)	1 (4)	0.503
MRS at discharge[d]	1 (2)	1 (1)	1 (1)	0.076
Neuroimaging factors				
Location of acute infarct (%)[c]				0.281
No infarction	28 (32.6)	17 (31.5)	11 (34.4)	
Supratentorial lesion	50 (58.1)	34 (63.0)	16 (50.0)	
Infratentorial lesion	8 (9.3)	3 (5.6)	5 (15.6)	
Number of acute infarct (%)[b]				0.804
No infarction	28 (32.6)	17 (31.5)	11 (34.4)	
Single lesion	41 (47.7)	25 (46.3)	16 (50.0)	
Multiple lesion	17 (19.8)	12 (22.2)	5 (15.6)	
MTA[d]	1 (1)	2 (2)	1 (1)	0
PVH[d]	1 (1)	1 (1)	1 (1)	0.074
DWMH[d]	1 (1)	1 (1)	1 (1)	0.042
GCA[d]	1 (1)	1 (1)	1 (0)	0

[a]mean ± SD, independent-sample t-test; [b]number (%), χ^2 test; [c] number (%), Fisher's exact test;[d]median (interquartile range, IQR), Mann--Whitney U test. Hhcy: hyperhomocysteinemia; HhbA1c: hyperglycated hemoglobin; Hnse: high neuron-specific enolase; NIHSS: National Institute of Health stroke scale; MRS: Modified Rankin Scale; MTA: medial temporal lobe atrophy; PVH: periventricular hyperintensity; DWMH: deep white matter hyperintense; GCA: global cortical atrophy.

3. Results

3.1 Clinical features

From December 2018 to June 2019, 86 subjects were recruited according to the inclusion and exclusion criteria. A total of 58 subjects (67.4%) had an acute mild ischemic stroke (mean age, 57.9 years), whereas 28 subjects (32.6%) had TIA (mean age, 56.5 years). The average education duration was 6.3 years. The demographics, clinical features, and neuroimaging data of the 86 subjects are given in Table 1. All subjects completed the MoCA-B and TMT-A on the day of discharge, an average of 10.0 ± 3.4 days after stroke onset. The MoCA-B score was 18.1 ± 6.6, and the completion time for the TMT-A was 90.3 ± 68.5 seconds. Subjects were divided into two groups, a low MoCA-B group (cognitive impairment) and a high MoCA-B group (no cognitive impairment), according to the MoCA-B cutoff score (21/22) (Saleh et al., 2019).

3.2 Factors associated with low MoCA-B scores

Univariate analysis showed age, years of education, previous stroke history, MTA, DWMH, and GCA were significantly differ-ent between the high and low MoCA-B score groups. Compared with the high MoCA-B group, subjects in the low MoCA-B group were older, less educated, had a previous stroke, and a higher degree of MTA, DWMH, and GCA (Table 1). Multivariate logistic regression analysis showed that GCA [OR (95% CI), 4.673 (1.149-19.006)], and education years [OR (95% CI), 0.775 (0.660-0.910)] remained significantly correlated with low MoCA-B scores (Table 3).

3.3 Factors associated with the completion time of TMT-A

Subjects were divided into groups according to the cutoff value for the TMT-A completion time (77.5 s). The univariate analysis showed age, education years, BMI, MRS at discharge, MTA, PVH, DWMH, and GCA were significantly different between the two groups (Table 2). In the multiple linear regression analysis, MTA (β = 0.375, P = 0.001) and length of education in years (β = -0.373, P = 0.000) remained significantly correlated with TMT-A completion time (R = 0.653, R^2= 0.426, adjustment R^2 = 0.395, analysis of variance P < 0.001) (Table 3).

Table 2. Clinical characteristics comparing patients with TMT-A completion times $\geq$ 77.5 seconds and $<$ 77.5 seconds after TIA/stroke.

Characteristics	Total (n = 86)	Completion time of TMT-A		P-value
		$\geq$ 77.5 s (n = 35)	$<$ 77.5 s (n = 51)	
Demography				
Age (years)[a]	57.5 ± 11.0	63.1 ± 10.1	53.6 ± 10.0	< 0.001
Males (%)[b]	58 (67.4)	21 (60.0)	37 (72.6)	0.249
Education (years)[a]	6.3 ± 4.3	4.5 ± 4.5	7.5 ± 3.8	0.001
Body mass index (kg/m^2)[a]	23.9 ± 2.9	23.0 ± 2.8	24.5 ± 2.8	0.016
Clinical features				
Hypertension (%)[b]	57 (66.3)	26 (74.3)	31 (60.8)	0.248
Diabetes mellitus (%)[b]	24 (27.9)	10 (28.6)	14 (27.5)	1
Previous stroke history (%)[c]	11 (12.8)	7 (20.0)	4 (7.8)	0.113
Smoking history (%)[b]	42 (48.8)	16 (45.7)	26 (51.0)	0.666
Excessive drinking (%)[b]	19 (22.1)	8 (22.9)	11 (44.4)	1
Hypercholesteremia (%)[b]	19 (22.1)	7 (20.0)	12 (23.5)	0.795
Hypertriglyceridemia (%)[b]	22 (25.6)	7 (20.0)	15 (29.4)	0.451
Hhcy (%)[b]	20 (23.3)	10 (28.6)	10 (19.6)	0.437
Hyperuricemia (%)[c]	12 (14.0)	4 (11.4)	8 (15.7)	0.754
HhbA1c (%)[b]	20 (23.3)	9 (25.7)	11 (21.6)	0.796
Hnse (%)[b]	13 (15.1)	8 (22.9)	5 (8.2)	0.128
Stroke scale scores				
NIHSS on admission[d]	2 (5)	1 (5)	2 (4)	0.386
NIHSS at discharge[d]	1 (3)	2 (4)	1 (3)	0.224
MRS at discharge[d]	1 (2)	1 (1)	1 (1)	0.013
Neuroimaging factors				
Location of acute infarct (%)[c]				0.129
No infarction	28 (32.6)	8 (22.9)	20 (39.2)	
Supratentorial lesion	50 (58.1)	25 (71.4)	25 (49.0)	
Infratentorial lesion	8 (9.3)	2 (5.7)	6 (11.8)	
Number of acute infarct (%)[b]				0.234
No infarction	28 (32.6)	8 (22.9)	20 (39.2)	
Single lesion	41 (47.7)	18 (51.4)	23 (45.1)	
Multiple lesion	17 (19.8)	9 (25.7)	5 (15.7)	
MTA[d]	1 (1)	2 (2)	1 (1)	0
PVH[d]	1 (1)	2 (1)	1 (0)	0.003
DWMH[d]	1 (1)	1 (1)	1 (1)	0.006
GCA[d]	1 (1)	2 (1)	1 (0)	0

[a]mean ± SD, independent-sample t-test; [b]number (%), χ^2 test; [c] number (%), Fisher's exact test; [d]median (interquartile range, IQR), Mann-Whitney U test. Hhcy: hyperhomocysteinemia; HhbA1c: hyperglycated hemoglobin; Hnse: high neuron-specific enolase; NIHSS: National Institute of Health stroke scale; MRS: Modified Rankin Scale; MTA: medial temporal lobe atrophy; PVH: periventricular hyperintensity; DWMH: deep white matter hyperintense; GCA: global cortical atrophy.

3.4 Correlation analysis between neuroimaging variables and neuropsychological assessment

There was a moderate correlation between the GCA and MoCA-B scores (r = -0.490, $P < 0.001$) and TMT-A completion times (r = 0.433, $P < 0.001$). MTA was also moderately correlated with MoCA-B scores (r = -0.503, $P < 0.001$) and TMT-A completion times (r = 0.472, $P < 0.001$). PVH was weakly associated with MoCA-B scores (r = -0.319, P = 0.003) but not with the completion times of the TMT-A (r = 0.193, P = 0.075). DWMH was weakly correlated with MoCA-B scores (r = -0.287, P = 0.007) and TMT-A completion times (r = 0.239, P = 0.027). There was a strong correlation between the MoCA-B scores and TMT-A completion times (r = -0.786, $P < 0.001$).

3.5 Correlation analysis between neuroimaging variables

GCA was strongly associated with MTA (r = 0.691, $P < 0.001$), while there were moderate intensity correlations with PVH (r = 0.579, $P < 0.001$) and DWMH (r = 0.493, $P < 0.001$). MTA had a moderate intensity association with PVH (r = 0.560, $P < 0.001$) and DWMH (r = 0.496, $P < 0.001$).

4. Discussion

The MoCA-B scale was used to assess the global cognitive function of subjects, and the TMT-A was performed to assess their mental processing speed. It was found that GCA and less education were related to global cognitive impairment after acute mild ischemic stroke/TIA. Alternatively, MTA and less education were significantly correlated with mental processing speed after acute mild ischemic stroke/TIA.

GCA and MTA are generally considered neuroimaging markers of neurodegenerative dementia, while PSCI is often associated with WMH (Burton et al., 2004; Jokinen et al., 2005) and stroke characteristics, such as infarct location, size, and number (Desmond et al., 2000; Schmidt et al., 1993). However, here it was found that GCA, instead of WMH, infarct location, or infarct number, was independently related to global cognitive impairment after mild stroke/TIA. Although MTA and DWMH were not strongly associated with MoCA-B scores after adjusting for confounding factors, they were significantly different between the lower and higher MoCA-B score groups in the univariate analysis.

Table 3. Risk factors associated with lower MoCA-B scores and TMT-A completion times after TIA/stroke in multivariate regression analysis.

A. Associations with MoCA-B in multivariate logistic regression		
Variables	Odds ratio (95% CI)	*P*-value
Education (years)	0.775 (0.660-0.910)	0.002
GCA	4.673 (1.149-19.006)	0.031

B. Associations with TMT-A in multivariate linear regression		
Variables	standardized *β*	*P*-value
Education (years)	-0.373	0
MTA	0.375	0.001

A. Associations with MoCA-B in multivariate logistic regression: Model adjusted for Age > 60, Previous stroke history, Body mass index, MRS at discharge, MTA, PVH, and DWMH.

B. Associations with TMT-A in multivariate linear regression: Age, Body mass index, MRS at discharge, PVH, DWMH, and GCA did not significantly contribute to the regression model.

MRS: Modified Rankin Scale; MTA: medial temporal lobe atrophy; PVH: periventricular hyperintensity; DWMH: deep white matter hyperintense; GCA: global cortical atrophy.

Therefore, these results may provide further evidence highlighting an important role for chronic brain injury in cognitive impairment after stroke, as has been reported by recent surveys (Yang et al., 2015; Yatawara et al., 2018).

Previous studies have shown that cortical atrophy is an independent predictor of cognitive impairment in subcortical ischemic vascular disease (Fein et al., 2000; Mungas et al., 2001). Altieri et al. (2004) found that cortical atrophy is associated with delayed PSD. In a recent clinical trial, Chen et al. (2016) also suggested that GCA is an independent risk factor for vascular cognitive impairment. When compared with stroke, GCA mediates more extensive damage to multiple cognitive domains in post-stroke subjects (Yatawara et al., 2018). All these results are consistent with the results reported here, suggesting that GCA predicts cognitive impairment after stroke.

A potential mechanism to explain this phenomenon is that chronic brain injury reduces brain reserve function (Mok et al., 2017), while decreased brain reserve reduces the performance threshold for PSCI (Chen et al., 2016). GCA is not caused by neurodegenerative pathology alone but may also be due to subclinical ischemic brain injury (Garcia et al., 1996). The results reported here show that GCA, WMH, and MTA are related to each other, and as shown by the univariate analysis, are associated with cognitive impairment. This suggests the possibility of the co-existence of vascular pathology and neurodegenerative pathology in PSCI. However, only GCA was independently associated with global cognitive impairment after stroke, which indicates that in subjects with mild ischemic stroke/TIA, the prevalence of GCA plays a leading role in cognitive impairment.

It was further found that MTA had a strong relationship with GCA. However, it was not an independent risk factor for global cognitive impairment, which was a similar result to that reported by Chen et al. (2016). Although recent studies have proposed MTA as a risk factor for PSCI (Arba et al., 2017; Akinyemi et al., 2015; Takahashi et al., 2019), some studies did not include assessment of GCA (Takahashi et al., 2019) and the inconsistencies in these findings may have been due to differences in assessment methods and

time. Also, patients with delirious symptoms upon arrival were excluded from the study reported here. However, a neuropsychological assessment was conducted in the acute phase of stroke, and delirium was common in acute stroke, so it was possible that post-stroke delirium in patients cannot be fully ruled out.

WMH is considered to be a marker of vascular pathology due to its strong association with vascular risk factors (Jeerakathil et al., 2004). More extensive WMH has been closely related to cognitive decline after stroke (Burton et al., 2004; Jokinen et al., 2005). However, here, the multivariate regression model showed no independent relationship between WMH and PSCI. One explanation for this is that the degree of WMH was not serious enough to reach the performance threshold for cognitive impairment. However, previous studies have also found that WMH was not a risk factor in predicting cognitive decline after stroke (Arba et al., 2017; Akinyemi et al., 2015; Firbank et al., 2007; Takahashi et al., 2019), while Mok et al. (2011) suggested that cognitive impairment caused by white matter lesion is mainly mediated by cortical atrophy.

In support of Mok et al. (2011), results reported here suggest that GCA, but not WMH, is independently associated with cognitive impairment. However, such a view should be interpreted with caution. As mentioned above, WMH is not serious, which may reduce the relationship between WMH and PSCI. Also, results did not show that cognitive impairment was related to the infarct location and infarct number. As moderate-to-severe stroke was excluded, this may weaken the impact of the stroke itself on cognitive impairment. However, previous studies have also found that the characteristics of stroke are not associated with PSCI, even if they were not restricted to mild stroke (Chen et al., 2016; Yang et al., 2015).

Although MTA was not an independent risk factor for the MoCA-B score, it was significantly associated with the completion time of TMT-A. This shows that MTA is closely related to the mental processing speed of the patients after stroke. In general, MTA is considered to be associated with episodic memory, while WMH is significantly associated with executive functions

and speed of mental processing in post-stroke patients (Jokinen et al., 2005). However, Jokinen et al. (2004) found MTA was associated with mental processing speed after adjusting for age, infarct volume, and cortical atrophy in elderly stroke patients. Also, Oosterman et al. (2008) also suggested that MTA was the only predictor of the mental flexibility of older people as WMH did not show a significant correlation with mental flexibility.

A recent study has shown that MTA independently predicted a longitudinal decline in psychomotor speed in patients with cerebral small vessel disease (Jokinen et al., 2012). Here, results also showed that MTA remained independently associated with the completion time of the TMT-A after adjusting for confounding factors, such as GCA and WMH. Therefore, it is suggested that there is a connection between MTA and mental processing speed. An explanation for this result may be due to the connection between MTA and prefrontal cortex function (Anderson et al., 2010; Takahashi et al., 2008) and that TMT can be used to assess frontal lobe functions (Stuss et al., 2001).

Moreover, a functional magnetic resonance imaging study has found that the brain-behavior correlations for TMT are not only restricted to the frontal lobe but also related to left middle and superior temporal gyrus (Zakzanis et al., 2005). Generally, TMT-B or TMT-B/TMT-A is considered to reflect frontal function than TMT-A better.

Results also showed that less education was an independent risk factor for PSCI, which is the same as previous studies (Pendlebury and Rothwell, 2009; Pendlebury, 2012). A higher education level generally indicated better cognitive reserve, where cognitive reserve refers to the ability of the brain to maintain the same level of cognitive function despite the presence of brain pathology (Mok et al., 2017). From this perspective, low education implies poor cognitive reserve, and such subjects may be less able to compensate for the destruction of brain function by stroke.

In conclusion, it was found that GCA and lower education levels can be used as markers for early cognitive impairment in subjects after TIA or mild ischemic stroke. Also, MTA appears to be associated with the mental processing speed of patients after TIA/mild ischemic stroke.

Author contributions

L. W. conceived this project and supervised the experiments. L. Y. supervised the experiments. Y. Y. wrote the paper. Y. Y., R. L., H. L., T. T., Y. C., J. Z. performed the experiments and analyzed the data.

Ethics approval and consent to participate

This research was approved by the Medical Research Ethics Committee of Second Affiliated Hospital of Fujian Medical University, Quanzhou, P. R. China, code FYFELLN0.214. All participants gave written consent after being informed about the procedure.

Acknowledgment

Conflict of Interest

The authors declare no conflict of interest.

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