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Association between leukoaraiosis and hemorrhagic transformation after cardioembolic stroke due to atrial fibrillation and/or rheumatic heart disease

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ABSTRACT

Cardioembolic stroke due to atrial fibrillation (AF) and/or rheumatic heart disease (RHD) often involves hemorrhagic transformation (HT), and we examined whether leukoaraiosis (LA) was associated with HT in these cases. We prospectively enrolled 251 patients who were admitted to two hospitals within one month of experiencing cardioembolic stroke due to AF/RHD. LA severity was assessed using three visual rating scales. HT was identified in 99 patients (39.4%) based on baseline computed tomography (CT) and post-admission magnetic resonance imaging or second CT. Univariate analysis identified risk of HT as higher in the presence of frontal LA based on the age-related white matter changes scale and in the presence of anterior LA based on the VSS scale. Multivariate analysis confirmed that moderate to severe LA was independently associated with higher HT risk. Of the various sites affected in LA, frontal LA correlated with highest risk of HT (OR 3.199, 95%CI 1.555–6.580). These results suggest that moderate to severe LA, especially at periventricular and anterior sites, is associated with HT after cardioembolic stroke due to AF/RHD. These findings suggest the need to take LA into account as a HT risk factor when considering the use of anticoagulation and thrombolysis in these patients.

1. Introduction

Hemorrhagic transformation (HT) occurs as part of the natural history of ischemic infarction, and it tends to be more severe and frequent when patients receive anticoagulant or thrombolytic drugs or when they undergo endovascular manipulations [1]. Cardioembolic stroke, which accounts for 10–26% of ischemic stroke cases in China [2] and is caused primarily by atrial fibrillation (AF) and rheumatic heart disease (RHD) [3], is associated with high frequency of HT and large infarct size [4,5]. This limits the use of effective therapeutic strategies such as oral anticoagulants and thrombolysis, which contributes to the particularly poor outcomes associated with cardioembolic infarction [5]. In fact, this type of infarction is associated with poorer functional outcome and higher mortality than stroke associated with large-artery atherosclerosis [3,6–9].

A clearer understanding of which patients with cardioembolic stroke are at higher risk of HT is critical for maximizing the safety and efficacy of oral anticoagulants, which can effectively reduce occurrence and recurrence of stroke. These anticoagulants are administered to only 19% of ischemic stroke patients with non-valvular AF in China, which is much lower than in the West [10]. Better understanding of HT risk would also help guide more rational use of active interventions such as thrombolysis, which is often not used for fear of HT, [6,11] even though official thrombolysis guidelines do not explicitly mention contraindications related to cardioembolic infarction [12], except for current use of anticoagulants.

Leukoaraiosis (LA) shows potential for being an easily assessable risk factor for HT in cardioembolic stroke, given substantial evidence linking it to risk of HT in ischemic stroke. LA refers to white matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI) caused by cerebral small vessel disease (CSVD) [13–16], which comprises various pathological processes affecting the small arteries and venules of the brain. CSVD has various causes, including aging, hypertension and amyloid deposition, resulting in parenchyma pathologies that include microbleeds, lacunar infarcts and white matter lesions, frequently observed in ischemic stroke [17]. Studies suggest that

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CSVD is a risk factor for HT in ischemic stroke after thrombolysis [18], and high burden of cerebral microbleeds may be independently associated with symptomatic HT in ischemic patients after thrombolysis [19]. Moreover, several studies suggest that LA increases risk of HT in ischemic stroke patients treated with thrombolysis and anticoagulants [20–23], and a meta-analysis by Charidimou et al. has concluded that LA on brain CT is associated with increased risk of symptomatic HT after thrombolysis [24]. This literature clearly indicates a link between LA and HT in ischemic stroke, but it is unclear whether the same association holds for cardioembolic stroke in particular.

We addressed this question by comparing the presence and severity of LA with occurrence of HT in a cohort of patients from two medical centers with cardioembolic stroke due to AF and/or RHD. LA severity was assessed using three widely accepted visual rating scales. Our results should help determine whether LA can reduce or negate the benefits of thrombolysis therapy in patients with cardioembolic stroke due to AF and/or RHD.

2. Methods

2.1. Study population

Patients with cardioembolic stroke due to AF and/or RHD were prospectively recruited from the neurology departments of West China Hospital, Sichuan University (Chengdu, China) and the People's Hospital of Deyang City (Deyang, China) between January 2014 and February 2016. Cardioembolic stroke was assessed using the Trial of Org 10,172 in acute stroke treatment (TOAST) classification [25]. A comprehensive evaluation was performed, including brain non-enhanced CT and MRI scans, imaging of intracranial and extracranial arteries (by MR angiography, CT angiography or digital subtraction angiography), carotid ultrasound, as well as electrocardiography and echocardiography during hospitalization. Patients were eligible for the study if they (1) had experienced either first-ever or recurrent ischemic stroke within one month of stroke onset, (2) had a history of AF and/or RHD, (3) underwent head CT on admission and (4) underwent MRI or CT after admission. AF was defined as a history of persistent AF or paroxysmal AF, supported by electrocardiography and/or 24-hour electrocardiography. RHD was diagnosed according to the criteria of the *International Classification of Diseases* (10th edition) and confirmed by echocardiography [9].

Patients were excluded if they (1) could not live independently with prestroke disability (modified Rankin Scale score ≥ 2), (2) had potential large-artery atherosclerotic sources of thrombosis or embolism, or (3) had contraindications for MRI, such as claustrophobia or mechanical valve prosthesis. This study was approved by the Scientific Research Department of West China Hospital, and the protocol conformed to local ethics criteria for human research. Informed content was obtained from all patients or their next of kin.

2.2. Data collection

On admission, baseline information was collected on age, sex, time from symptom onset to admission, National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, previous medical history (hypertension, diabetes mellitus, hyperlipidemia and stroke), history of smoking and alcohol consumption, blood pressure on admission, laboratory tests, brain imaging and therapies. Laboratory data on the first visit included platelet count, international normalized ratio and levels of blood glucose, serum urea, creatinine, triglyceride, cholesterol, low-density lipoprotein and high-density lipoprotein.

2.3. CT and MRI scans

All CT examinations were performed within 24 h of admission, followed by scheduled MRI within 5 days (±2 days) after admission or second CT immediately whenever hemorrhage was suspected, such as because of headache or neurological deterioration. Mean time from baseline scan to follow-up scan was also 5 days (±2 days). CT was performed using a 64-section scanner (Siemens) with 7-mm slice thickness. MRI was performed on a 1.5-T Philips scanner (People's Hospital of Deyang City) with a slice thickness of 6 mm, or on a 3-T Siemens scanner (West China Hospital) with a slice thickness of 5 mm. Matrix size was 256 × 256 pixels on both MRI scanners. MRI included sequences of T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Repetition time (TR) and echo time (TE) were as follows for the three types of imaging at the Deyang site: T1-weighted, TR was 450 ms and TE was 15 ms; T2-weighted, TR was 3563 ms and TE was 100 ms; FLAIR, TR was 11,000 ms and TE was 140 ms. The corresponding TR and TE at West China Hospital site were as follows: T1-weighted, TR was 1600 ms and TE was 8.6 ms; T2-weighted, TR was 4500 ms and TE was 105 ms; FLAIR, TR was 6000 ms and TE was 100 ms.

HT was defined as hemorrhage within the infarct territory or parenchyma hemorrhage outside the infarct zone that was present on a second CT or MRI during hospitalization but not on head CT on admission [26]. Given that all patients went through MRI scans according to the medical plan in this study, HT was diagnosed based on combined analysis of T1-weighted, T2-weighted and FLAIR MRI sequences. HT was confirmed again on a second CT scan in patients showing progressive neurological deterioration. Cases of HT were subclassified as symptomatic HT (sHT) when the patient showed an increase of >4 points on the NIHSS score during hospitalization [27], or as asymptomatic HT (aHT) when the patient showed no worsening of neurological manifestations. Cases of HT were also subclassified as hemorrhagic infarction (HI), when the patient showed small petechiae along the margins of the infarct (HI-1) or more confluent petechiae within the infarcted area but without a space-occupying effect (HI-2); or as parenchymal hematoma (PH), when the patient had hematoma in 30% of the infarcted area with a slight space-occupying effect (PH-1) or dense hematoma in 30% of the infarcted area with a substantial space-occupying effect or any hemorrhagic lesion outside the infarcted area (PH-2) [28]. Given the small size of our study, we aggregated the HI-1 and HI-2 subgroups together into a single HI group and the PH-1 and PH-2 subgroups into a single PH group in all analyses.

Since MRI was more sensitive than CT for assessing LA, MRI was the only radiological technique used to evaluate LA in this study. LA was defined as the presence of hyperintense lesions on both FLAIR and T2-weighted MRI sequences, in the absence of prominent hypointensities on the T1-weighted sequence [29,30]. LA severity was assessed using three widely accepted MRI-based visual rating scales: the Fazekas scale [31], Van Swieten scale (VSS) [32], and age-related white matter changes (ARWMC) scale [33]. The Fazekas scale is easy to use even by inexperienced researchers, and it classifies lesions as being either in the periventricular or deep white matter. The VSS scale is also a simple scale and it shows good reliability; it classifies lesions as being anterior or posterior to the central sulcus. The ARWMC scale classifies lesion location among five sites in each hemisphere (frontal, parieto-occipital, temporal, basal ganglia and infratentorial). In this study, we combined the same sites in each hemisphere into a single site for the normal ARWMC score and kept total five sites (frontal, parieto-occipital, temporal, basal ganglia and infratentorial) for the modified ARWMC score. Two trained neurologists blinded to patient data independently assessed LA based on all MRI data. Inter-rater agreement was at least substantial (defined as $\kappa = 0.61–0.80$) (Supplementary Table S1). It reached almost perfect agreement (defined as $\kappa = 0.81–1.0$) for periventricular ($\kappa = 0.843$), deep white matter ($\kappa = 0.861$), anterior ($\kappa = 0.821$) and posterior regions ($\kappa = 0.827$). Exceptions were the ARWMC scores at the left temporal site ($\kappa = 0.478$) and at both infratentorial sites; κ could not be calculated at the infratentorial sites because not any participants had LA at those sites. Therefore ARWMC scores for the left temporal and infratentorial sites were excluded from subsequent analysis.