Increased Serum Alkaline Phosphatase as a Predictor of Symptomatic Hemorrhagic Transformation in Ischemic Stroke Patients with Atrial Fibrillation and/or Rheumatic Heart Disease

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Background and Objective: Elevated alkaline phosphatase (ALP) is considered as a marker of liver function in clinical practice. Furthermore, it has been identified that liver function can contribute to hemorrhagic transformation (HT). However, whether ALP levels play a role in HT after stroke remains an open question, especially in cardioembolic stroke patients. *Methods:* We prospectively and consecutively enrolled ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease. Baseline data including ALP levels within 48 hours after admission were collected. ALP levels were divided into tertiles. The presence of HT, hemorrhagic infarction (HI), parenchymal hematoma (PH), and symptomatic HT was evaluated according to brain magnetic resonance imaging and European-Australasian Acute Stroke Study III definitions. We used logistic regression to examine the associations between ALP levels and risk of HT, HI, PH, and symptomatic HT. *Results:* Of the 130 patients (56 male; mean age: 63 years) included finally, 50 (38.5%) developed HT and 13 (10.0%) developed symptomatic HT. ALP levels were not associated with risk of HT, HI, and PH. However, compared with the first ALP tertile, patients in the third tertile were 8.96 times more likely to have symptomatic HT (95% confidence interval: 1.33-60.21; $P = .02$) after adjusting for age, gender, alanine aminotransferase levels, aspartate aminotransferase levels, antiplatelet therapy, anticoagulation therapy, and thrombolysis therapy. *Conclusion:* Elevated ALP levels may help identify high-risk symptomatic HT in ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease. However, further studies with larger cohorts are needed to identify our results. **Key Words:** Acute ischemic stroke—alkaline phosphatase—hemorrhagic transformation—atrial fibrillation—rheumatic heart disease.

Introduction

Hemorrhagic transformation (HT) is part of the natural history of ischemic infarction,[1] and it also can be the major complication of using tissue plasminogen activator (tPA), antiplatelets, and anticoagulants after ischemic stroke.[1,2] HT has been identified to associate with poor outcomes in stroke patients.[3-5] In addition, among the subtypes of ischemic stroke, cardioembolism has been linked to the highest frequency of HT.[6,7] Considering those, it is necessary to explore and identify the risk factors of HT in ischemic stroke, especially in cardioembolic stroke, which may help clinicians assess the risk of HT in cardioembolic stroke patients more accurately and design treatments accordingly.

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It is well known that alkaline phosphatase (ALP) is generally used as a marker of liver dysfunction in clinical practice.[8] The widely used HAS-BLED score includes liver dysfunction as a fundamental item for assessing hemorrhagic risk,[9] and liver dysfunction has also been found to contribute to hematoma enlargement in intracerebral hemorrhage[10] and HT in ischemic stroke,[11] which boosted and enhanced the role of liver dysfunction in HT.

In addition, growing studies have identified that elevated serum ALP levels are related to increased risk of cardiovascular,[12] ischemic/hemorrhagic stroke events[13] and small cerebral vascular disease.[14,15] It can be explained by the function of ALP associating with vascular calcification,[8] systemic inflammation,[16,17] atherosclerosis,[8] and vascular homeostatic activity,[13] all of which have been identified to have an influence on the risk of HT. However, there were few studies investigating the associations between elevated serum ALP levels and risk of HT after ischemic stroke, especially in cardioembolic stroke patients.

Therefore, we aimed to investigate whether ALP levels play an important role in the risk of HT and are symptomatic in ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease (AF and/or RHD) in China.

Methods

This research was supported by the National Natural Science Foundation of China project "Study on small vessel pathological mechanism of cerebral hemorrhage after cardioembolic stroke using SWI markers" in 2 stroke centers over defined time periods in Chengdu and Deyang, China. The two hospitals were the West China Hospital, Sichuan University (January 2014 to December 2015), and the People's Hospital of Deyang City (September 2014 to July 2015). The study protocol was approved by the Medical Ethics Committee of West China Hospital, Sichuan University. Written informed consent was obtained from participants or their guardians.

We prospectively and consecutively enrolled ischemic stroke patients with AF and/or RHD. All patients received a clinical diagnosis of stroke according to World Health Organization criteria,[18] and this diagnosis was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). AF[19] was defined as a history of persistent AF or paroxysmal AF, supported by previous electrocardiograms or by electrocardiography (24 hours or not) during admission. RHD[20] was diagnosed according to criteria in the International Classification of Diseases (10th edition) and confirmed by echocardiography.

All patients completed brain CT within 24 hours after admission. Follow-up brain MRI was performed for all patients within 7 days after admission. CT was also performed immediately when patients were found with abrupt clinical worsening. Patients were excluded from the study if they refused to undergo electrocardiography, if ALP levels were not obtained, if they did not undergo follow-up MRI, or if they had history of liver disease including active hepatitis, liver cirrhosis, and hepatoma.

A standardized form was used to collect data on information about patient demographics, time of stroke onset, stroke severity on admission (National Institutes of Health Stroke Scale [NIHSS] score[21]), renal impairment (based on medical history or on prospective measurement of estimated glomerular filtration rate < 60 mL/min/1.73 m[22,23]), risk factors, diagnostic tests, neurological imaging, treatments administered, and stroke-related complications during hospitalization.

Venous blood samples (4-6 mL) were collected from all patients within 48 hours after admission. Serum levels of ALP were measured with an Olympus AU-5400 automatic analyzer (Olympus, Tokyo, Japan). If serum ALP levels were examined several times within 48 hours, we used the first value to analyze. The normal reference values of serum ALP range from 40 to 160 IU/L.

HT was defined as hemorrhage in the infarct zone not detected by CT immediately after stroke, but observed later during MRI.[24,25] According to the European-Australasian Acute Stroke Study III definitions,[26] we classified HT as hemorrhagic infarction (HI) and parenchymal hematoma (PH). HT was defined as symptomatic[26] when it was associated with early neurologic deterioration, and neurologic deterioration was diagnosed when the NIHSS score worsened by greater than or equal to 4. The presence of HT was determined independently by 2 neurologists blinded to clinical data. In case of disagreement, a third neurologist was consulted, and a consensus decision was reached.

Differences in continuous data were assessed using Student's *t*-test or the Mann–Whitney nonparametric test; the χ^2 or Fisher exact tests were used to compare categorical variables. Possible associations between patient variables and risk of HT were identified using binary logistic regression. When appropriate, results were reported using odds ratios (ORs) and 95% confidence intervals (95% CIs). All statistical analyses were performed using SPSS 20.0 (IBM, Chicago, IL) and a significance threshold of $P < .05$ (two sided).

Results

During the study period, 130 patients were enrolled in our research, all of which were included in the final analysis (West China Hospital, Sichuan University, n = 92; People's Hospital of Deyang City, n = 38) and with ages ranging from 42 to 92 years (mean 63.15 ± 12.08 years); there were 56 men (43.1%). In the current study, 99 patients had AF only, 7 with RHD only, and 24 with both conditions. In the end, 50 (38.5%) patients developed HT, of which 32 (24.6%) were found with HI, 18 (13.8%) with PH, and 13 (10.0%) with symptomatic HT (Table 1).

Patients were subgrouped into tertiles according to serum levels of ALP within 48 hours after admission (Table 2):