Severity of White Matter Lesions Correlates with Subcortical Diffusion-Weighted Imaging Abnormalities and Predicts Stroke Risk

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Background and Purpose: The severity of white matter lesions (WMLs) has been strongly linked to small-vessel diseases or lacunar infarction. The present study aimed to investigate the correlation between severity of WMLs and distribution of diffusion-weighted imaging (DWI) hyperintensities, and to explore whether the severity of WMLs is an independent neuroimaging predictor of stroke risk after transient symptoms with infarction (TSI). *Methods:* We evaluated the presence and severity of WMLs on fluid-attenuated inversion recovery sequences using the age-related white matter changes scale and the location and size of hyperintensities on DWI sequences, respectively, in a prospective cohort study of TSI patients. The primary end point was recurrent stroke within 90 days. *Results:* A total of 191 consecutive TSI patients were eligible for inclusion in the present analysis. The average age of the patients was 57.3 ± 12.8 years. DWI abnormalities occurred more often in the deep white matter with increasing severity of WMLs ($P < .001$). During 90-day follow-up, Kaplan–Meier analysis showed that recurrent stroke was correlated to the severity of WMLs ($P = .01$). The Cox proportional hazards model revealed that WMLs were predictive of recurrent stroke (hazard ratio, 1.748; 95% confidence interval, 1.16-2.634; $P = .008$). *Conclusions:* Severe WMLs were correlated with DWI hyperintensities in the deep white matter in TSI patients and contributed to an increased risk of recurrent stroke. **Key Words:** White matter—infarction—magnetic resonance imaging—stroke—leukoencephalopathies—ischemic attack, transient—transient symptoms with infarction.

Introduction

Patients with transient ischemic attack (TIA) are at high risk of early recurrent stroke, and it is important to triage TIA patients as quickly as possible so as to prevent subsequent stroke.[1-3] A number of TIA patients have acute ischemic lesions on diffusion-weighted imaging (DWI), which are defined as transient symptoms with infarction (TSI). Those TSI patients have been proved to portend a higher risk of recurrent ischemic events, independently of ABCD^2 score and vascular risk factors.[4-6]

The ABCD^2 score has been recommended to predict stroke risk in international guidelines to improve early stroke risk stratification after TIA.[7,8] Recently, risk stratification tools incorporating acute DWI lesions such as

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Received June 13, 2017; revision received July 14, 2017; accepted July 23, 2017.

Grant support: The study was supported by the project of the Health Department of Henan Province (201403036), the Education Department of Henan Province (17A320060), and the Science and Technology Agency of Henan Province (152102310059).

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.07.025

the ABCD[3]-I score for identifying and triaging high-risk TIA patients have been suggested to better predict stroke risk after TIA. In particular, stratified, urgent evaluation and immediate management have substantially reduced the overall stroke risk and led to improved clinical outcomes.[9-12]

However, imaging parameters of small vessel disease, such as white matter lesions (WMLs), which are considered to be markers of chronic ischemia and predictors of recurrent stroke, have not been well explored in TSI patients. In addition, there has been no study on the pattern of acute ischemic lesions on DWI in TSI patients with different severities of WMLs. In the present study, we aimed to investigate the impact of WMLs on the distribution of acute ischemic lesions in TSI patients and the prognostic significance of WMLs on the 90-day rate of recurrent stroke.

Methods and Subjects

We conducted a prospective cohort study in the Department of Neurology in the First Affiliated Hospital of Zhengzhou University, a large tertiary teaching hospital. As described in our previous studies,[13] patients were prospectively registered into the Henan TIA Registry database. TIA was defined as an acute loss of focal cerebral or ocular function lasting less than 24 hours and attributed to embolic or thrombotic vascular disease according to the World Health Organization diagnostic criteria.[14] TSI was defined as TSI on DWI sequence. Demographic data, vascular risk factors, and past medical history were collected at the time of admission on a standardized case report form, and patients were regularly followed up by trained stroke specialists. Patients with DWI and T2-weighted fluid attenuated inversion recovery (FLAIR) examinations for the index TSI within 7 days of symptom onset, and with acute ischemic lesions present on DWI images, were included in the current study. The overall registry project was approved by the Ethics Committee in the First Affiliated Hospital of Zhengzhou University. All participants provided written informed consent for study participation.

Image Evaluation

Acute ischemic lesions and WMLs were assessed on DWI and FLAIR imaging, respectively. Acute ischemic lesions were defined as a hyperintense lesion on the DWI sequence (b = 1000) with corresponding hypointensity on the apparent diffusion coefficient map. According to the involvement of anatomic sites, the distribution of acute ischemic lesions was divided into frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, deep white matter (including corona radiate and centrum semiovale), infratentorial region (including brain stem and cerebellum), and multi foci (if more than 1 of the above 8 areas were involved). WMLs were defined as areas with high signal intensities on the FLAIR sequence, without prominent hypointensity on T1-weighted imaging. The WMLs were classified into 4 grades according to the age-related white matter changes (ARWMC) scale[15]: grade 0, no lesions (including symmetrical, well-defined caps or bands); grade 1, focal lesions; grade 2, beginning confluence of lesions; and grade 3, diffuse involvement of the entire region, with or without involvement of U fibers. WMLs and the DWI hyperintensities were evaluated by 2 independent neurologists who were blinded to the clinical data. WMLs were separately assessed in each hemisphere, but only the score from the nonischemic hemisphere was considered after unblinding.

Follow-Up and Outcome

Patients were followed up regularly in our outpatient clinic or by telephone calls every 3 months. The outcome of the present study was stroke occurrence at 90-day follow-up after the index TSI, which was defined as a new neurological deficit persisting for more than 24 hours with a confirmed new infarct relevant to clinical symptom on brain computed tomography or magnetic resonance imaging (MRI) scan and not attributable to other causes of neurological deterioration. Each stroke occurrence was reviewed by a physician blinded to the results of the MRI.

Statistical Analyses

Baseline characteristics were compared by one-way analysis of variance test or Student's *t*-test for continuous variables and the chi-square test or Fisher's test for categorical variables as appropriate. The multiple ordinal logistic regression model was performed to explore the associations between the potential risk factors and the severity of WMLs. Kaplan–Meier analysis was used to calculate the cumulative incidence of stroke occurrence, and risks of stroke stratified according to the severity of WMLs were compared by log-rank test. The Cox proportional hazards regression model was conducted to evaluate the prognostic impact of WMLs as a predictor of the risk of stroke occurrence, adjusting for potential confounding factors. A P value of less than .05 was regarded as statistically significant. Statistical analysis was performed using SPSS statistics version 17.0.

Results

From October 2010 to January 2015, a series of 785 consecutive patients with a diagnosis of TIA based on the classic definition were prospectively enrolled in the TIA database. To determine the effect of WMLs as a predictor of recurrent stroke, 41 patients who had endarterectomy or stenting, 1 patient receiving surgical operation for Moyamoya disease, and 1 patient undergoing patent foramen ovale closure were excluded. Sixty-eight patients were also excluded for unavailable DWI sequence. Of the remaining 674 patients, 203 had acute ischemic