Correlation between Fibrinogen and White Matter Hyperintensities among Nondiabetic Individuals with Noncardiogenic Ischemic Stroke

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Objective: The aim of the present study is to confirm the correlation between fibrinogen and the severity of cerebral white matter hyperintensities (WMHs) among nondiabetic patients with noncardiogenic acute ischemic stroke. *Patients and Methods:* A cross-sectional study of 170 consecutive patients with noncardiogenic acute ischemic stroke who underwent magnetic resonance imaging and vascular imaging was conducted. WMHs were classified into periventricular hyperintensity (PVH) and deep and subcortical WMH (DSWMH) using Fazekas rating scale. After adjustment for fibrinogen and other vascular risk factors, we determined which factors were independent of WMHs. *Results:* After adjustment for the vascular risk factors, prior ischemic stroke (odds ratio [OR] 4.153, 95% confidence interval [CI] 1.077-16.020, $P = .039$), fibrinogen level (OR 2.114, 95% CI 1.034-4.322, $P = .040$), and glycosylated hemoglobin A1c (OR .633, 95% CI .423-.947, $P = .026$) were independently and positively associated with PVH ($P < .05$); prior ischemic stroke (OR 2.841, 95% CI 1.469-5.493, $P = .002$), lipoprotein(a) (OR 1.002, 95% CI 1.000-1.005, $P = .047$), and fibrinogen levels (OR 1.788, 95% CI 1.170-2.732, $P = .007$) were independently and positively associated with DSWMH ($P < .05$). *Conclusions:* Our study demonstrated that prior ischemic stroke and higher fibrinogen are associated with WMHs, regardless of PVH and DSWMH, in nondiabetic patients with noncardiogenic acute ischemic stroke. In addition, lipoprotein(a) might be an independent predictor of DSWMH in patients with noncardiogenic acute ischemic stroke. **Key Words:** Fibrinogen—cerebrovascular disease—leukoaraiosis—magnetic resonance imaging—small vessel disease.

Introduction

Cerebral white matter hyperintensities (WMHs), also known as leukoaraiosis (LA) or cerebral white matter lesions (WML), are rounded areas of decreased attenuation on computed tomography, increased signal on T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR), often decreased on T1-weighted magnetic resonance imaging (MRI). WMHs are considered to be one of the manifestations of cerebral small vessel disease.[1] WMHs detected by MRI are classified into periventricular hyperintensity (PVH) and deep and subcortical WMH (DSWMH).

WMHs have been linked to the increased risk of stroke, progression of cognitive decline, and functional disability.[2-4]

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Risk factors of WMHs are multifactorial. It is known that age[5-7] and diabetes mellitus[8-11] are the well-established risk factors related to WMHs. With the wide attention of WMHs, the risk factors of WMHs are still more controversial.

Previous studies have reported fibrinogen levels were significantly and independently associated with the presence of WMLs.[3,12-14] There is substantial evidence from previous studies that levels of fibrinogen are higher in patients with atrial fibrillation.[5,7,15-20] The cardioembolic stroke had higher concentrations of fibrinogen than noncardioembolic stroke.[21] However, some studies found fibrinogen levels were not related to the subtypes of the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.[22,23] However, to our knowledge, there have been no reports among nondiabetic patients with noncardiogenic acute ischemic stroke on the association and WMHs. Therefore, we conducted this study excluding patients with cardioembolism or with history of diabetes mellitus to control confounders. We aimed to resolve these gaps whether there is a relationship between fibrinogen and WMHs in nondiabetic patients with noncardioembolic stroke.

Patients and Methods

Patients

We consecutively recruited patients with acute ischemic stroke admitted to Department of Neurology of the first clinical hospital of Harbin Medical University during the period from August 2015 to January 2017. Inclusion criteria were the onset time less than 1 week, recent (within the 48 hours after admission) MRI, and diffusion-weighted images (DWI). Exclusion criteria were cardiac source of embolism, other secondary WMHs (such as multiple sclerosis, metabolic encephalopathy, toxic encephalopathy, tumor, familial central nervous system disease, and infectious diseases), and severe organ dysfunction.

This study was approved by the biomedical ethics committee of the first clinical hospital of Harbin Medical University. Written informed consents were obtained from the patients or their families.

All the patients accomplished standardized investigation questionnaire inquiry record and measure, including name, gender, age, body mass index, history of diseases (high blood pressure, diabetes, coronary heart disease, history of previous stroke, etc.), smoking, and alcohol status. Hypertension was defined as systolic blood pressure at or above 140 mm Hg, and/or diastolic blood pressure at or above 90 mm Hg, or taking antihypertensive medications. Hyperlipidemia was defined as total cholesterol above 6.0 mmol/L, or low-density lipoprotein cholesterol above 4.14 mmol/L, or taking lipid-lowering agents.

The subjects were evaluated with detailed clinical and neuropsychological assessments at baseline, including name, gender, age, body mass index, history of diseases (high blood pressure, diabetes, coronary heart disease, history of previous stroke, etc.), smoking status and alcohol intake. Hypertension is present if the resting blood pressure is persistently at or above 140/90 mm Hg or taking antihypertensive medications. Hyperlipidemia was defined as total cholesterol above 6.0 mmol/L, or low-density lipoprotein cholesterol above 4.14 mmol/L, or taking lipid-lowering agents.

Blood was collected from the antecubital vein of patients after an overnight fasting. All patient underwent routine laboratory tests, including assays for fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), serum total cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol, serum low-density lipoprotein cholesterol, lipoprotein(a), homocysteine, high-sensitivity C-reactive protein (HCRP), creatinine, uric acid, blood urea nitrogen, fibrinogen, etc. Fibrinogen was tested by the Clauss method. All tests were performed in the Department of Laboratory Medicine of the first clinical hospital of Harbin Medical University.

When patients were admitted to the hospital, neurologists in our department evaluated the neurological signs and symptoms. National Institutes of Health Stroke Scale were evaluated on admission. Acute ischemic stroke was diagnosed according to the criteria: acute focal neurological dysfunction persisting for 24 hours or longer, low signal intensity on brain MRI T1-weighted images, high signal intensity on T2-weighted images, FLAIR images, and DWI observed in a region corresponding to the focal neurological sign.[24]

MRI Scans and Assessment of WMHs

The subjects were imaged using a 3.0T MRI system produced by Philips with a standard 16-channel phased-array head coil. The MRI protocol consists of T1-weighted images (repetition time = 2000 ms; echo time = 20 ms), T2-weighted images (repetition time = 1628 ms; echo time = 80 ms), and FLAIR (repetition time = 8000 ms; echo time = 125 ms) on the sagittal plane with a thickness of 6 mm, and the matrix size was 288×252 pixels.

WMHs were evaluated by 2 trained radiologists who were blind to the clinical information and who judged on the results of the MRI according to Fazekas rating scale,[25] excepting ischemic stroke lesions on the DWI. Both PVH and DSWMH are divided into 4 grades (0-3), respectively. The groups with grade 0 were treated as negative one; conversely, the groups with grades 1-3 were treated as positive one.

Statistical Analysis

All statistical analyses were performed with SPSS software (version 13.0, Stats Data Co. Ltd. Beijing, China). For comparison between the 2 groups, the Student *t* test