Association between Fibrinogen and Leukoaraiosis in Patients with Ischemic Stroke and Atrial Fibrillation

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Background: Leukoaraiosis (LA), a surrogate of cerebral small-vessel diseases (CSVD), has been increasingly recognized because of its high prevalence and strong prognostic value in stroke. But the mechanism of LA is incompletely clarified. Fibrinogen is a crucial role in coagulation cascade and inflammation. There are inconsistent reports on the association of fibrinogen with LA in the general population. We aimed to investigate the association between fibrinogen and LA in patients with stroke and atrial fibrillation (AF), which was not ever reported before. *Methods:* Patients with ischemic stroke and AF were prospectively and consecutively recruited. Clinico-demographic data and fibrinogen levels were collected within 48 hours from stroke onsets and analyzed according to the presence and distribution of LA (periventricular hyperintensity [PVH] and deep white matter hyperintensity). *Results:* Of 186 patients (34.4% male; mean age, 68.76 ± 12.76 years) enrolled, 134 patients (72.0%) presented with LA. Elevated fibrinogen levels were associated with higher presence of LA ($P = .005$) and PVH ($P = .002$). After adjustment for the confounders, the fibrinogen levels were independently correlated with LA and PVH (all $P < .05$). Patients with elevated fibrinogen levels (≥3.5 g/L) were more likely to present with LA and PVH, with the odds ratios of 14.037 (95% confidence interval [CI] 2.588-76.131) and 12.567 (95% CI 2.572-61.395), respectively. *Conclusion:* This study found that fibrinogen was independently and positively associated with LA and PVH in patients with stroke and AF. These results provide further evidence for the key role of fibrinogen in LA, even the total CSVD burden.
Key Words: Fibrinogen—leukoaraiosis—ischemic stroke—atrial fibrillation.

Introduction

Cerebral small-vessel disease (CSVD) refers to a large group of pathological processes affecting the small arteries and venules of the brain, with various etiologies like aging, hypertension, and amyloid angiopathy, accounting for cognitive decline, gait and mood disturbances, as well as urinary problems.[1] The term leukoaraiosis (LA) was proposed in 1987 by Hachinski et al,[2] to describe the white matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI) caused by CSVD.[3] The clinical significance of LA has been increasingly recognized recently because of its high prevalence and strong prognostic value in stroke. Several lines of evidence reported that LA is associated with the incident of stroke in the general population,[4] and contributes to recurrent stroke, vascular dementia, hemorrhagic transformation,

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mortality, and disability after stroke.[5-8] The pathogenesis of LA is generally considered to be chronic hypoperfusion or brief and repeated ischemic insult of moderate severity occurring in the white matter.[9] But the mechanism of LA is still incompletely clarified and could be multifactorial, including atherosclerosis, blood-brain barriers alteration, chronic brain edema, genetic factors, and others.[1]

Fibrinogen is a 340-kDa plasma glycoprotein, which has a crucial role in coagulation cascade and inflammation.[10] High fibrinogen levels increase plasma viscosity, resulting in reduction of blood circulation.[11] Besides, elevated plasma fibrinogen concentration is involved in endothelial injury, cerebrovascular permeability, and neurovascular dysfunction.[12] These pathological changes are associated with the presence or severity of LA. Does fibrinogen play a dominant role in the pathogenesis and molecular mechanism of LA? Several community-based studies focus on the association of fibrinogen with LA, but there are inconsistent conclusions. Two Japanese studies showed that elevated plasma fibrinogen levels are closely and independently associated with the risk of LA.[13,14] However, Knuiman et al and Aribisala et al did not find this association.[15,16]

The fibrinogen levels are elevated in patients with atrial fibrillation (AF).[17,18] Turgut et al also reported that fibrinogen levels are higher in patients with stroke and AF than in healthy subjects.[19] Meanwhile, Kobayashi et al reported that LA, especially in the deep white matter, is more severe in patients with AF than in control subjects.[20] Considering all these above studies, we conducted this study to determine the association between fibrinogen and LA in patients with ischemic stroke and AF, verifying the hypothesis that high fibrinogen levels were associated with LA.

Methods

Subjects

Patients with ischemic stroke and AF admitted to the Department of Neurology, West China Hospital of Sichuan University (Chengdu, China) within 48 hours from stroke onset were prospectively and consecutively recruited between January 2014 and August 2016. To be recruited, all patients should have received a clinical diagnosis of stroke according to World Health Organization criteria,[21] and then confirmed by brain CT or MRI. AF was defined as a history of persistent AF or paroxysmal AF, supported by past electrocardiogram (ECG) or diagnosed by the attending physicians based on ECG or 24-hour ECG monitoring during hospitalization.[22] If the patients did not undergo MRI scans, or plasma fibrinogen levels were unavailable within 48 hours after the onset, they would be excluded.

This study was approved by the biomedical ethics committee of West China Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consents were obtained from the participants or their guardians.

Data Collection

A standardized form was used to collect baseline information on demographics, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, previous stroke, current smoking, and alcohol consumption), National Institutes of Health Stroke Scale score, blood pressure on admission, platelet count, blood glucose, urea nitrogen, creatinine, and serum lipids (triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein) on first visit. Hypertension was defined as current use of antihypertensive medications, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as current use of antidiabetic agents or a fasting serum glucose level ≥7.0 mmol/L. Hyperlipidemia was defined as current use of lipid-lowering agents, total cholesterol >6.0 mmol/L, or low-density lipoprotein cholesterol >4.14 mmol/L.

Fibrinogen Measurement

Venous blood samples (4-6 mL) were collected from all participants within 48 hours from symptoms onset. The fibrinogen levels were measured with the calibrated CS5100 analyzer (Sysmex Corporation, Hyogo, Japan). All tests were performed in the Department of Laboratory Medicine, West China Hospital. The laboratory adhered to the guidelines of both the National System of External Assessment of the Quality of Results and the College of American Pathology. Patients were dichotomized into 2 groups based on fibrinogen levels: elevated (≥3.5 g/L) and normal (<3.5 g/L) fibrinogen levels.[23]

MRI Scans and Assessment of LA

All patients in our study underwent brain MRI scans within the first 5 days after admission. MRI scans were performed using a 3-T MR imaging system (Magnetom, Siemens, Erlangen, Germany). The imaging protocol was as follows: axial T1-weighted (repetition time = 1600 ms; echo time = 8.6 ms), T2-weighted (repetition time = 4500 ms; echo time = 105 ms), and fluid-attenuated inversion recovery images (repetition time = 6000 ms; echo time = 100 ms). Slice thickness was 5 mm and matrix size was 256 × 256 pixels.

LA was defined as the hyperintensity detected on both fluid-attenuated inversion recovery and T2-weighted images, without prominent hypointensity on T1-weighted image.[24] In the perspective of LA distributions, LA was distinguished as periventricualr hyperintensity (PVH) and deep white matter hyperintensity (DWMH) according to the Fazekas scale.[25] Imaging data were independently read and assessed by 2 trained neurologists blinded to the clinical data. All disagreements were resolved by consensus.