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The combination of plasma glutamate and physical impairment after acute stroke as a potential indicator for the early-onset post-stroke depression

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ABSTRACT

Objects: The present study aimed to investigate the relationship of plasma glutamate levels with the early-onset of post-stroke depression (PSD) and to further explore the prognostic value of plasma glutamate combined with clinical characteristics for the early-onset PSD in the acute ischemic stroke patients.
Methods: Seventy-four patients who admitted to the hospital within 24 h of acute ischemic stroke were consecutively recruited and followed up for 2 weeks. The Beck Depression Inventory (BDI) and 17-item Hamilton Depression Rating Scale (HAMD-17) were used to screen for depressive symptoms 14 days after stroke. Diagnoses of depression were made in accordance with DSM-IV. Plasma glutamate levels were determined by High Performance Liquid Chromatography (HPLC) on days 1 and 14 after stroke for all patients.
Results: Plasma glutamate levels were significantly lower in PSD patients than those of non-PSD patients on day 1 after stroke. ROC curve analyses revealed an AUC (area under the ROC curve) of 0.724 (95% CI: 0.584–0.863, $p = 0.004$) and of 0.669 (95% CI: 0.523–0.814, $p = 0.030$) for National Institute of Health Stroke Scale (NIHSS) scores and plasma glutamate levels on day 1 respectively. Combined ROC analyses using the two factors revealed the highest AUC of 0.804 (95% CI: 0.685–0.922, $P < 0.0001$).
Conclusions: These results indicated an association between the early-onset PSD and a low plasma glutamate level following acute ischemic stroke. The combination of reduced plasma glutamate levels and physical impairment (determined by NIHSS) 1 day after acute ischemic stroke was a potential diagnostic indicator for early-onset PSD.

1. Introduction

Post-stroke depression (PSD) is the most common affective disorder after stroke, affecting about 33% of the stroke patients [25]. Patients with PSD have more serious physical and mental disabilities [18].

In recent decades, various bio-psychosocial risk factors linking stroke and depression have been investigated. The current hypotheses of etiology have focused on levels of physical impairment, lesion location, amine dysfunction, psychosocial and demographic risk factors [18,33,59]. However, findings are inconsistent and there is as yet little insight into the underlying neurobiological mechanisms of PSD [33].

Growing evidence suggested that the glutamatergic system plays an important role in the neurobiology and treatment of depression [36]. Animal models for depression, such as chronic unpredicted mild stress (CUMS) [62,65], learned helplessness (LH) [2,72] and Flinders Sensitive Line (FSL) [35,55] all showed glutamatergic dysfunction with abnormal glutamate transporters and/or dysfunction of glutamate receptors [61]. Moreover, several postmortem studies from depressed patients have shown altered mRNA and protein of glutamate receptors in prefrontal cortex and superior temporal cortex [4,44]. A number of reports indicated the alterations in glutamate levels of cerebrospinal fluid (CSF) and blood in patients with depression, although the results were inconsistent. An early study by Kim et al. [28] reported that serum levels of glutamate in patients with depression were significantly higher than those of healthy controls, and positively correlated with the severity of depressive symptoms [38]. This result has been confirmed by other groups [3,34]. However, another study showed low glutamate levels in the CSF of patients with refractory affective disorder [20]. In this respect, it is relevant that the glutamatergic system is a potential target for a new

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generation of antidepressants with fast-onset effects, such as NMDA antagonists [48]. Taken together, these findings suggest that abnormalities in glutamate function in the brain are likely to be involved in the pathophysiology of depression.

Glutamate also play a crucial role in the excitotoxic pathogenesis of ischemic stroke [31]. Significant increases of glutamate in plasma and CSF have been demonstrated in patients with acute ischemic strokes from early hours of onset, and continued to two weeks after stroke [1, 14]. The extent and duration of increased glutamate have predictive value for determining the severity and outcome of the stroke [10].

However, we currently understand little about the relationship of glutamate with PSD. As a crucial factor in both stroke and depression, what role does glutamate play in the early-onset PSD? Given the paucity of available data, we have undertaken a prospective study to investigate the relationship of plasma glutamate levels following ischemic stroke with the early-onset PSD and to further explore the prognostic value of plasma glutamate combined with clinical characteristics for the early-onset PSD.

2. Subjects and methods

2.1. Clinical subjects and assessment

A prospective and observational study with a 2-week follow-up was conducted in the Department of Neurology, Affiliated ZhongDa Hospital of Southeast University, which consecutively recruited 78 patients who admitted to the hospital within the first 24 h after an acute ischemic stroke (AIS). All patients aged between 18 and 80 were diagnosed as ischemic stroke according to the World Health Organization (WHO) criteria [32]. Exclusion criteria included: (1) patients in serious pathogenic condition and/or with dementia, aphasia, dysarthria and deafness severe enough that they were not able to participate in clinical psychological tests; (2) patients with a history of any psychiatric illnesses or psychiatric family history; (3) patients with Parkinson's disease; (4) patients with hepatic, renal, hematological or immunological diseases, thyroid hormone disorders, infectious or inflammatory diseases, and epileptic seizures in the previous month. Finally, 74 patients were evaluated for the entire analysis. None of the patients had received antidepressant drugs during the first two weeks after stroke. All participants signed informed consent, which had been approved by the Institutional Ethical Review Board of Clinic Medical College of Southeast University.

Relevant tests such as electrocardiography, blood pressure, blood routine test and biochemical test have been carried out for all patients. Cranial CT scans were finished within 24 h after admission to exclude cerebral and subarachnoid hemorrhage. All patients underwent cranial MR scans within 24 h after admission. The number, hemisphere, lesion locations and volume of infarcts were determined according to the diffusion weighted imaging (DWI) sequences of the MRI scan as previously reported [66].

Clinical information were collected on admission, including: demographics (age, gender, residence, education, marriage status), past medical history and vascular risk factors. Physical and psychological evaluations were performed as followed: physical impairment after stroke were assessed by the National Institute of Health Stroke Scale (NIHSS) at the first day (time1) and 14 days (time2) after admission. The patients' disability or dependence in activities of daily living 14 days after admission was evaluated by modified Rankin Scale (mRS). Cognitive function was assessed using Mini-Mental State Examination (MMSE) once at the first days after admission. We screened for the existence of major depressive symptoms in accordance with a Beck Depression Inventory (BDI, 21-items) score ≥ 7 at 2 weeks after stroke, and PSD diagnoses were made based on the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) criteria by two senior neurologist and psychiatrist. 17-item Hamilton Depression Rating Scale (HAMD-17) was administered to determine the severity of depressivesymptoms14 days after stroke.

2.2. Blood sampling and laboratory procedures

A total of 2 mL sample of blood obtained from the cubital vein was collected after an overnight fasting between 6:30 and 7:00 am at the first days (time1) and 14 days (time2) after admission in all patients. HPLC (High Performance Liquid Chromatography) was used to determine the plasma glutamate levels. For quality control, the clinical diagnosis of all samples was blinded to technician, negative control was used, 20% of the samples were analyzed on the same day in duplicates. The results were expressed as concentrations of glutamate in plasma (μg/mL).

2.3. Statistical analysis

The analyses were performed with SPSS software (version 13.0; Inc., Chicago, IL, USA). The categorical variables are shown as number (percentage), and the continuous variables were shown as the mean ± standard deviation (SD) or median (inter-quartile range). Normally distributed variables were analyzed with Student's *t*-test, while the non-normal distributed variables were analyzed with the Mann–Whitney *U* test. The paired *t*-test was adopted to compare the difference of plasma glutamate levels at the first days (time1) and 14 days (time2) in each group. Pearson or spearman rank correlation analyses were used to evaluate the linear correlations between plasma glutamate levels and clinical characteristics. The forward conditional logistic regression, including all factors which have significant differences between the PSD and non-PSD groups, was used to find independent risk factors for the development of PSD. Receiver-operating characteristic (ROC) curves were used to assess the feasibility of using the risk factors as diagnostic tools for detection of PSD.

3. Results

Among 74 AIS patients, 26 patients (35.0%) were diagnosed as having PSD 2 weeks after stroke, with 16.38 ± 7.16 mean scores of HAMD. There were no significant differences in age, gender, education, the history of hypertension, diabetes, stroke, and the personal history of smoke and drinking between the PSD and non-PSD subgroups. However, the severity of physical impairment (NIHSS) was higher both in beginning and 2 weeks after stroke in PSD group, cognition function (MESS) and the mRS measurement were worse in the PSD group than in the non-PSD group.

The analysis of blood routine and biochemical parameters between PSD and non-PSD group were described in Table 1. Among all blood parameters, low density lipoprotein cholesterol (LDL-C) was significantly different between PSD and non-PSD patients (3.54 ± 1.00 mmol/L vs 3.10 ± 0.83 mmol/L, $t = 2.021$, $P = 0.047$). The MRI scan found that neither the side or volume of acute infarcts was related to PSD, but the PSD group had a higher frequency of lesion at temporal/insular lobe and cerebral cortex than that of the non-PSD group. The demographics and clinical characteristics of the patients in the two subgroups were summarized in Table 1

There are differences between PSD and non-PSD groups in the plasma glutamate levels according to time. On the first day, there was a significant reduction of plasma glutamate levels in the patients with PSD as compared with non-PSD (4.83 ± 2.41 μg/mL vs 6.43 ± 2.71 μg/mL, $t = 2.28$, $P = 0.026$). After 14 days, the plasma glutamate levels was elevated significantly in the patients with PSD (4.83 ± 2.41 μg/mL vs 6.07 ± 2.53 μg/mL, $t = -2.925$, $P = 0.012$) compared to that of the patients in the first day. However, this measure showed no significant difference within non-PSD patients (Fig. 1).

Correlation analyses revealed that plasma glutamate levels on the first day were negatively correlated with the HAMD scores 2 weeks after stroke in all patients ($r = -0.311$, $P = 0.013$), but not in the PSD or non-PSD subgroup (Fig. 2).