Original Article

White Matter Lesions Predict Recurrent Vascular Events in Patients with Transient Ischemic Attacks

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Abstract

Background: White matter lesions (WMLs) are common findings in brain magnetic resonance imaging (MRI) and are strongly associated with stroke incidence, recurrence, and prognosis. However, the relationship between WMLs and transient ischemic attacks (TIAs) is not well established. This study aimed to determine the clinical significance of WMLs in patients with TIA.

Methods: A total of 181 consecutive inpatients with first-ever TIA were enrolled. Brain MRIs within 2 days of symptom onset were used to measure WML volumes. Recurrent vascular events within 1 year of TIA onset were assessed. The relationship between WMLs and recurrent risk of vascular events was determined by a multivariate logistic regression.

Results: WMLs were identified in 104 patients (57.5%). Age and ratio of hypertension were significantly different between patients with and without WMLs. The incidence of vascular events in patients with WMLs significantly increased in comparison to those without WMLs (21.15% vs. 5.19%, 95% confidence interval [*CI*]: 1.18–15.20, $P = 0.027$) after controlling for confounders. Furthermore, distributions of WML loads were found to be different between patients who developed vascular events and those who did not. WML volumes were demonstrated to be correlated with recurrent risks, and the fourth quartile of WML volumes led to an 8.5-fold elevation of recurrent risk of vascular events compared with the first quartile (95% *CI*: 1.52–47.65, $P = 0.015$) after adjusting for hyperlipidemia.

Conclusion: WMLs occur frequently in patients with TIA and are associated with the high risk of recurrent vascular events, suggesting a predictive neuroimaging marker for TIA outcomes.

Key words: Recurrent Vascular Events; Risk factors; Transient Ischemic Attack; Volumetric Measurement; White Matter Lesion

Introduction

White matter lesions (WMLs) are characterized mainly by white matter hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain, and they are usually categorized into periventricular and subcortical lesions. As the availability and quality of imaging techniques improve, WMLs are common neuroimaging findings in the general population, especially in the elderly. The reported prevalence varies from 25% to 92% in healthy elderly people, depending on different study designs.[1-3]

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The clinical manifestation of WMLs is asymptomatic, mild, or unrecognized in the early stages, but their progression in the advanced stages may result in critical neurological dysfunctions.[4] The volume of WMLs tends to increase over time, and the WML load at the baseline is found to be

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a significant predictor of lesion progression.[5,6] WMLs are associated with not only structural lesions but also functional changes.[7] Recent longitudinal studies described WML as a predictor of incident stroke, disability, cognitive decline, depression, and mortality in the general population.[8-11]

Increasing evidence supports the fact that WMLs are more prevalent and severe in patients with stroke than in healthy controls and is strongly associated with high risks of infarct growth, stroke severity, stroke recurrence, and bad prognosis.[12-16] A transient ischemic attack (TIA) is a medical emergency associated with a high risk of recurrence, subsequent stroke, and cardiovascular events.[17,18] However, the relationship between WMLs and TIA is still unclear. Consequently, this study attempted to determine the association of the incidence and volume of WMLs at admission with the prognosis of patients with TIA.

Methods

Ethical approval

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University.

Study population

First-ever patients with TIA who were admitted consecutively to Nanjing Drum Tower Hospital Clinical College of Nanjing Medical University between August 2010 and April 2016 within 48 h of symptom onset were recruited. TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia lasting <24 h, without acute infarction on imaging.[19] A total of 181 eligible patients were present after excluding 40 patients with prior history of TIA or stroke, 23 with brain injury on diffusion-weighted MRI, 5 with other medical diagnoses that could confound or interfere with the analysis of WMLs, such as multiple sclerosis, neuromyelitis optica, and leukodystrophy, three who underwent endovascular therapy, and three without complete follow-up.

Baseline data collection and definition of covariates

Patient demographics (age and sex), vascular risk factors, TIA symptom details, and ABCD2 score were collected by reviewing medical records. The definitions of vascular risk factors are as follows: hypertension was defined as systolic blood pressure ≥140 mmHg (1 mmHg = 0.133 kPa), diastolic blood pressure ≥90 mmHg, or the use of blood pressure-lowering medication. Hyperlipidemia was defined as total cholesterol ≥5.72 mmol/L, triglycerides ≥1.70 mmol/L, low-density lipoprotein cholesterol ≥3.10 mmol/L, or the use of lipid-lowering medication. Diabetes mellitus was defined as fasting glucose level ≥7.0 mmol/L, 2-h plasma glucose level after a 75 g oral glucose tolerance test, or nonfasting glucose level ≥11.1 mmol/L at least 3 days after TIA, glycated hemoglobin level ≥6.5%, or the use of antidiabetic medication.

A history of coronary heart disease was considered based on a history of angina pectoris, myocardial infarction, a revascularization procedure, and so on. Atrial fibrillation was considered according to the electrocardiogram and Holter monitoring manifestation on admission or previously documented diagnosis. Meanwhile, the current smoking status was also recorded. The ABCD2 score combines five clinical variables (age, blood pressure, clinical features, duration of symptoms, and history of diabetes mellitus) into a seven-point scale. In general, patients with TIA were prescribed antithrombotics, statins, and treatment of vascular risk factors during hospitalization and at discharge. Statins were prescribed for 169 patients (93.4%) and antithrombotics for 171 patients (94.5%) including anticoagulant (n = 6) and antiplatelet therapy (n = 165). All patients with hypertension were prescribed antihypertensive medication, and the blood pressure was lowered to below 140/90 mmHg. According to Chinese Guidelines for the Prevention of Stroke in Patients with Ischemic Stroke or TIA, these patients were routinely visited in the department of neurology, and medication was supervised to rigorously control vascular risk factors. The primary end points were recurrent vascular events (recurrent TIA, stroke, myocardial infarction, and vascular death) at 1 year. Acute stroke was defined based on a neurological deficit attributed to an acute focal cerebral injury by a vascular cause.[20] Acute myocardial infarction was defined as the elevation of cardiac troponins either with symptoms of ischemia or with presumed new electrocardiogram changes. Vascular death was defined as death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia.

Image acquisition and analysis

MRIs within 2 days of TIA onset were available for all participants, which included T1-weighted image, T2-weighted image, diffusion-weighted imaging (DWI), and FLAIR. MRI scans were performed on a 1.5 Tesla scanner (Philips Intera Master Medical Systems, Best, The Netherlands). The acquisition protocols were as follows: T1-weighted (fast field echo, repetition time: 458 ms and echo time: 14 ms); T2-weighted (turbo spin echo, repetition time: 4070 ms and echo time: 110 ms); T2-weighted FLAIR (repetition time: 9002 ms and echo time: 143 ms); DWI (single-shot echo planar imaging, repetition time: 3200 ms and echo time: 95 ms); thickness/gap: 5 mm/0 mm; matrix: 304 × 512; and field of view: 230 mm × 230 mm.

WMLs were defined as hyperintense lesions on both T2 and FLAIR images, without cavitation, and without prominent hypointensities on T1-weighted scans. MRIcron was applied for image analyses.[21-23] So far, no widely accepted rules are available for defining periventricular and subcortical WML.[24] In the present study, only the total WML volume was segmented and calculated based on a semiautomatic technique: (1) for the first layer, the intensity threshold filter was used to create a layer of regions of interest corresponding to WMLs. (2) For the second layer, experienced neuroradiologists who remained blinded to the patients' clinical details were required to manually outline the gross contouring of all WMLs on every slice.

(3) The intersection of the first and second layers was then obtained to serve as a WML map for further volumetric analysis.[22] WML volumes were set as categorical variables using quartiles. Total WML volumes ranging from 0.95 to 3.31 ml, 3.32 to 5.00 ml, 5.00 to 9.05 ml, and 9.06 to 49.13 ml were defined as the first, second, third, and fourth quartiles, respectively.

Experienced neuroradiologists who remained blinded to the patients' clinical details analyzed all the MRI data. Disagreements were resolved by discussion with a third rater.

Statistical analyses

Quantitative values were reported as mean ± standard deviation (SD). Categorical variables are expressed as numbers (percentages). Continuous variables were tested by the independent samples' *t*-test, while categorical variables were tested by Chi-squared tests or continuity correction. A multivariable logistic regression analysis was used to identify the independent risk factors of WMLs and the clinical outcome. Independent variables for this model were chosen using a conservative threshold of $P < 0.10$ in the univariable analysis. Values of $P < 0.05$ were considered statistically significant. All analyses were performed with the SPSS software package (version 23.0, SPSS Inc., USA).

Results

Demographic and clinical characteristics of patients with transient ischemic attack with and without white matter lesions

As shown in Table 1, demographic and clinical characteristics were analyzed in patients with TIA with and without WMLs. Among the 181 patients, 108 patients (59.7%) were male. The mean age was 61.4 years (range: 29–85 years; SD: 11.1). Hypertension, present in 97 patients (53.6%), was the main vascular risk factor. Anterior circulation TIA accounts for 75.7% of all patients, whereas posterior circulation TIA accounts for 24.3%. In the univariate analysis, age, hypertension, hyperlipidemia, coronary heart disease, sensory disturbance, and ABCD2 score were associated with WMLs. The multivariate analysis showed a significant difference in age (66.1 ± 9.6 vs. 55.1 ± 9.8, odds ratio [*OR*]: 1.21, 95% confidence interval [*CI*] 1.08–1.17, $P < 0.001$) and ratio of hypertension (62.5% vs. 24.6%, *OR*: 2.11, 95% *CI*: 1.06–4.21, $P = 0.034$) between the two groups.

Recurrent vascular events increased in patients with transient ischemic attack with white matter lesions

The risks of recurrent vascular events were evaluated in patients with TIA with and without WMLs. At the 1-year follow-up, 26 (14.4%) recurrent vascular events occurred, including 16 recurrent TIAs, 7 strokes, 2 myocardial infarctions, and one vascular death. All strokes were ischemic. A univariate analysis showed that the recurrent rate of vascular events in TIAs with WMLs was significantly higher than that in TIAs with no WMLs (21.15% vs. 5.19%, $P = 0.002$). Furthermore, the significant difference was kept well between those two groups by the multivariate analysis after controlling for age, hyperlipidemia, diabetes mellitus, duration of symptoms, and antithrombotics (*OR*: 4.24, 95% *CI*: 1.18–15.20, $P = 0.027$).

Table 1: Demographic and clinical characteristics between TIA patients with and without WMLs

Variables	TIA without WMLs ($n = 77$)	TIA with WMLs ($n = 104$)	χ^2 or t	P
Male, *n* (%)	44 (57.1)	64 (61.5)	0.355*	0.551
Age (years), mean ± SD	55.1 ± 9.8	66.1 ± 9.6	−7.552†	<0.001
Vascular risk factors, *n* (%)				
Hypertension	32 (24.6)	65 (62.5)	7.801*	0.005
Diabetes mellitus	13 (16.9)	28 (26.9)	2.545*	0.111
Hyperlipidemia	33 (42.9)	30 (28.8)	3.828*	0.050
Smoking current	15 (19.5)	30 (28.8)	2.077*	0.149
Atrial fibrillation, *n* (%)	1 (1.3)	6 (5.8)	1.328*	0.249
Coronary artery disease, *n* (%)	2 (2.6)	10 (9.6)	3.520*	0.061
Clinical features, *n* (%)				
Unilateral weakness	37 (48.1)	51 (49.0)	0.017*	0.896
Sensory disturbance	26 (33.8)	23 (22.1)	3.042*	0.081
Speech impairment	20 (26.0)	27 (26.0)	0.000*	0.998
Duration, *n* (%)				
≥60 min	26 (33.8)	29 (27.9)	0.874*	0.646
10–59 min	29 (37.7)	40 (38.5)		
<10 min	22 (28.6)	35 (33.7)		
ABCD2 scores, mean ± SD	3.1 ± 1.2	3.6 ± 1.6	−2.516†	0.013
Lesion location, *n* (%)				
Anterior circulation	58 (75.3)	79 (76.0)	0.010*	0.921
Posterior circulation	19 (24.7)	25 (24.0)		

*t values; †χ^2 values. TIA: Transient ischemic attack; WMLs: White matter lesions; SD: Standard deviation.

Severe white matter lesions occurred frequently in patients with transient ischemic attacks who developed recurrent vascular events

An attempt was made to find out the differences in the demographic and clinical characteristics of patients with TIA as well as WML, who did or did not develop recurrent vascular events. In the univariate analysis, diabetes mellitus, hyperlipidemia, and WML severity were associated with recurrent vascular events. After the multivariate analysis, the proportion of hyperlipidemia (*OR*: 5.21, 95% *CI*: 1.71–15.90, $P = 0.004$) was higher in patients with TIA who developed recurrent vascular events in comparison to those who did not. Notably, the distribution of WMLs with varying severities was different between those who had recurrent vascular events and those who did not ($P = 0.045$), and the more severe the WMLs, the more frequent the recurrence of the vascular events that occurred in patients with TIA [Table 2].

White matter lesions were correlated with the recurrent risks of vascular events in patients with transient ischemic attack

This study also attempted to evaluate whether the extent of WMLs was correlated with the recurrent risk of vascular events in patients with TIA with WMLs. The incidence rates of vascular events according to the quartile of the total WML volume are shown in Table 3. The multivariate logistic analysis demonstrated that the fourth quartile of WMLs (>9.05 ml) was correlated with a higher risk of vascular events relative to the first quartile (≤3.31 ml) (*OR*: 8.51, 95% *CI*: 1.52–47.65, $P = 0.015$) after adjusting for hyperlipidemia.

Discussion

The present study showed that WMLs were present in 57.5% of the patients with first-ever TIA, even reaching 95% of patients aged >70 years on MRI. In one large sample of 1643 healthy people aged ≥65 years, the median volume of WMLs was 4.0 ml (IQR: 2.75–6.20 ml).[25] Patients with TIA had a higher WML volume compared with healthy people. Previous studies showed that the risk of stroke increased significantly as the baseline WML grade increased independently of traditional risk factors for stroke in population-based samples.[25-27] In agreement with these reports about WMLs in stroke, the present study found that, in patients with TIA, the presence of baseline WMLs increased recurrent vascular incidences by up to 4.2-fold. Moreover, the incidence of vascular events increased with increasing volumes of WML, reaching an 8.5-fold higher rate in the fourth quartile as compared with the first

Table 2: Recurrent vascular events in patients with WMLs

Variables	No recurrent vascular events ($n = 82$)	Recurrent vascular events ($n = 22$)	χ^2 or t	P
Male, *n* (%)	51 (62.2)	13 (59.1)	0.071*	0.790
Age (years), mean ± SD	65.7 ± 9.4	67.5 ± 10.5	−0.772†	0.442
Vascular risk factors, *n* (%)				
Hypertension	52 (63.4)	13 (59.1)	0.138*	0.710
Diabetes mellitus	18 (22.0)	10 (45.5)	4.870*	0.027
Hyperlipidemia	18 (22.0)	12 (54.5)	8.978*	0.003
Smoking current	24 (27.3)	6 (27.3)	0.034*	0.854
Atrial fibrillation, *n* (%)	5 (6.1)	1 (4.5)	0.000*	1.000
Coronary artery disease, *n* (%)	8 (9.8)	2 (9.1)	0.000*	1.000
Clinical features, *n* (%)				
Unilateral weakness	40 (48.8)	11 (50.0)	0.010*	0.919
Sensory disturbance	16 (19.5)	7 (31.8)	0.894*	0.344
Speech impairment	19 (23.2)	8 (36.4)	1.571*	0.210
Duration of symptoms, *n* (%)				
≥60 min	20 (24.4)	9 (40.9)	2.355*	0.308
10–59 min	33 (40.2)	7 (31.8)		
<10 min	29 (35.4)	6 (27.3)		
ABCD2 score, mean ± SD	3.49 ± 1.56	4.09 ± 1.54	−1.616†	0.109
Lesion location, *n* (%)				
Anterior circulation	60 (73.2)	19 (86.4)	1.653*	0.198
Posterior circulation	22 (26.8)	3 (13.6)		
WML volume, *n* (%)				
First quartile	24 (29.3)	2 (9.1)	8.071*	0.045
Second quartile	22 (26.8)	4 (18.2)		
Third quartile	20 (24.4)	6 (27.3)		
Fourth quartile	16 (19.5)	10 (45.5)		
Discharge medications, *n* (%)				
Antithrombotics	78 (95.1)	18 (81.8)	2.653*	0.103
Statins	77 (93.9)	20 (90.9)	0.000*	0.985

*χ^2 values; †t values. TIA: Transient ischemic attack; WMLs: White matter lesions; SD: Standard deviation.

Table 3: Relationship between volume of WMLs and recurrent vascular events in TIA patients

Outcomes	No recurrent vascular events (n = 82)		Recurrent vascular events (n = 22)		*OR* (95% *CI*)	*P*	Adjusted *OR** (95% *CI*)	*P**
	n	Proportion (%)	*n*	Proportion (%)				
First quartile	24	29.3	2	9.1	–	–	–	–
Second quartile	22	26.8	4	18.2	2.18 (0.36–13.11)	0.394	1.96 (0.31–12.55)	0.478
Third quartile	20	24.4	6	27.3	3.60 (0.65–19.84)	0.141	2.38 (0.40–14.18)	0.342
Fourth quartile	16	19.5	10	45.5	7.50 (1.45–38.85)	0.016	8.51 (1.52–47.65)	0.015

*Adjusted for hyperlipidemia. –: Not applicable; TIA: Transient ischemic attack; WMLs: White matter lesions; *OR*: Odds ratio; *CI*: Confidence interval.

quartile. As a result, severe WML was progressive and even malignant, and WMLs needed to be carefully assessed and quantified. With the promotion of clinical guidelines and early treatment after TIA, a measurable decrease in the risk of stroke and other vascular events has been reported over the past decade.[28-31] However, the recurrent vascular event rate remains unacceptably high in patients with WMLs. The current finding has shifted the importance of WMLs from an incidental neuroimaging description to a radiological surrogate marker for risk stratification in patients with TIA.

WMLs are commonly considered as an expression of chronic cerebral ischemia although the underlying pathogenesis is probably multifactorial. Along with the previous findings, the results of the present study supported the fact that age and hypertension were the most common risk factors for both the presence and the severity of WMLs.[32-36] Accumulating studies suggested that WMLs may be associated with arteriosclerotic narrowing, plaque, artery stiffening, small vessel disease, hemodynamic injury, and impaired autoregulation.[37-41] In addition to vascular changes, WMLs are associated with high levels of mean platelet volumes, platelet hyperaggregability, endothelial dysfunction, and blood-brain barrier dysfunction.[42-45] All alterations mentioned earlier may further modulate cerebral tissue perfusion, capacity for handling ischemia, and dysfunctional white matter tracts, impairing plasticity in patients with TIA, which can contribute to bad prognosis after a TIA. Meanwhile, diffuse vascular damage involved not only cerebral arteries but also peripheral and coronary arteries.[46] Further studies are needed to clarify the mechanism of the relationship between WMLs and clinical outcome of TIA. Special attention should be given to patients with TIA with WMLs for secondary prevention and long-term prognosis. In the present study, except for WMLs, age, hyperlipidemia, diabetes mellitus, and duration of symptoms were independent predictors of recurrent vascular events. Furthermore, antithrombotics significantly reduced the risk, exerting protective effects against vascular events. To date, no definitive effective treatment is available for WMLs. Several pieces of evidence show that good blood pressure control, antiplatelet therapy, and endothelium stability may be feasible.[36,47,48] Treating the underlying causes may delay WML progression and improve prognosis.

The unique aspect of the present study is that it focuses on WMLs in patients with TIA rather than on stroke. Consequently, this study was able to provide more detailed information about the relationship between WMLs and TIA outcomes. Another advantage of this study was that volumetric measurements of WMLs were used, which could offer a more reliable, reproducible, and objective result relative to visual rating scales such as the Fazekas score.[49] This study had several limitations. First, it was a single-center study, and the sample size was low, which may lower data reliability and robustness. Second, sampling bias was a potential limitation. Only hospitalized patients were evaluated. Third, the progression of longitudinal WML volumes was not assessed.

In conclusion, WMLs occur frequently in patients with first-ever TIA and are associated with high risks of recurrent vascular events. Consequently, this could serve as a predictive neuroimaging marker for the unfavorable prognosis of patients with TIA in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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