



Plasma levels of glutamate during stroke is associated with development of post-stroke depression



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KEYWORDS

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Summary

Background: Depression is a frequent mood disorder that affects around 33% of stroke patient. Our aim was to test the possible association between plasma glutamate and the development of post-stroke depression (PSD) in Chinese patients.

Methods: The subjects were first-ever acute ischemic stroke (AIS) patients who were hospitalized during the period from November 2011 to September 2013. Clinical information and stroke severity was collected at admission. Neurological and neuropsychological evaluations were conducted at the 3-month follow-up. Plasma glutamate levels were analyzed at baseline using liquid chromatography followed by tandem mass spectrometry. Glutamate oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT) and blood markers were also tested. Multivariate analyses were performed using logistic regression models.

Results: During the study period, 209 patients were included in the analysis. Seventy patients (33.5%) were diagnosed as having major depression at 3 month. Patients with major depression showed higher levels of plasma glutamate [299 (235–353) vs. 157 (108–206) μM , $P < 0.0001$] and lower GOT [14 (11–20) vs. 21 (15–32) U/L, $P < 0.0001$] at admission. In multivariate analyses, plasma glutamate and GOT were independent predictors of PSD at 3 months [odds ratio (OR): 1.03 (1.02–1.04), $P < 0.0001$; 0.84 (0.75–0.97), $P = 0.003$]. Plasma levels of glutamate $> 205 \mu\text{M}$ were independently associated with PSD (OR, 21.3; 95% CI, 8.28–67.36, $P < 0.0001$), after adjustment for possible variables.

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Conclusion: The present study demonstrates a strong relationship between plasma glutamate and GOT levels at admission and the development of PSD within 3 months. Further studies are necessary to confirm this association, which may open the way to the proposal of new therapeutic options.

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1. Introduction

China has 2.5 million new stroke cases each year and 7.5 million stroke survivors (Liu et al., 2011). Studies suggest that depression is particularly prevalent among stroke survivors, affecting approximately a third of individuals (Ellis et al., 2010). Post-stroke depression (PSD) worsened stroke-related outcomes in the form of greater functional disability and higher mortality (Masskulpan et al., 2008). PSD is associated with an increased disability, increased cognitive impairment, increased short and long term mortality, increase risk of falls and, finally, with worse rehabilitation outcome (Paolucci, 2008). Patients with PSD show far less recovery from functional impairments compared with no depressed patients with stroke and are 3.4 times more likely to die during the first 10 years after stroke (Hadidi et al., 2009). It increases the cost of treatment and burden of care to families, making the prevention and management of PSD an important area of research.

Glutamate is the major excitatory neurotransmitter in the central nervous system and acts through the activation of N-methyl-D-aspartate (NMDA) receptors. Animal models and human clinical studies reveal the association of pathologically elevated glutamate levels and several acute and chronic neurodegenerative disorders and stroke (Castillo et al., 1996). Ischemic stroke is associated with an excessive release of glutamate in brain. Previous studies have demonstrated that neurological deterioration of patients with acute ischemic stroke is associated with higher glutamate levels in blood and cerebrospinal fluid (Castillo et al., 1997). Moreover, *in vivo* experiments by Rink et al. (2011) concluded that under hypoglycemic conditions extracellular glutamate can be transformed from a neurotoxin to a survival factor by glutamate oxaloacetate transaminase (GOT) in mouse. In this study it has been shown that GOT can protect brain against ischemic stroke, and over expression of GOT minimized lesion volume, whereas GOT knockdown worsened stroke outcomes.

A growing body of evidence indicates that the glutamatergic system is involved in the pathophysiology of depression (Mitchell and Baker, 2010). Several studies associate major depression with elevated blood glutamate levels compared with healthy controls (Küçükibrahimoğlu et al., 2009). Multiple studies have reported findings of elevated glutamate content in the plasma of depressed patients compared to healthy comparison subjects (Sanacora et al., 2012). Croarkin et al. (2013) suggested that major depressive disorder in children and adolescents is associated with increased intracortical facilitation and excessive glutamatergic activity. Further, Auer et al. (2000) reported a reduction in glutamate levels in patients with depression relative to the levels in control subjects.

However, the origins of the plasma glutamate and the pathophysiological mechanisms accounting for the different levels in the depressed patients have not yet been determined. Wang et al. (2012) have suggested that PSD is accompanied by changes in glutamate levels in the frontal lobe. However, there have been no studies on blood glutamate levels in patients with PSD. The lack of data in this field provided the impetus for the study reported herein. Our aim in this study was therefore to evaluate the possible association between plasma glutamate and the development of PSD in one cohort Chinese patients with acute ischemic stroke (AIS).

2. Methods

2.1. Study population

The subjects were first-ever AIS patients who were hospitalized at XinQiao Hospital, Third Military Medical University during the period from November 2011 to September 2013. Patients admitted to the hospital within the first 24 h after stroke onset were consecutively recruited and followed up for 3 months. AIS was defined according to the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO-MONICA) criteria, and were verified from computed tomography (CT) or magnetic resonance imaging (MRI) reports performed within 24 h after admission in all patients. Exclusion criteria were: pre-stroke diagnosis of dementia or significant cognitive impairment, a patient self-report of having been hospitalized for any psychiatric illness, primary hemorrhagic stroke, decreased level of consciousness, severe aphasia or dysarthria, liver insufficiency, metabolic abnormalities, significant acute medical illness (e.g. infection, autoimmune disease, malignant tumor), and significant acute neurological illness other than stroke. The patients used psychotropic drugs prior to stroke onset were also excluded.

The control group consisted of 120 healthy volunteers without a history of psychiatric or neurological disorders. The control group also received clinical assessment, and their score on the Hamilton Scale was less than seven. Written informed consent was obtained from all patients; and, this study conformed to the principles of the Declaration of Helsinki was approved by the investigational review board of the Third Military Medical University.

2.2. Clinical variables

At baseline, demographic data (age and sex) and history of conventional vascular risk factors were obtained. Stroke severity was evaluated by trained neurologists using the

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