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Elevated circulating homocysteine and high-sensitivity C-reactive protein jointly predicts post-stroke depression among Chinese patients with acute ischemic stroke

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ABSTRACT

Background: Homocysteine (HCY) and high sensitivity C reactive protein (hs-CRP) were suggested to be involved in post-stroke depression (PSD), which is a frequent mood disorder after stroke. However, the combined effect of HCY and hs-CRP on PSD remains unclear.

Methods: A total of 598 acute ischemic stroke patients from 7 of 26 centers participating in the China Antihypertensive Trial in Acute Ischemic Stroke with HCY or hs-CRP measurements were included in this analysis. PSD status was evaluated by 24-item Hamilton Depression Rating Scale at 3 months after stroke.

Results: Two hundred and forty-one (40.30%) participants were considered as PSD. HCY and hs-CRP levels were not significantly different between PSD and non-PSD patients. Interesting, in a maximally adjusted model, the odds ratio (95% confidence interval) of PSD was 1.90 (1.18–3.06) for coexistence of HCY ≥ 14.65 μmol/l and hs-CRP ≥ 1.90 mg/l compared with the other levels (HCY < 14.65 μmol/l and/or hs-CRP < 1.90 mg/l). Adding combination of HCY and hs-CRP to a model containing conventional risk factors could significantly improve risk reclassification for PSD.

Conclusions: Coexistence of both higher HCY and higher hs-CRP in the acute phase of ischemic stroke were associated with subsequent PSD, independently of established conventional risk factors.

1. Introduction

Stroke is a devastating health problem worldwide [1], and becomes the leading cause of death and adult disability in China [2]. Post-stroke depression (PSD) is a common neuropsychiatric complication after stroke [3], and affects approximately a third of stroke survivors [4]. PSD has a negative impact on stroke-related outcomes in the forms of greater functional disability, poorer cognitive impairment, higher mortality and bigger chance of stroke recurrence [5, 6]. Therefore, the early recognition of depression symptoms and introduction of pharmacological treatment in stroke patients may lead to better functional outcome.

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Age, gender, medical history, subtypes and severity of stroke were proposed to be main risk factors of PSD [7]. Meanwhile, evidence suggests that inflammation have fundamental roles in PSD through the stimulation of different proinflamatory markers, such as high sensitivity C reactive protein (hs-CRP) [8, 9]. Homocysteine (HCY) could influence inflammatory process [10, 11], it was also known to be directly toxic to neurons [12] and related to psychiatric and neurodegenerative disorders [13, 14]. Several studies showed that HCY and hs-CRP were independently associated with PSD [15, 16], but inconsistent results were also reported [17, 19]. In addition, although interaction between HCY and hs-CRP was proposed in many diseases [20, 21], the effect of HCY and hs-CRP on PSD were generally studied separately, and their interplay has not been well-studied. Our aim in this study was therefore to evaluate associations between HCY and hs-CRP as well as combination of the two biomarkers and the development of PSD at three months after stroke among 598 acute ischemic stroke (AIS) patients from 7 of 26 centers participating in the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS).

2. Materials and methods

2.1. Study design and participants

The CATIS study was a multicenter, single-blinded, blinded endpoints randomized clinical trial conducted among 4071 patients with AIS. The principle purpose of the CATIS study was to test whether moderate lowering of blood pressure (BP) within the first 48 h after the onset of an AIS would reduce death and major disability at 14 days or hospital discharge [22]. Eligible participants were ≥22 years who had ischemic stroke, confirmed by computed tomography or magnetic resonance imaging within 48 h of symptom onset, and who had an elevated systolic BP between 140 to < 220 mmHg. Participants of the preplanned ancillary study were systemically selected prior to randomization from seven participating hospitals for cognitive function and psychological evaluation at their 3-month follow-up visit [23]. The ancillary study excluded patients who had difficulties in communicating or finishing psychological assessments, such as severe psychiatric illness. The seven participating hospitals recruited 660 patients (17 of 677 patients were excluded because of visual or hearing impairment) consecutively, and the recruitment completed by November 2012. At the 3-month visit, 15 patients were lost to follow-up and 7 patients were deceased, 638 participants were remained. Of these participants, some patients did not offer blood samples or some collected samples were hemolyzed in storage or transport, 598 participants were finally included in the present analysis (Fig. 1). Most baseline characteristics of enrolled and excluded patients in this analysis were well-balanced (**Supplemental Table A**).

This study was approved by the institutional review boards at Soochow University in China and Tulane University in the United States, as well as ethical committees at the participating hospitals. Written consent was obtained from all study participants or their immediate family members.

2.2. Assessment of circulating hsCRP, HCY and potential covariates

Blood samples were collected after at least 8 h of fasting within 24 h of hospital admission. All serum and plasma samples were separated and frozen at −80 °C in the Central Laboratory of School of Public Health at Soochow University until laboratory testing. Plasma HCY was determined by enzymatic cycling assay on the Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, IN). Serum hs-CRP was measured by latex enhanced immuno-turbidimetric assay on the Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, IN). HCY and hs-CRP determinations were performed by laboratory technicians blinded to the clinical characteristics and outcomes.

Data on demographic characteristics, lifestyle risk factors, medical history, and medication history were collected at the time of enrollment. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) by trained neurologists at admission [24]. Three BP measurements were obtained at baseline by trained nurses according to a common protocol adapted from procedures recommended by the American Heart Association [25]. Blood pressure was measured with the participant in a supine position using a standard mercury sphygmomanometer and 1 of 4 cuff sizes (pediatric, regular adult, large adult, or thigh) based on participant arm circumference. If the patient self-reported to have a mean systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or take antihypertensive medications before hospitalization, then personal history of hypertension was defined.

2.3. Assessment of outcomes

The primary endpoint was PSD at 3 months after stroke, which was assessed by trained neurologist and psychologist. All patients were interviewed using the structured clinical interview of DSM-IV (SCID-I-R) [26]. The severity of depressive symptoms was measured with the validated version of 24-item Hamilton Depression Rating Scale (HAMD-24) [27, 28] for the Chinese population. According to the recommendation, a score of 8 was considered to be the cut-off point for diagnosing depressive symptoms [29–31].

2.4. Statistical analysis

Results were expressed as percentages for categorical variables and as means (standard deviation, S.D.) or medians (inter-quartile range) for the continuous variables, depending on the normal or non-normal distribution of the data. Proportions were compared using the Chi-square test, and Student's t-tests were employed for the normally distributed variables, while the Mann–Whitney U test was employed for the asymmetrically distributed variables. HCY and hs-CRP were dichotomized using a median split. The influence of hs-CRP/HCY separately or jointly on PSD were examined by binary logistic regression analyses, resulting in odds ratios (ORs) and 95% confidence intervals (CIs). We also performed three multiple-adjusted logistic regression models. Model 1 adjusted for age, sex, education status, body mass index, current smoking, alcohol drinking and widowhood. Model 2 included the factors in model 1 as well as time from onset to randomization, systolic BP, fasting glucose, baseline NIHSS score, ischemic stroke subtype and use of antihypertensive medications. Model 3 included the factors in model 2 as well as family history of stroke, personal history of hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease. In addition, net reclassification index (NRI) and integrated discrimination improvement (IDI) were calculated to evaluate the predictive value of adding hs-CRP/HCY to conventional risk model (covariates in model 3) [32]. What's more, we performed stratified analyses and explored the potential effect modification by age (< 65 and ≥65 years), sex (men and women), education (< 8 and ≥8 years), body mass index (< 24 and ≥24 kg/m^2), admission NIHSS score (< 4 and ≥4), smoking status (yes/no), alcohol consumption (yes/no), personal history of hypertension (yes/no), stroke subtype (lacunar and thrombotic) and receiving immediate BP reduction (yes/no). The interplay between hs-CRP and HCY and interested factors was tested by the likelihood ratio test of models with interaction terms. Finally, sensitivity analysis was also conducted to test the robustness of our findings based on other suggested cut-off values (≤9 = none, > 9 = PSD) [33, 34]. All *P* values were 2-tailed, and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.4, Cary, North Carolina, USA).