Longitudinal follow-up of patients with mild traumatic brain injury by magnetic resonance spectroscopic technique

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ARTICLE INFO

Article history:
Received 10 March 2013
Received in revised form 15 April 2013
Accepted 15 May 2013
Available online 20 May 2013

Objectives: To explore the changes in the concentrations of neural markers immediately or several months after mild traumatic brain injury (mTBI). Methods: The metabolic markers of neurons in white matter tissues above the lateral ventricle were semi-quantitatively determined by employing 1H magnetic resonance spectroscopic technique (1H-MRS) in 30 clinically diagnosed cases of mTBI. At the same time, the neurological functions of the subjects, including ability to pay attention, memory, working memory, and operational capacity etc were also assessed. Results: The patients were followed up for, on average, 13 days after mTBI and the results showed that Cre, PCr, and Glx in white matter tissues were significantly elevated in mTBI patients. 17 patients (57%) recovered from the injury during the follow-up (median was defined as the 40th post-trauma day). Comparison in terms of intelligence among groups revealed that there were no significant differences in intelligence scores. Conclusions: Change in Glx concentrations is most sensitive during trauma or in ensuing repair processes, and might be different from normal status in the following months and Glx level needs to be accompanied with change in Cre, another energy-related marker.

1. Introduction

With the increase in brain traumas over years, it is of critical importance to accurately assess the severity of brain injury, especially mild traumatic brain injury (mTBI). The accuracy of traditional neuropsychological evaluation is low and it cannot distinguish between post-trauma stress and other injuries including cerebral injury. Commonly used CT and MRI could identify less than 20% of mTBI patients[1]. Creatine (Cre) and phosphocreatine (PCr) are important markers of cellular metabolism and changes in Cre/PCr can, to some extent, reflect the level of cell metabolism. Recently, attention has been increasingly paid to the ratio of N-acetylaspartate (NAA) to Cre (NAA/Cre) and Choline (Cho/Cre. However, little is known about the changing patterns of glutamate–glutamine (Glx), two vital signal molecules of neurons in the brain injury[2–5]. This study examined the change of Cre and Glx, as energy–and signal transferring molecules, in mTBI patients and, by studying the change of neuron metabolites over time, found their changing pattern during convalescence.

2. Materials and methods

2.1. General data

Observation group consisted of 32 mTBI patients, including 14 males and 18 females, with their age ranging from 23–35 years. 32 normal subjects (including 14 males and 18 females) who received physical checkup at the hospital served as controls. The inclusion criteria of mTBI subjects were as follows: (1) scores of 13–15 on Glasgow Coma Scale; (2) trauma taking place within last 24 h and (3) coma time less than 30 min. All the cases of mTBI were
subjected to clinical neuropsychological examination and neuroimaging examination including MRS (Table 1). No statistically significant differences were found between the two groups in descriptive statistics ($P>0.05$).

Table 1
Neuropsychological scores.

<table>
<thead>
<tr>
<th>Items</th>
<th>Observation group</th>
<th>Control group</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.30±9.52</td>
<td>26.87±9.24</td>
<td>0.05</td>
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<tr>
<td>Neuropsychological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOMM</td>
<td>55.07±4.31</td>
<td>51.48±11.95</td>
<td>0.41</td>
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<tr>
<td>WTAR</td>
<td>50.11±8.68</td>
<td>54.67±7.74</td>
<td>-0.56</td>
</tr>
<tr>
<td>Attention</td>
<td>51.78±4.39</td>
<td>53.60±6.26</td>
<td>-0.34</td>
</tr>
<tr>
<td>Working memory</td>
<td>51.47±6.16</td>
<td>51.88±7.10</td>
<td>-0.06</td>
</tr>
<tr>
<td>Memory</td>
<td>51.72±8.01</td>
<td>51.36±6.36</td>
<td>0.05</td>
</tr>
<tr>
<td>Reaction speed</td>
<td>46.43±5.82</td>
<td>47.55±6.45</td>
<td>-0.18</td>
</tr>
<tr>
<td>Executive function</td>
<td>47.79±5.43</td>
<td>48.75±4.95</td>
<td>-0.18</td>
</tr>
<tr>
<td>Severity of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB-Somatic</td>
<td>6.95±6.02</td>
<td>1.78±2.31</td>
<td>1.16</td>
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<tr>
<td>NB-Cognitive</td>
<td>4.09±3.02</td>
<td>2.05±2.61</td>
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<tr>
<td>NB-Emotional</td>
<td>6.78±4.80</td>
<td>3.11±3.63</td>
<td>0.45</td>
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<tr>
<td>Mood</td>
<td>48.62±7.63</td>
<td>43.36±5.96</td>
<td>0.48</td>
</tr>
</tbody>
</table>

TOMM, Test of memory and malingering; WTAR, Wechsler test of adult reading; NB, Neurobehavioral symptom inventory.

2.2. Neuroimaging examination and 1H–MRSI

The two groups were all subjected to CT and MRI. 1H–MRSI was performed on GE 3T Sigma MR scanner. The sequences parameters for 1H–MRSI were: high resolution TIWI (MPRAGE: TE=1.64 msec; TR=2.53 sec; TI=1.2 sec; flip angle=15; NEX=1; slice thickness=1 mm; matrix 256×256); T2WI (FSE: TE=77.0 msec; TR=1.55 sec; flip angle=180; NEX=1; slice thickness=1.5 mm; matrix 256×256); 1H–MRSI (PRESS: TE=40 msec; TR=1.500 sec; slice thickness=15 mm; FOV=220 mm<220 mm; acquisition time=582 sec). T2WI was used as a reference, with imaging field being 1 cm above the lateral ventricle and parallel to parallel to the anterior/posterior commissure line (Figure 1).

2.3. Processing of 1H–MRSI data

All MRS image post-processing was performed on GE AW work–station by using Functool software package (version 4.4).

2.4. Neuropsychological scoring

Attention, working memory, executive function, memory, reaction speed and cognitive ability and emotion etc were measured by using corresponding scales. The processes, methods and standards/criteria for the measurement were commonly used ones in clinical practice. All tests were conducted on double–blind basis.

2.5. Statistical analysis

The differences in neuro–metabolites (markers) between the patients and normal controls were evaluated by using Chi-square method. Data were expressed as mean±SD. All statistical analyses were performed using SPSS 13.0. A $P<0.05$ was considered to be statistically significant.

3. Results

3.1. Image data of anatomic structure

T1- and T2–weighted images were employed to eliminate trauma–related complications but CT revealed that 2 of 20 mTBI patients had small bleeds at right lateral fissure cistern.

3.2. 1H–MRSI data

Cre and Glx levels in white matter (WM) were elevated in mTBI patients (Figure 2) while no significant differences in NAA and Cho were found between the two groups ($P>0.05$) (Figure 3). Figure 4 shows the changes in the markers at different time points in the two groups (WM Cre: $r=0.35$, $P=0.06$; WM Glx: $r=0.34$, $P=0.06$). The intra–group differences in the concentrations of the markers were negatively related to the post–trauma time passed. Further analysis revealed that neuropsychological manifestations bore no relationship with the major neuron metabolites.

![Figure 1. Slice location of 1H MRSI.](image1)

![Figure 2. WM Cre and WM Glx in patients with mTBI (Black bars) and normal controls (Gray bars). ** $P < 0.05$ (t test).](image2)
3.3. Results of longitudinal follow-up

The second test exhibited that WM Cre and WM Glx in mTBI patients ($n=17$) were similar to the findings of the first test. Further examination showed that changes in intelligence were positively related to GM Glx ($r=0.55$, $P<0.023$) but were negatively related to the magnitude of WM Glx change ($r=0.77$, $P<0.001$).

4. Discussion

This study showed a series of changes in the metabolic markers of neurons took place after mTBI and these changes after mTBI but their sensitivity as indicators was far from being satisfactory. Our results showed that elevated Cre level in white matter was an sign of increased activity of white matter, which was consistent with our previous finding that FA value was increased in mTBI patients. On the basis of the finding, we postulated that total Cre (Cre and PCre) in white matter can provide more energy–rich phosphate bonds (Pcre and ATP), which may help maintain the ion balance between extra- and intra–cellular compartments and promote other cell–repairing processes. This study also examined the change of Glx at different stages of mTBI, since Glx is an indicator of glutamine/glutamic acid pathway, which is a pathway of both signals and energy. Glx in white matter is mostly glutamine and therefore, presence of large amount of Glx is indicated increased brain activity[6]. So far, little is known about the role of Glx in white matter. Higher Glx level indicated higher metabolism, which is also the effect of elevated Cre. This might account for the positive association between Cre and Glx in white matter[7].

This study failed to show the differences in NAA and Cho, two traditional metabolites, between mTBI patients and normal controls, suggesting that energy- or signal–related markers are more sensitive than their structure–related counterparts (NAA and Cho). The changes in the latter two markers take place only in serious cerebral trauma.

To sum up, this study proposed that change in Glx concentration was most sensitive during trauma or in ensuing repairing processes and might be different from normal status in the following months and Glx level tends to be increased, paired with change in Cre, another energy–related marker.

Conflict of interest statement

We declare that we have no conflict of interest.

References