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ORIGINAL PAPER

Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression

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Abstract In recent studies, the glutamate (Glu) level has been quantified using the modified STEAM sequence on 3T MRI. We enrolled 15 healthy volunteers and a group of 51 patients who experienced stroke for the first time and had a good prognosis. The patients with infarction were divided into three groups according to their scores by using the DSM-IV diagnostic criteria for major depressive disorder and the 17-item Hamilton Depression Rating Scale (HDRS). We studied the association between post-stroke depression and ^{1}H-MRS measurements in unaffected frontal lobes. Single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) was performed to assess *N*-acetylaspartate/creatine (NAA)/Cr, (Glu)/Cr, choline (Cho)/Cr, and myoinositol (mI)/Cr ratios in stroke patients. The 11 patients (21.5%) who met the criteria for depression and 9 patients (17.6%) who had a high score for HDRS, (>14) but were not depressed, had a significantly higher Glu/Cr ratio than patients who scored ≤14 on HDRS and control groups ($p < 0.001$). No differences were found in NAA/Cr, Cho/Cr, or mI/Cr between the groups after stroke. These findings suggest that post-stroke depression is accompanied by changes in glutamate levels in the frontal lobe.

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Introduction

Depression is a common complication associated with stroke, having a prevalence of 25–79% [1], with a pooled estimate of 33% of stroke patients affected [2]. Hospital-based studies have reported a prevalence between 22 and 28% [3]. There is high comorbidity of anxiety and depression after stroke. Post-stroke depression causes significant impairment in multiple domains of psychosocial functioning and may have an even greater impact on the quality of life than physical disability. It is important to improve the detection of distress and provide appropriate interventions to alleviate distress to improve outcomes. The mechanism of post-stroke depression is not well understood. Possible risk factors include the presence of metabolic factors in the brain, impairment of cognitive function, and social factors. The importance of infarct size and lesion has been postulated but has not been consistently confirmed.

Magnetic resonance spectroscopy (MRS) allows non-invasive imaging of metabolic changes in the brain, impaired brain function, and brain biochemistry [4]. It can reliably determine the level of compounds, including *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), myoinositol (mI), γ-aminobutyric acid (GABA) and Glx—the combination of glutamate (Glu) and glutamine (Gln) [5]. Several ^{1}H-MRS studies have addressed the issue of biochemical changes. Levels of *N*-acetyl aspartate (NAA) are of particular interest in spectroscopic studies of patients with psychiatric illnesses since this metabolite is considered a marker of neuronal integrity [6]. Recently, some

scholars [7] have quantified Glu by using the modified stimulated-echo acquisition mode (STEAM) sequence on 3T MRI, and the results have been confirmed to be stable and reliable.

The prefrontal lobe, which has many efferent and afferent fibers, plays a very important role in the regulation of emotion; therefore, impairment of prefrontal lobe function was considered as the pathophysiological basis for mental disorders. Studies [8] on depression suggest that the frontal lobe involvement is a consistent finding across a wide range of depressive disorders. Structural changes in the frontal lobe [9], abnormalities in glucose metabolism, and altered patterns of functional MRI (fMRI) activations [10] have all been demonstrated in clinically depressed populations of different age groups. Laboratory studies have shown that reappraisal recruits cognitive control-related brain regions, including the prefrontal cortex and cingulate cortex, which in turn modulate the response of brain regions associated with the generation of emotion, including the amygdala and insula [11]. In particular, it has been shown that BOLD responses in the cingulate cortex predict success at employing cognitive reappraisal [12]. The objectives of this study were to detect metabolic changes (NAA, Cho, MI, Glu) in the cingulate cortex after cerebral infarction and to clarify whether the metabolic changes can predict the occurrence of depression after cerebral infarction.

Materials and methods

Patients

Eighty-one first-time stroke patients (57% women) and 15 controls (40% women) were registered for the study. The inclusion criteria were the diagnosis of first ischemic stroke, clinically defined according to the WHO criteria [13] and no signs of cerebellar or brainstem injury on MR examination. In every case, MR was performed on admission when patients' condition allowed. The exclusion criteria were as follows: cerebral hemorrhage, visibility of more than one stroke lesion on MR images, localization of the lesion to the frontal lobes, age over 80 years, severe aphasia, poor general clinical status, disturbances of consciousness, history of demyelinating or neurodegenerative disorders, head injury, history of schizophrenia, history of disorders related to substance abuse, or use of psychotropic drugs in the month preceding the study. A history of major depression before stroke, as confirmed by interview with the patient and their family members, was also considered as an exclusion criterion. We aimed to follow-up on handicap outcomes only of patients with a first disabling stroke; therefore, patients with a moderate or severe premorbid handicap level (modified Rankin scale score >2) were excluded. Patients who suffered a recurrent stroke during the follow-up period were also excluded, since our study objective was to investigate psychosocial changes after a single stroke episode.

The control group consisted of 15 healthy volunteers without a history of psychiatric or neurological disorders. The mean (SD) age of the controls was 65.3 (8.2) years (range 50–75 years). Written informed consent was obtained. The control group also received clinical assessment, and their score on the Hamilton Scale was less than seven.

Patients who satisfied the inclusion criteria underwent follow-up study in the neurology outpatient clinics of the hospital 3 months after the stroke. The study was approved by the local ethics committee (The ethics committee of Sixth Affiliated People's Hospital, Shanghai Jiao Tong University), and all subjects provided written informed consent.

MRS examination and analysis

MR imaging and in vivo single-voxel MRS were performed using Philips 3T MRI system (Achieva) equipped with an 8-channel phase coil. Anatomical T1-weighted spin-echo MR images were obtained using the following parameters: repetition time (TR) = 550 ms; echo time (TE) = 10 ms; flip angle = 60; field of view (FOV) = 21 cm; slice thickness = 3 mm; slice spacing = 0.1 mm. ^{1}H-MRS was performed for quantification analysis of metabolite concentrations in the brain. First, 2D-spin-echo images in the coronal and sagittal regions were obtained for image-guided localization of voxels of interest (VOIs) for spectroscopic data acquisition. Single-voxel MRS was performed by a stimulated-echo acquisition mode (STEAM) sequence by using the following parameters: TE = 20 ms; TR = 1,500 ms; VOX = 15 × 15 × 15 mm; total number of points = 2,048; total number of average = 128. Eight-step phase cycling was used to suppress unwanted signals or artifacts. To ensure the position consistency in each scan, we used the localization methods described in Fig. 1. Scans were referenced to readily identifiable anatomic landmarks within the brain; the base of the voxel was aligned perpendicular to the tip of the genu corporis callosi.

The volumes of the diffusion-weighted images (DWIs) of lesions were measured by the neuro-radiologist at the stroke center. The areas of hyperintensity on DWIs were manually traced onto each slice, summed, and multiplied by the slice thickness and inter-slice gap to obtain the DWI lesion volume.

Spectrum analysis was performed off-line with the use of the jMRUI 3.0 software. Fitted areas of resonances of interest were calculated in the water-suppressed spectrum

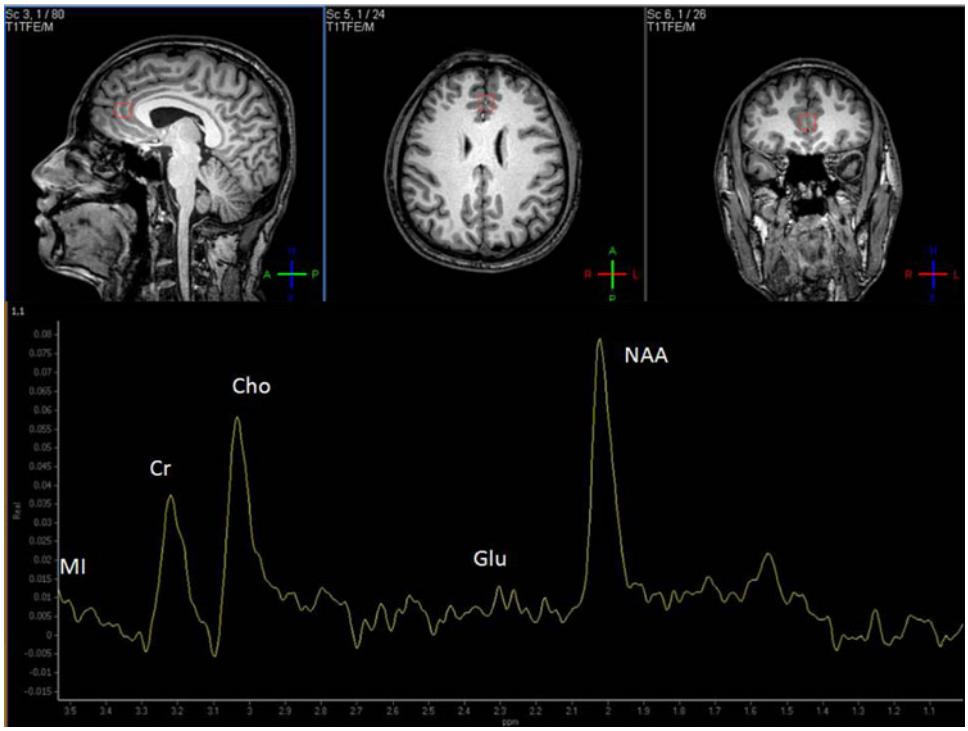

Fig. 1 Anatomic image of the anterior cingulum with voxel borders for MRS. *Left* sagittal plane, *arrows* indicate the position of the voxel regarding the anatomic landmark, *middle* transaxial plane, *right* coronal plane, *down* ^{1}H-MRS spectra

with the AMARES quantitation algorithm. The assignment of resonances of interest, NAA compounds at 2.02 ppm, Glu at 2.35 ppm, Cr at 3.03 ppm, Cho compounds at 3.20 ppm, and mI at 3.55 ppm was based on previous documented studies [14].

Clinical assessment

Clinical characteristics of patients and controls are summarized in Table 1. The clinical status before treatment was assessed by an experienced stroke neurologist by using the NIH stroke scale (NIHSS). The modified Rankin scale (mRS) was used to assess clinical outcome 3 months after the stroke. All outcomes were assessed independently by physicians who were unaware of the patients' initial stroke severity.

All patients were interviewed by use of both the depression section of the Structured Clinical Interview for DSM-IV (SCID-I-R) [15] and the Hamilton Depression Rating Scale (HAM-D) [16]. The SCID is a structured psychiatric diagnostic interview allowing DSM-IV diagnosis of major or minor depression. The HAM-D is a clinical rating scale that measures the severity of depressive symptoms. All interviews were administered by the same clinician, who was trained to use these instruments. The patients were divided into 3 groups: Group I consisted of stroke patients with no depression and an HDRS score $<$14 points, Group II included stroke patients with normal mood but an HDRS score $\geq$14 and Group III comprised stroke patients diagnosed with depression, having an HDRS score $\geq$14.

Statistical analysis

Frequency counts and percentages were used to describe categorical data. The Chi-square test was used to determine significant differences between stroke groups. The mean and standard error were used to describe continuous data. Analysis of covariance (ANCOVA) was used to determine significant differences between treatment groups, with the baseline value as covariant. The statistical package used in this study is SAS v9.2.

Results

There were 51 patients in the final analysis. Another 30 patients were found to be ineligible for the following reasons: absence at follow-up within 3 months (14 patients), poor prognosis with mRS $>$2 (6 patients), death (4 patients), recurrent cerebral infarction (6 patients). The remaining patients were divided into the following groups: Group I had 31 patients; Group II, 9 patients; and Group III, 11 patients.

The ratio of Glu/Cr increased in all infarction groups (Groups I, II, and III), and the increase was statistically significant, except Group II and Group III. The ratio of Glu/Cr in patients with depression after infarction was the

Table 1 Characteristics and metabolite ratio in control group and patients with post stroke

	Control group	Group I	Group II	Group III	*p*
Age	65.3 ± 8.2	61.6 ± 7.9	59.6 ± 11.3	63.4 ± 10.1	NS[a]
M/F	8/7	18/13	5/4	7/4	NS[b]
Infarction of left side	–	19 (61.2%)	5 (55.5%)	6 (54.5%)	NS[b]
Volume of infarct	–	21.71 ± 18.15	30.38 ± 26.2	55.36 ± 31.1	
p value (vs. group I)[c]	–	–	0.57	<0.01	
p value (vs. group II)[c]	–	–	–	<0.01	
NIHSS	–	9.86 ± 1.93	10.02 ± 4.52	12.36 ± 3.33	
p value (vs. group I)[c]	–	–	0.72	<0.01	
p value (vs. group II)[c]	–	–	–	<0.01	
HDRS	4.0 ± 2.2	9.2 ± 4.5	17.2 ± 2.3	26.3 ± 5.1	NS[b]
p value (vs. control group)[c]	–	<0.01	<0.01	<0.01	
p value (vs. group I)[c]	–	–	<0.01	<0.01	
p value (vs. group II)[c]	–	–	–	<0.01	
NAA/Cr	1.352 ± 0.235	1.341 ± 0.293	1.401 ± 0.242	1.429 ± 0.185	NS[b]
Cho/Cr	0.316 ± 0.043	0.293 ± 0.032	0.305 ± 0.039	0.315 ± 0.046	NS[b]
bMI/Cr	0.803 ± 0.171	0.845 ± 0.110	0.819 ± 0.146	0.877 ± 0.098	NS[b]
Glu/Cr	1.031 ± 0.092	1.237 ± 0.272	1.348 ± 0.375	1.502 ± 0.336	
p value (vs. control group)[c]	–	<0.01	<0.01	<0.01	
p value (vs. group I)[c]	–	–	0.22	<0.01	
p value (vs. group II)[c]	–	–	–	<0.01	

[a] *p* values are based on the Chi-square test

[b] *p* values are based on ANOVA model with term for treatment

[c] *p* values are based on ANCOVA model with term for treatment code and baseline value as covariant

highest, followed by that in the patients with high HDRS after infarction. The differences in the ratios of other metabolites (NAA, Cho, MI) were not significant. Also no difference exists in age, sex and location of side. There was difference exists in NHISS and infarct volume between Group II and Group III. The ages of the patients and healthy subjects were not significantly different. The patients had a mean (SD) age of 61.1 (6.7) years, and the control subjects had a mean age of 65.3 (8.2) years. The age difference among these three infarction groups was not significant. The differences in infarction volume and NIHSS score between Group I and II were not significant, but Group III differed significantly from Groups I and II. Moreover, the differences in NAA/Cr, Cho/Cr, and MI/Cr between the control and any infarction groups were not significant. The difference in Glu/Cr between control and Group I was not significant, but differences in Glu/Cr among infarction groups were statistically significant.

Discussion

The main finding of our study is that there was a significant difference in Glu/Cr between depressed and non-depressed stroke patients. Furthermore, the difference exists between patients with high HDRS and low HDRS scores.

Some studies [17, 18] had reported that in patients with depression, ^{1}H-MRS measurements of Glx decreased in the anterior cingulate cortex. Further, Auer [19] reported a reduction in glutamate levels in patients with depression relative to the levels in control subjects, in the anterior cingulate cortex, both in adults and children. Single-voxel ^{1}H-MRS was performed in 19 patients with major depressive episodes and 18 age matched healthy controls within the anterior cingulate cortex and the parietal white matter. Considering only severely depressed patients, both Glx and Glu (-14.3%, $p = 0.03$) showed a significant decrease. There was no significant group effect for the neuronal marker NAA, creatine, choline or myo-inositol in their study. These studies demonstrated that the mechanism of depression concomitant with the infarction might be not consistent with that of acute depression. In a previous study [20], glutamine concentration in the cerebrospinal fluid of patients with acute depression was higher than that in healthy subjects, perhaps reflecting abnormalities in the glutamine/glutamate cycle. As glutamate and glutamine are combined at a ratio of 5:1, it is likely that pathological elevation of glutamine influences the signal and results in

an increased Glx/Cr ratio. It was reported that in some studies higher level Glx or Glu was been observed. Glodzik-Sobanska [21] studied the association between post-stroke depression and ^{1}H-MRS measurements in unaffected frontal lobes. Twenty-six patients with a first ischemic stroke located outside the frontal lobes were included in their study. They found that patients with depression in the immediate post-stroke phase had significantly higher Glx/Cr ratios in the contralesional hemisphere than non-depressive patients. Our result had more patients than their study and our study was focused on the level of Glu/Cr. Also Taylor [22] used MRS to measure GABA and glutamate in parieto-occipital cortex in young people with a family history of parental depression. Participants with a parental history of depression had significantly higher levels of glutamate than controls in parieto-occipital cortex. So we conjectured that pathology of depression after stroke may be different with the primary patients with depression. In our study, we stratified the patients according to the depression standard and HDRS score. This insight may help us to understand the pathogenesis and prognosis of depression after infarction. However, the mechanism needs to be studied further.

In our study, 11/41 (26.8%) patients were diagnosed with depression 3 months after they had a stroke, a figure comparable to those in previous studies. Maree reported that depression was diagnosed in 29% of patients in first week after stroke [23], while Aben [24] reported that 30% of stroke survivors had depressive symptoms between 7 and 30 days. The occurrence of depression in our study was lower than that in the previous study, possibly because patients with high NIHSS scores were excluded. These patients with serious outcomes may be more prone to depression than patients with a good outcome after a stroke. The results of our study support this hypothesis. There was a significant difference between Group III and Groups I and II in terms of the infarct volume. It is obvious that the incidence of depression is higher in patients with poor prognosis and a high NIHSS score, but the correlation between infarction volume and depression remains controversial. In our study, infarction volume differed among these three groups; however, we did not analyze the correlation between infarction volume and depression levels because the small sample size was small. Therefore, this correlation needs to be confirmed.

The creatine/phosphocreatine resonance was reported to be stable, even with changes in energy metabolism [25]; however, some researchers do not agree with this assumption. Michael et al. [26] reported a correlation between Cr levels and the severity of depressive symptoms, but no significant difference between controls and depressed subjects was noticed. However, Gruber et al. [27] observed higher prefrontal Cr levels in depressed patients. In stroke patients, decreases in Cr levels in the regions adjacent to cortical strokes were previously reported [28]. In our study, the infarction areas were excluded from the calculations of Glu/Cr, and the results obtained for other metabolites (NAA, Cho, MI) were stable; therefore, the result of Glu/Cr is reliable.

Limitations

The objectives of this study have led to some bias in the selection of cases. Since the patients enrolled in this study had a good prognosis, the results may contain some errors. The ROIs of MRS was restricted to the anterior cingulate cortex because of the scan time. Some studies have reported that the sites correlated with depression include the hippocampus as well as the prefrontal lobe; therefore, further research is warranted. Because of the limitations of the MRI scanner and sequences, we only quantified the Glu that was present at high levels in the Glx, and Gln and GABA were not quantified. However, since the functions of Glu, Gln, and GABA are different, further research on Gln and GABA is required.

The sample size is rather small, because group homogeneity was required (i.e., the study patients were all people experiencing stroke for the first time). Although the results were highly significant in Glu/Cr level, we did not correct it for multiple testing and false positive may not been exclude. The results may also be biased by different tissue compositions in terms of white versus gray matter and the individual variability of VOI positioning.

Conclusions

The ratios of Glu/Cr at the anterior cingulate cortex increased in all 3 infarction groups (normal after infarction, high HDRS but no depression after infarction, and depression after infarction), the inter-group differences being significant. The significantly increased level of Glu/Cr may be associated with a corresponding significant increase in the possibility of depression.

Conflict of interest None.

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