Neural injury and recovery near cortical contusions: a clinical magnetic resonance spectroscopy study

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Object. Proton magnetic resonance (MR) spectroscopy can detect neural metabolic alterations noninvasively after traumatic brain injury (TBI) even in areas that appear normal. Unlike metabolic depression in diffuse TBI, focal metabolic alterations near cortical contusions in humans have not been previously investigated in a longitudinal study. The object of this study was to identify these alterations and examine their course.

Methods. At 1 week and 1 month after mild to moderate TBI involving cortical contusion, 30 patients underwent 1H MR spectroscopy examination that focused bilaterally on normal-appearing frontal and temporal white matter. Levels of N-acetylaspartate (NAA), choline (Cho) compounds, and creatine (Cr) were measured to obtain two metabolite ratios, NAA/Cr and Cho/Cr. The ratios were compared with those of 11 healthy individuals.

At 1 week after TBI, the NAA/Cr ratio was significantly lower near cortical contusions than it was in white matter remote from the injury or in controls, while the Cho/Cr ratios did not differ significantly. At 1 month, the decreased NAA/Cr ratios near contusions had increased significantly from 1 week, as had the Cho/Cr ratio.

Conclusions. Metabolic depression reflecting neural injury was apparent in subjacent normal-appearing white matter at 1 week after cortical contusion; this had normalized substantially at 1 month.

Key Words • traumatic brain injury • contusion • choline • creatine • N-acetylaspartate • proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy can detect neural metabolic alteration noninvasively in various neurological diseases. In TBI, 1H MR spectroscopy has demonstrated decreased levels of NAA and elevated levels of Cho compounds, but little is known about longitudinal changes of these metabolites after clinical TBI.

Another unresolved issue concerning 1H MR spectroscopy after TBI is the relationship between type of injury and metabolic alteration. A few studies have focused on metabolic alteration in patients with diffuse injury, whereas many studies have dealt with a variety of types of injury in various locations. Accordingly, the relationship between focal injury and metabolic alteration has not been clearly determined. Although metabolic alterations have been measured both close to and remote from experimentally induced cortical contusions, no clinical studies concerning metabolic changes near cortical contusions have been reported.

In the present study we used 1H MR spectroscopy to measure cerebral metabolites of NAA, Cho, and Cr in patients with cortical contusion, focusing on the time course of changes in the ratios of NAA/Cr and Cho/Cr near cortical contusions in white matter that appeared normal on MR imaging.

Clinical Material and Methods

Approval for the study was obtained from the ethics committee at our hospital. If a patient had impaired consciousness at the time of the MR spectroscopy examination, informed consent was obtained from a family member. Otherwise, written informed consent was obtained from all patients and controls before the investigation.

Study Participants

We studied 30 patients with mild to moderate TBI. Their Glasgow Coma Scale scores ranged from 9 to 15. All patients had one or more cortical contusions within the frontal and/or temporal lobe. Other eligibility criteria were age between 16 and 65 years, absence of general contraindications for MR imaging, and sufficient clinical stability to allow MR imaging within 10 days after TBI. Patients with extraxial lesions having mass effect on the cortex were excluded in order to isolate the effects of cortical contusion. For the same reason, we also excluded patients with ischemic findings, extraxial fluid collections evident on delayed examination, any evidence of increased intracranial pressure

Abbreviations used in this paper: Cho = choline; Cr = creatine; GOS = Glasgow Outcome Scale; NAA = N-acetylaspartate; MR = magnetic resonance; TBI = traumatic brain injury.
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such as appearance of herniation signs or deterioration to coma, and findings of diffuse injury such as small hemorrhagic lesions in the deep white matter, corpus callosum, or brainstem, or isolated intraventricular hemorrhage. Clinical outcome was assessed using the GOS at 3 months post-TBI. To examine the relationship between the MR spectroscopy data and outcome, patient outcomes were divided into two groups: good outcome, showing good recovery according to the GOS criteria; and poor outcome, showing less than good recovery according to the GOS. This grouping was considered appropriate for patients with mild to moderate TBI.

To obtain normal values, 11 neurologically healthy persons underwent 1H MR spectroscopy examination; these control individuals included healthy volunteers and neurologically healthy persons with a clinical indication for MR imaging.

Protocol for MR Spectroscopy

Proton MR spectroscopy examination was performed using a 1.5-tesla MR imaging unit (Signa Twin Speed) with a spectroscopy software package (PROBE, General Electric Medical Systems). After standard MR imaging including T₁- and T₂-weighted imaging of axial sections, volumes for spectroscopy were selected in normal-appearing white matter. Using the T₁-weighted images, four volumes of interest identical with those in the first examination. To examine the relationship between contusion volume and metabolite ratios, MR spectroscopy were selected in normal-appearing white matter remote from a cerebral contusion, and white matter in healthy individuals. Metabolite ratios were compared in four different combinations: NAA/Cr in the frontal lobe, NAA/Cr in the temporal lobe, Cho/Cr in the frontal lobe, and Cho/Cr in the temporal lobe. Longitudinal changes were compared using a paired t-test. Relationships between contusion volume and metabolite ratios were examined using the Pearson test. A probability value less than 0.05 indicated that a difference was statistically significant.

Results

During the study period, 30 patients underwent 1H MR spectroscopy examination twice. In each patient, MR spectroscopy data were obtained from four specified areas (both frontal and temporal lobes), yielding 120 data sets. The patients’ characteristics are summarized in Table 1. Of the 30 patients, 22 had a single contusion, six had two contusions, and two had three contusions. Thus, a total of 40 contusions were observed in 120 lobes, including 16 frontal lobes and 24 in temporal lobes. In the patients, early and late MR spectroscopy examinations were performed at 7.2 ± 1.3 and 34.3 ± 4.0 days after TBI, respectively. In controls, metabolite ratios were: NAA/Cr in frontal white matter, 1.93 ± 0.43; Cho/Cr in frontal white matter, 1.18 ± 0.22; NAA/Cr in temporal white matter, 1.68 ± 0.35; and Cho/Cr in temporal white matter, 1.40 ± 0.28.

In Fig. 3, early metabolite ratios in each lobe are compared between white matter near and remote from a contusion and between patients and controls. The NAA/Cr ratio near a cortical contusion was significantly lower than in white matter remote from a cortical contusion and also lower than in controls (frontal, 1.59 ± 0.25 compared with 1.96 ± 0.30 and 1.95 ± 0.38; temporal, 1.34 ± 0.30 compared with 1.61 ± 0.24 and 1.61 ± 0.31). The Cho/Cr ratio, in contrast, did not show significant differences related to lesion proximity or subject group.

Longitudinal changes in metabolite ratios between 1 week and 1 month are shown in Fig. 4. At 1 month, decreased NAA/Cr ratios near cortical contusions had increased significantly in frontal lobes (from 1.59 ± 0.25 to 1.76 ± 0.27) and temporal lobes (from 1.34 ± 0.30 to 1.55 ± 0.29), whereas no such change was observed in corresponding ratios in white matter remote from a contusion. Similar results were observed for Cho/Cr ratios in frontal lobes (from 1.13 ± 0.12 to 1.32 ± 0.11) and temporal lobes (from 1.26 ± 0.22 to 1.46 ± 0.19). No significant correlation was evident between early metabolite ratios and contusion volume in either the frontal or temporal region (Fig. 5).

At 3 months after TBI, 19 (63%), nine (30%), and two (7%) of the patients were categorized as showing good recovery, moderate disability, and severe disability, respectively. The 19 patients with good recovery had 11 frontal and 13 temporal contusions; the 11 patients with less than good recovery had five frontal and 11 temporal contusions. There was no significant difference between these recov-
ery-defined groups in the early NAA/Cr ratios in either the frontal lobe (good outcome 1.66 ± 0.21, poor outcome 1.45 ± 0.14; p = 0.120) or the temporal lobe (good outcome 1.38 ± 0.14, poor outcome 1.29 ± 0.32; p = 0.780).

Discussion

To date, this is the first 1H MR spectroscopy study performed to determine the effects of a cortical contusion on nearby white matter in human TBI. Major findings included significant reduction of the NAA/Cr ratio near the cortical contusion at 1 week after TBI and partial normalization at 1 month. In contrast, the Cho/Cr ratio had not changed significantly at 1 week but had increased significantly beyond the 1-week value at 1 month.

Proton MR Spectroscopy in TBI

In 1H MR spectroscopy studies after human and experimental TBI, a decrease in the NAA/Cr ratio or in the level of NAA is a consistent metabolic alteration, although some experimental studies have recorded an initial transient rise in NAA in extracellular fluid immediately after TBI.2 In TBI in humans, the decreases have been found in the corpus callosum following diffuse injury4,5 and in contused areas,6 zones of pericontusional edema,7 the brainstem,8 basal ganglia,9 and normal-appearing white and gray matter after various types of injury.10,11,17–21 Moreover, the change was found to occur diffusely in patients with mild TBI without apparent influences from specific traumatic findings.22 In experimental studies, the decrease also was found both near and remote from contusions.22,32

Controversy exists concerning longitudinal changes in NAA levels following TBI, but in the present study we found the NAA/Cr ratio to be decreased at 1 week and substantially recovered at 1 month. Results of several studies have demonstrated various changes over time in NAA levels after TBI. In studies of experimental TBI, the NAA/Cr ratio has been found to decrease immediately after the injury, with this change persisting for several hours, days, or weeks.30,32,36 One of the more rapid recoveries of this ratio was reported by Gasparovic et al.,22 who found that the reduced NAA/Cr ratio at 2 days was considerably normalized at 6 days postinjury. In a study of TBI in humans, Brooks and colleagues6 reported that NAA levels in white matter were decreased at 3 months and had returned to normal at 6 months after TBI, although Garnett and coauthors19 reported a significant decrease from 15 days to 6.3 months.

Because the NAA level is an indicator of neural metabolism,5,12 an increase following an initial decrease might indicate metabolic reversibility; on the other hand, an early decrease in the NAA level without subsequent improvement might suggest irreversible loss of neural function.5,13–15 The early recovery of neural metabolism observed in the present study might reflect several factors. First, severity of TBI is likely to be important.16 In the present study most patients had mild TBI, which favors early normalization of the

Fig. 1. Axial T2-weighted MR images showing frontal (left) and temporal (right) volumes in which the 1H MR spectroscopy spectra were acquired.

Fig. 2. A representative MR spectroscopy image showing the type of data obtained in each volume. Ratios of NAA and Cho to Cr (upper right) were calculated automatically with the PROBE software package.
Metabolic changes near cortical contusions

TABLE 1  
Patient characteristics and outcome*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex, GCS Score</th>
<th>Cause of TBI</th>
<th>Contusion Location (vol in cm³)</th>
<th>Timing of MRS Studies (days postinjury)</th>
<th>Early</th>
<th>Late</th>
<th>Outcome†</th>
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* GCS = Glasgow Coma Scale; GR = good recovery; MD = moderate disability; MRS = MR spectroscopy; SD = severe disability.  
† Based on the GOS.

NAA/Cr ratio; all but two patients could live independently 3 months post-TBI. Second, recovery might be affected by type of injury (diffuse or focal). We chose to study only focal injury in this investigation, which decreased the likelihood of direct injury to examined white matter. Third, because hypoxia and hypotension have been shown to reduce total NAA levels in the injured brain in an experimental model,1 the presence of secondary brain injury might affect reversibility of these levels. Although the prehospitalization clinical course could not be assessed in our patient group, no participant experienced significant hypoxic or hypotensive episodes after admission.

One hypothesis that could explain reversibility relates to glial cells and the extracellular space. Astrocytic swelling around the contusion might reversibly decrease local NAA concentrations,7 and edema (accumulation of extracellular fluid) would also be expected to decrease local NAA concentrations. After resolution of glial swelling and interstitial edema, the concentration of NAA would tend to normalize. Better clarification of the causes of reversibility of the NAA/Cr ratio should increase its utility as an in vivo marker of neural injury and recovery.

Another metabolite ratio, the Cho/Cr ratio, had not changed significantly at 1 week post-TBI. This finding stands in disagreement with the findings of Garnett et al.19–21 and Shutter et al.,33 who reported that Cho levels increased early after TBI in a manner that correlated with injury severity and clinical outcome, suggesting membrane disruption. In the present study, NAA was considered a specific neural marker that could be elevated as a result of neural membrane injury. Because we found a decrease in the NAA/Cr ratio, we doubt that early changes in the Cho/Cr ratio represented the degree of initial damage.

In regard to long-term changes in the Cho/Cr ratio, persistent elevation in Cho levels has been observed for up to 6 months post-TBI.6,19 This finding would suggest that the elevation reflected ongoing inflammation or glial proliferation. In terms of spectral components, changes in the peak of Cho at 3.3 ppm in 1H MR spectroscopy correlate with the concentration of water-soluble Cho-containing compounds such as free Cho and phosphocholine, or with cell density.27,28 Therefore, processes distinct from membrane repair, such as an increase in cell density (that is, glial proliferation) or changes in cholinergic activity,11,16 might contribute to the delayed rise in the Cho level. Determining the role of Cho after TBI ultimately requires absolute quantitation of
water-soluble Cho-containing compounds post-TBI as well as correlation of the concentrations of these compounds with cholinergic activity following TBI.

Cortical Contusion and Surrounding Injury

One major finding in this study was the detection of metabolic depression near the cortical contusion in areas of white matter in which standard imaging disclosed no structural change. Several reasons might account for this metabolic depression. First, widespread impact at the time of development of the contusion must be considered. Cortical contusions result when the moving brain surface collides with the irregular inner table of the skull base. This impact might reach deep structures within the white matter even though no structural damage may be evident on MR images. Indeed, when Gasparovic and colleagues observed a reduction in the NAA/Cr ratio remote from a contusion, they postulated widespread metabolic depression as a possible reason. A second possibility involves pressure injury from hemorrhage and edema in surrounding tissue, although we found no correlation between metabolic depression and contusion volume in our study. Third, indirect injury may be caused by pericontusional reduction of regional blood flow, abnormalities of cerebral oxygen metabolism, or elevation of a neurotoxic substance such as an excitatory amino acid. Fourth, the relationship between cortical injury and axonal pathways should be considered. If the examined volume of white matter included axons projecting from injured cortical neurons, metabolism within this tissue could change. It is difficult, however, to determine whether the examined volume contains axons from injured cortex.

Study Limitations

Finally, limitations of our study should be considered. Absolute quantities of each metabolite could not be compared in our clinical setting. Instead, metabolite ratios based on Cr were used because Cr is believed to show minimal change after TBI. Constancy of Cr levels has generally been demonstrated, although in one experimental study an alteration was found; Schuhmann and colleagues demonstrated that Cr levels changed significantly over time after experimental TBI, also noting significantly increased

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**Fig. 3.** Graphs depicting comparisons of metabolite ratios in each lobe between white matter with no cortical contusion nearby (Contusion[-]); white matter near a cortical contusion (Contusion[+]); and white matter in controls (Normal). Values shown are the means ± standard deviations. *p < 0.001 compared with Contusion(-); **p < 0.01 compared with Normal.
lactate levels. Creatine is related to energy metabolism; in the present study no lactate was detected in any patient, suggesting that anaerobic energy metabolism was not induced. We therefore believe that the level of Cr within the volume studied was constant at the time of MR spectroscopy examination. In future studies, the relationship between the presence of lactate and changes in Cr level should be clarified.

In this study we used the terms “near” or “nearby” to indicate that the volume examined was within the same lobe as the cortical contusion. However, the actual distance from the margin of the contusion to the area of the MR spectroscopy volume could not be measured precisely, and might well have varied considerably between patients. The volume of interest would have been technically difficult to delineate within white matter near the irregularly shaped cortical contusion. Moreover, comparisons of localized metabolite ratios in our patients with those in controls required standardized volume placement.

A relationship between metabolite ratios and clinical outcome was difficult to detect in the present study, reflecting the selection of participants who mostly had mild TBI, with the potential to achieve a good outcome. In a study that included patients with severe TBI undergoing serial MR spectroscopy examination, a closer relationship between degree of initial metabolic injury and functional recovery might be revealed.

Conclusions

Measurements of NAA/Cr and Cho/Cr ratios using 1H MR spectroscopy provided two important kinds of information about metabolic alterations after cortical contusion: 1) presence or absence of initial functional damage, and 2) subsequent recovery near the cortical contusion. The noninvasiveness of MR spectroscopy is an important consideration, and the information it provides might be especially useful for managing cases of mild to moderate TBI involving patients who do not require invasive monitoring. For MR spectroscopy to become more useful for prognosis, the relationship between longitudinal changes in the NAA/Cr ratio and clinical recovery, the role of the Cho/Cr ratio during the recovery process, and the relationship between Cr and lactate levels will require further clarification.

Acknowledgments

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