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Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) Study of Early Traumatic Brain Injury in Rabbits

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Background: The aim of this study was to investigate the relationship between dynamic changes of cerebral metabolism and degree of trauma in rabbit models of traumatic brain injury (TBI) by using proton magnetic resonance spectroscopy (^{1}H-MRS).

Material/Methods: Thirty-five Chinese rabbits were randomly divided into control, mild, moderate, and severe TBI groups. ^{1}H-MRS was performed 1, 6, and 24 h after trauma. The concentrations of NAA, Cr, Cho, and Lac, and NAA/Cr and Cho/Cr ratios in each group, were estimated.

Results: Compared with the control group, NAA, Cr, and Cho peaks were decreased. NAA/Cr ratio in the ipsilateral cortex was reduced in the mild, moderate, and severe TBI groups by 12.79%, 28.90%, and 45.02% at 1 h, and decreased by 25.11%, 39.81%, and 51.18% at 24 h after trauma, respectively. There were significant negative correlations between NAA/Cr ratio and severity of attack. Cho/Cr ratio in the ipsilateral cortex in the mild, moderate, and severe TBI groups was decreased by 10.86%, 15.94%, and 34.78% at 1 h, and reduced by 24.63%, 29.71%, and 42.02% at 6 h, respectively, and increased slightly at 24 h after trauma. The Lac/Cr ratio in the injured side was increased, most obviously in the severe TBI group. NAA/Cr ratio and Cho/Cr ratio showed significant changes between each group at the same time point.

Conclusions: ^{1}H-MRS can noninvasively and dynamically detect metabolic changes in early TBI. The NAA/Cr ratio is most sensitive, and has positive significance for early diagnosis and prognosis assessment of TBI.

MeSH Keywords: Brain Injuries • Magnetic Resonance Imaging • Magnetic Resonance Spectroscopy

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Background

Traumatic brain injury (TBI), due to its high incidence, disability, and mortality, has become one of the major risk factors that threaten human life. Proton magnetic resonance spectroscopy (^{1}H-MRS) can noninvasively reflect the severity of brain injury in the early stage, and is very important for disease evaluation, follow-up treatment, and prognosis. ^{1}H-MRS is a diagnostic test for measuring *in vivo* specific atomic nuclei and compounds by magnetic resonance and chemical shifts. As a supplement to conventional magnetic resonance imaging (MRI), MRS can noninvasively detect changes of metabolite concentrations in brain tissue in normal or pathological state so as to reflect microscopic abnormal changes due to brain trauma [1]. Thus, the diagnosis of brain trauma is increased to the level of molecular metabolism [1]. MRS technology has been widely used in the diagnosis of systemic diseases such as neurological disease, as well as in prostate, breast, and liver lesions, and the first reported use of MRS was in the diagnosis of nervous system diseases. There are many studies on MRS for TBI, but there is no systematic *in vivo* study using a rabbit model of TBI. The present study established rabbit models of TBI by mild, moderate, and severe free-falls; performed MRS at 1, 6, and 24 h after injury; observed the changes in metabolites over time; and investigated the value of ^{1}H-MRS in assessing the severity of TBI and predicting prognosis.

Material and Methods

Choice of experimental animals

Thirty-five male and female Chinese rabbits weighing 2.5–3.0 kg were provided by the Animal Center, Medical School of Nantong University of China. All rabbits grew well, had sensitive responses, and ate normal diet, and did not have the history of injury or infection. Conventional MRI did not reveal obvious abnormality. The rabbits were acclimated in a suitable environment for 2 weeks. The rabbits were randomly assigned to 4 groups: control (sham surgery; n=5), mild (n=10), moderate (n=10), and severe (n=10) TBI. The study was approved by the Institutional Review Board of Yancheng First People's Hospital.

Establishment of TBI models

After fasting for 12 h but with free access to water, rabbits were intraperitoneally injected with 10% chloral hydrate 0.35 g/kg and placed on the table in prone position. After shaving and disinfecting, an approximately 4.0-cm incision was made to expose the skull. A bone window (1.0 cm) was opened at 1.5 cm left to the intersection of the posterior orbital margin and midline. The cerebral dura mater was complete. Rabbit models of TBI were established by contusions according to modified Fenney's method [2]. The impactor (0.5 cm in diameter, and 40 g and 60 g in weight) fell from different heights along a stainless-steel pipe, and impacted the surface of the left parietal lobe dura to induce mild, moderate, and severe contusions. Gelatin sponge was used to terminate the bleeding. The bone window was closed with bone cement and the scalp was sutured. Five rabbits in the control group (sham surgery) did not receive free-falling impact, but received other procedures the same as the experimental groups.

Manufacture of cap-like coil [3]

A coil was made by a 75-mm diameter hollow cylinder at 120°, which was 80 mm long and 90 mm high. The quality factor (Q) of the coil was 98. The frequency was 127.74 MHz and the impedance was 50 Ω.

Conventional MR and MRS

We used a GE 3.0T MR scanner and made a cap-like coil. The rabbit was fixed on the frame in prone position, with its head in the head slot. The coil was closed to rabbit head and fixed. Limbs were fixed on the frame. The intersection of the posterior orbital margin and midline was located in the center of the coil. Scanning sequence included coronal T1WI, T2WI, diffusion tensor imaging (DWI), and sagittal and axial T2WI.

^{1}H-MRS was performed at 1, 6, and 24 h after injury. Point-resolved spectroscopy sequence was used in the center of the median level of coronal T2WI. Voxel size was 14×4 mm. The parameters were: repetition time = 1000 ms, echo time=145 ms, field of view 8.0×8.0 cm, matrix 18×18, and NEX 1. The saturation zone was set at left and right (R/L), anterior and posterior (A/P), and superior and inferior (S/I) of field of view. The width of the saturation zone was 10 mm. Imaging time was 4 min and 18 s. Images were post-processed in the ADW4.2 workstation. The areas under a peak of N-acetylaspartate (NAA), creatine (Cr), choline-compound (Cho), and lactic acid (Lac) at the injury site were measured, and the NAA/Cr, Cho/Cr, and Lac/Cr ratios were determined.

Pathological examination

After MRS, 1 rabbit was taken from each TBI group and intraperitoneally anesthetized with 3% sodium pentobarbital 3 mg/kg. The chest was opened, and blood in the circulatory system was washed by perfusion. After slow perfusion with 10% formaldehyde, the rabbit was decapitated and the whole brain was obtained. The changes in the brain were macroscopically observed. The brain was fixed in 10% formaldehyde for 48 h, cut into blocks, dehydrated, sliced into frozen sections, and stained with hematoxylin and eosin.

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Table 1. Correlation between NAA/Cr ratio and neurological impairment scores at 24 hours after injury.

	Control group	Mild TBI group	Moderate TBI group	Severe TBI group	*r* value	*P* value
Neurological impairment scores	0	11.70±2.83	20.30±3.46	36.5±2.17	-0.83	<0.01
NAA/Cr	2.11±0.16	1.58±0.21	1.27±0.33	1.03±0.16		
n	10	10	10	10		

n – number of spectral acquisition.

Statistical analysis

All data are expressed as the mean ± SD, and analyzed using SPSS 18.0 software. The ratio of cortical metabolites was compared at the same time point in different groups, and between TBI groups and control group by one-way analysis of variance. At 24 h after injury, the correlation of NAA/Cr ratio with neurological impairment score and attack intensity was analyzed. A value of $P<0.05$ was considered statistically significant.

Results

Animal response after TBI

Immediate death of animals did not occur after injury. Rabbits in the moderate and severe TBI groups presented limb spasm twitching, and light, fast breathing. Rabbits were placed in the isolation cage until conscious. Rabbits regained consciousness quickly in the mild TBI group, but slowly in the severe TBI group. Limb movement disorder was noticeable in the moderate and severe TBI groups. Physiological response was small in the mild TBI group. At 24 h later, physiological response recovered to the normal level in the mild, moderate, and severe TBI groups. Contralateral limb paralysis was found in 5 and 8 rabbits in the moderate and severe TBI groups, respectively. Rabbits in the severe TBI group were listless; their activities were decreased significantly, and drinking and eating were also reduced.

Neurological impairment scores

In accordance with previous criteria [4], neurological function was assessed from the aspects of perception, vision, movement, posture, walking-level awareness 24 h after injury. Neurological function scores were 11.70±2.83, 20.30±3.46, and 36.50±2.17 in the mild, moderate, and severe TBI groups, and the scores were significantly different among different groups ($F=192.253$, $P<0.01$). The neurological impairment scores were negatively correlated with NAA/Cr ratio ($r=–0.83$, $P<0.01$) (Table 1).

Conventional MRI manifestations and MRS manifestations

Conventional MRI did not reveal obvious abnormality at 1 h after injury (Figure 1A, 1B), but exhibited abnormal signal at the parietal lobe on the injured side at 6 h after injury. Iso-signal intensity was visible on T1WI, and high-signal intensity was observed on T2WI (Figure 1D–1F). Mean NAA/Cr ratio (2.11±0.16) and mean Cho/Cr ratio (1.38±0.06) were not significantly different on the injured side in the control group at various time points.

MRS was performed at 3 different time points within 1 day after injury. MRS results are displayed in Table 2. Typical spectra are exhibited in Figure 2.

Conventional T1WI, T2WI, and DWI images did not show obvious abnormal signals at 1 h after injury (Figure 1). MRS detected the decreased NAA/Cr ratio (Figures 3, 4). Compared with the control group, NAA/Cr ratio was reduced by 12.79%, 28.90%, and 45.02% in the mild, moderate, and severe TBI groups, respectively. Thereafter, the ratio continued to decline. NAA/Cr ratio was decreased by 25.11%, 39.81%, and 51.18% in the mild, moderate and severe TBI groups, respectively, at 24 h after trauma. NAA/Cr ratio was significantly different between the TBI groups and the control group at each time point. Paired comparison showed that NAA/Cr ratio was significantly different between different TBI groups at the same time point. At 24 h, a significant negative correlation was determined between NAA/Cr ratio and severity of injury ($r=–0.92$, $P<0.01$; Table 3).

Cho/Cr ratio in the mild, moderate, and severe TBI groups was decreased by 10.86%, 15.94%, and 34.78% at 1 h and reduced by 24.63%, 29.71%, and 42.02% at 6 h, respectively, and increased slightly at 24 h after trauma. Cho/Cr ratio was significantly different between the TBI groups and the control group at various time points. Cho/Cr ratio was not significantly different between the mild and moderate TBI groups at 24 h (Table 2).

Pathological changes

After MRS, at 24 h after injury, mild swelling was observed, but there was no obvious hematoma on the injured side in

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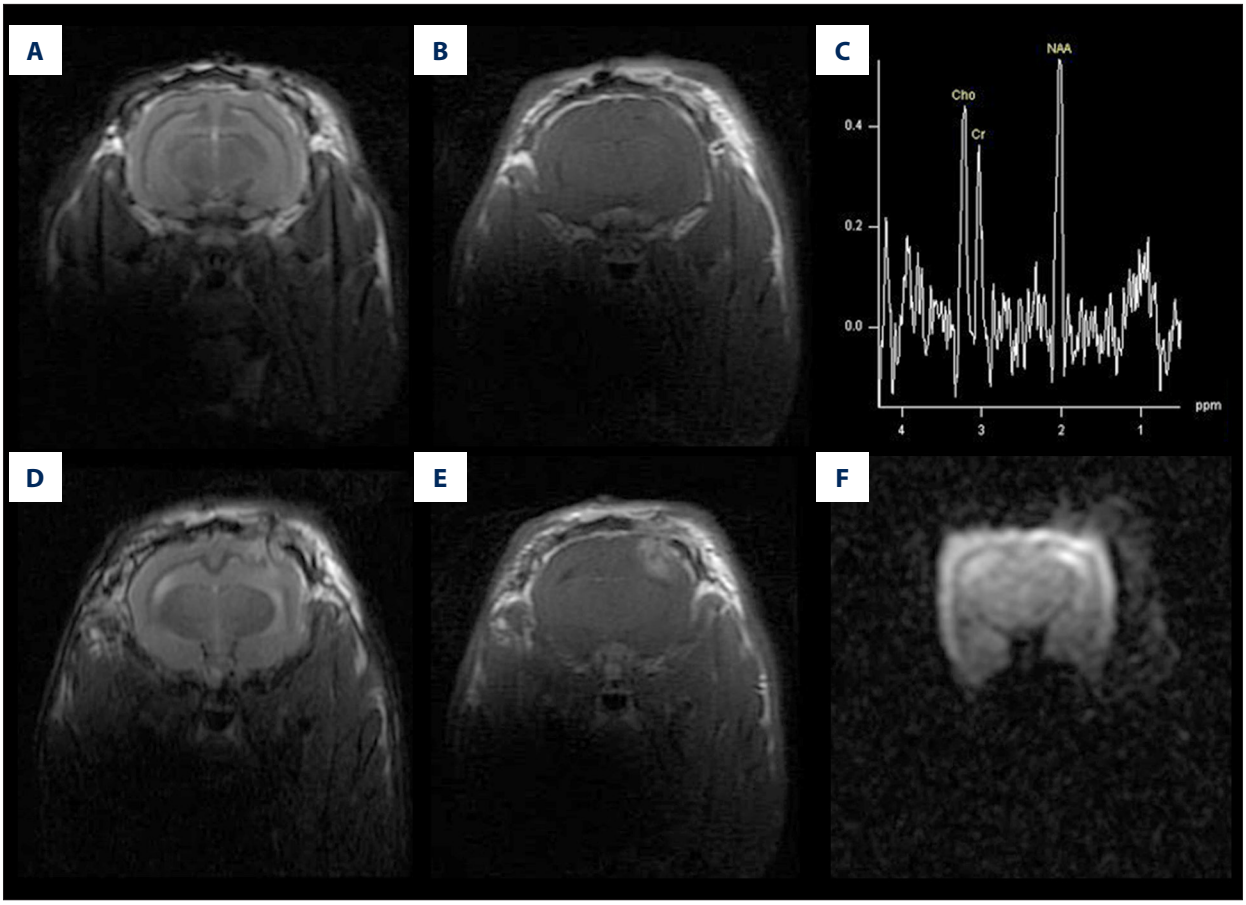

Figure 1. Conventional MRI and MRS manifestations. (**A, B**) T2WI and T1FLAIR did not reveal remarkable abnormal signals on the left frontal lobe at 1 hour after injury. (**C**) MRS spectral line at 1 hour after injury in the mild TBI group shows a decreased NAA/Cr ratio. (**D–F**) T2WI, T1FLAIR and DWI demonstrate patchy abnormal signals on the left frontal lobe at 6 hours after injury.

Table 2. Mean NAA/Cr and Cho/Cr ratios at various time points.

Group	n	NAA/Cr			Cho/Cr		
		1 h post injury	6 h post injury	24 h post injury	1 h post injury	6 h post injury	24 h post injury
Control Group	5		2.11±0.16*			1.38±0.08*	
Mild TBI group	30	1.84±0.10*	1.73±0.12*	1.58±0.08*	1.23±0.05*	1.04±0.06*	1.06±0.09#
Moderate TBI group	30	1.50±0.09*	1.37±0.09*	1.27±0.10*	1.16±0.05*	0.97±0.04*	1.01±0.05#
Severe TBI group	30	1.16±0.11*	1.10±0.10*	1.03±0.09*	0.90±0.12*	0.80±0.04*	0.83±0.11*

n – number of spectral acquisition. * P<0.05 between two groups at the same time point; # P>0.05 between two groups.

the mild TBI group. Hematoma was obvious on the injured side in the severe TBI group. Noticeable swelling was seen after removal of hematoma. In the mild TBI group, there was mild cerebral contusion, accompanied by a small amount of subarachnoid hemorrhage. In the moderate and severe TBI groups, there were remarkable cerebral contusion and different sizes of hemorrhage foci. The degree and range of brain injury were dramatically larger in the severe TBI group than in the mild and moderate TBI groups. Brain midline shifted to the right side in the severe TBI group. Hematoxylin-eosin staining did not demonstrate noticeable abnormal changes in the brain tissue of the control group. Under the light microscope, neurons were swollen to different degrees, and brain edema was observed in the mild TBI group. In the moderate

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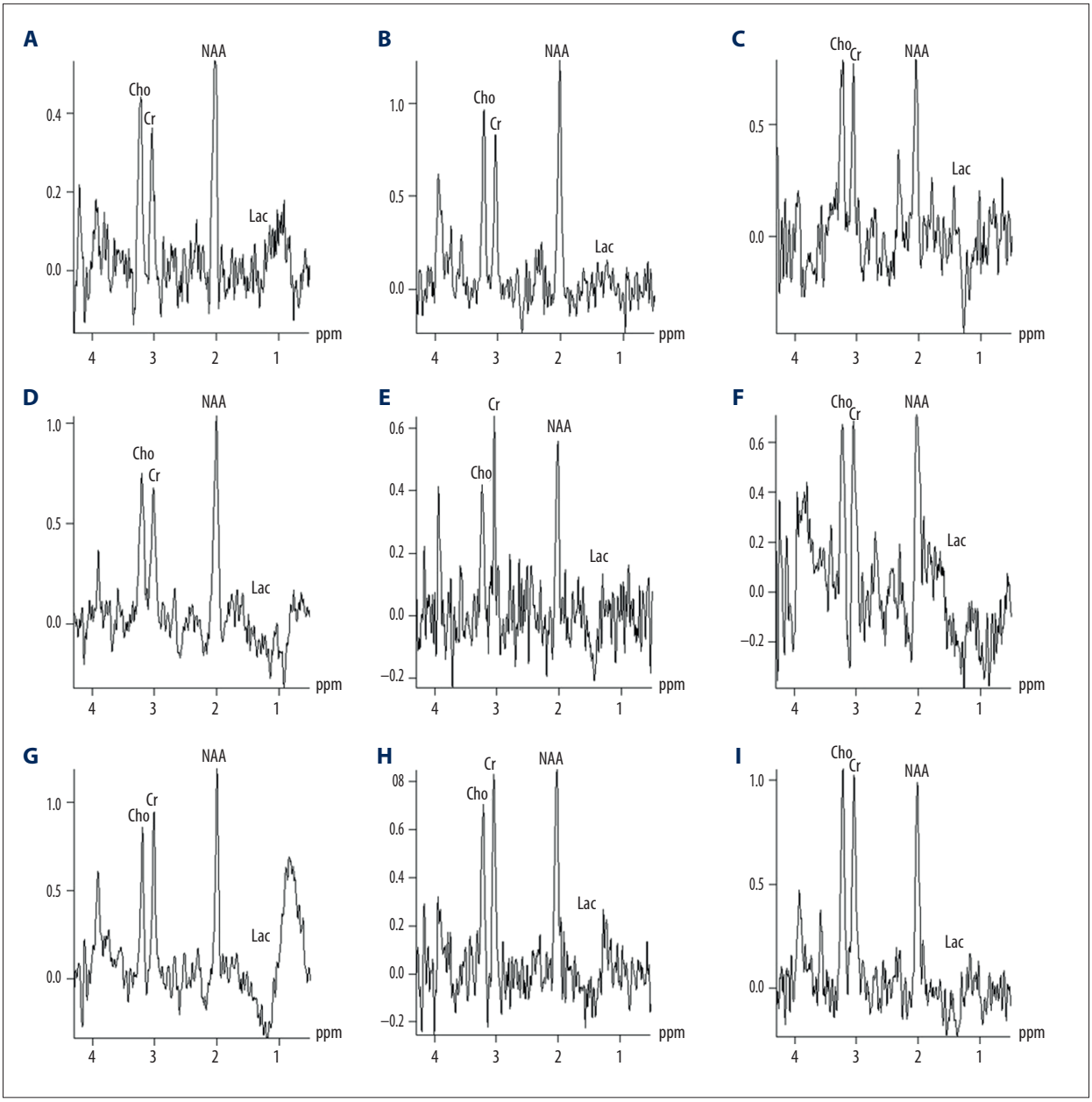

Figure 2. Typical spectra. Spectra in the mild, moderate, and severe TBI groups at 1 hour (**A–C**), 6 hours (**D–F**), and 24 hours (**G–I**) after injury. NAA – N-acetylaspartate; Cho – choline-compound; Cr – creatine; Lac – lactic acid.

TBI group, a large number of inflammatory cell infiltrations and degenerated neurons were found surrounding glial cells. In the severe TBI group, there were a large number of necrotic glial cells and degenerated neuronal cells with peripheral vacuolization. MRI showed abnormal signals in the parietal cortex and hippocampus on the injured side, and presented long T1 and long T2 alterations. The area of abnormal signal was largest in the severe TBI group. MRI manifestations were consistent with pathological results (Figure 5).

Discussion

In recent years, the incidence of TBI increases year by year. Some patients with mild TBI can be self-recovered. Most of the patients with moderate to severe TBI present poor recovery, thereby seriously affecting their quality of life. Early diagnosis, and timely and effective treatment are particularly critical for patient rehabilitation. This study simulated the pathophysiological state of human TBI in rabbits, and analyzed the changes in the metabolite concentrations in the brain by using MRS. Our results showed that, compared with conventional MRI,

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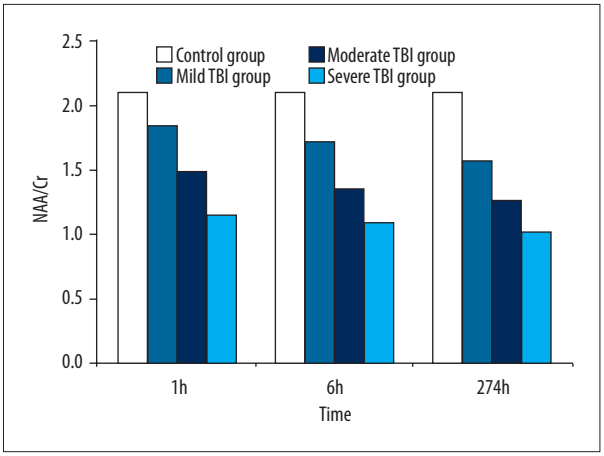

Figure 3. NAA/Cr ratio at various time points after injury.

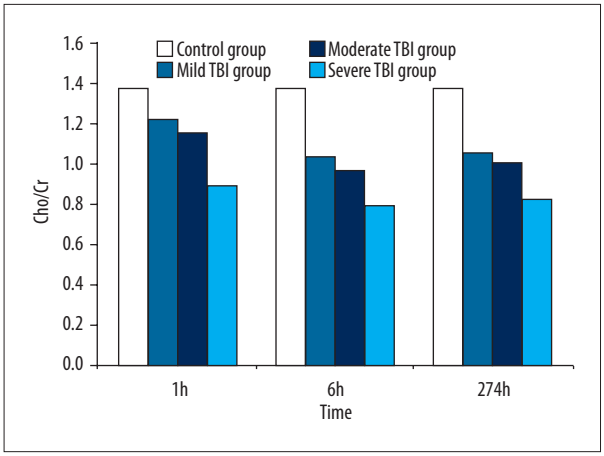

Figure 4. Cho/Cr ratio at various time points after injury.

Table 3. Correlation between NAA/Cr ratio and severity of attack at 24 hours post injury.

	Control group	Mild TBI group	Moderate TBI group	Severe TBI group	r value	P value
Severity of attack (g/cm)	–	400	600	1000	–0.92	<0.01
NAA/Cr	2.11±0.16	1.58±0.21	1.27±0.33	1.03±0.16		
n	10	10	10	10		

MRS detected the pathological changes of intracranial abnormalities earlier, and provided earlier accurate determination of the severity of TBI.

MRS, as an effective supplement to conventional MRI, has high requirements for coils. Previous studies have reported use of a human coil in the study of animal MRI, especially 8-channel knee coils and head coils. The rabbit brain is relatively smaller than the human brain, so signal-to-noise ratio (SNR) cannot be distinctly revealed due to low SNR when using human coils. ^{1}H-MRS also has difficulty detecting stable spectral lines. In this study, coil SNR measurement of aqueous solution model demonstrated that the SNR of self-made cap-like coil according to the size of rabbit brain was remarkably higher than that of using 8-channel knee coil and 8-channel head coil [3]. However, the uniformity of the volume coil is higher than that of the cap-like coil. Effective detection depth of the cap-like coil is 1/2 the effective diameter of the coil. In this study, the effective diameter of the cap-like coil was 8 cm, so its effective detection depth was 4 cm, which mets our requirement. Moreover, the left and right sides of our cap-like coil were symmetrical. The device was selected to block the generation of an interference magnetic field, thus enhancing the stability of the coil.

Among spectra, the NAA peak is highest in normal brain, as revealed by ^{1}H-MRS. NAA mainly exists in mature neurons, and its content can reflect the functional status of neurons. NAA peak reduction does not necessarily mean the loss of neurons, but temporary neurological dysfunction can also lead to NAA decline [5]. The specific function of NAA is not clear. A significant decrease in NAA after trauma occurs because NAA, as an acetyl compound, is decomposed for the synthesis of acetyl coenzyme A [6]. In this study, MRS was conducted at 1 h after injury. Decreased NAA/Cr ratio was detected in the injured white matter. NAA/Cr ratio was still reduced within 24 h after injury. Lin et al. [7] found that the NAA peak was significantly decreased in the semioval center, splenium of corpus callosum, and white matter of bilateral frontal lobe of mild TBI patients in long-term follow-up. The decreased NAA peak in the white matter indicated decreased axonal activity, but did not suggest neuronal death [7], which was consistent with the pathological results in our mild TBI group. A previous study showed that repeated mild brain injury reduced the NAA peak to baseline, and it cannot be restored [8]. The phenomenon of the NAA peak falling to baseline was not found in this study. This may be because our rabbits were only injured once. Moreover, MRS detection is limited to the acute stage of TBI. Our results demonstrated that, compared with the control group, the decrease of NAA/Cr ratio was positively correlated with the degree of injury. Previous studies [9,10] have confirmed similar conclusions to our study in the traumatic spectrum of the pons and midbrain. This provides a strong basis for judging the severity of brain injury by NAA/Cr ratio.

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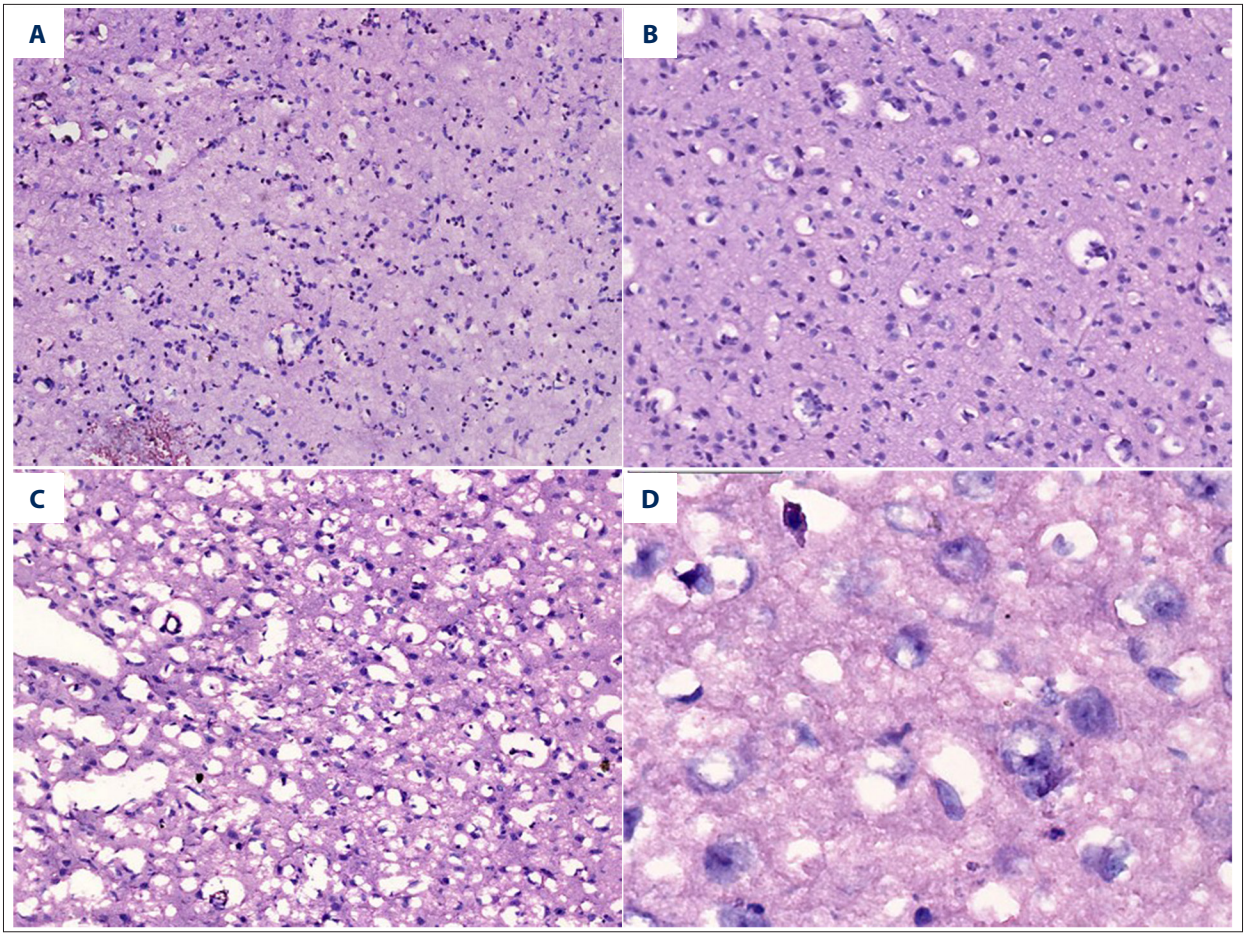

Figure 5. Pathological results at 24 hours after injury under a light microscope. (**A**) Mild TBI group: mild swelling in some neurons (hematoxylin-eosin staining, ×100). (**B**) Moderate TBI group: inflammatory cell infiltration, some neuronal degeneration (hematoxylin-eosin staining, ×100). In the severe TBI group, a large number of necrotic glial cells and inflammatory cell infiltration (hematoxylin-eosin staining, ×100, **C**), obvious neuronal swelling and vacuoles (hematoxylin-eosin staining, ×400, **D**).

Cho is a general term for choline phosphate, phosphatidylcholine, and choline glycerophosphatide, and reflects total choline reserves in the brain. Cho is the precursor of acetylcholine and phosphatidylcholine. Acetylcholine affects memory cognitive function and mental state. Phosphatidylcholine participates in the synthesis and metabolism of cell membranes. Within 24 h after injury, Cho peaks in the brain diminish to different degrees. Our results demonstrated that, compared with the control group, the Cho/Cr ratio was also reduced at 1 h after injury, and the decrease was most significant in the severe TBI group compared with the mild and moderate TBI groups. The reduction in Cho/Cr ratio was probably associated with the cell necrosis and cell number decrease induced by cell membrane damage. The Cho/Cr ratio was lowest at 6 h, and gradually increased by 24 h, but was still lower than in the control group. Partial recovery of Cho/Cr ratio was possibly associated with cell injury-induced increased myelin degradation or glial cell proliferation after TBI, indicating that damage in a certain range of brain tissue has some self-repair capacity [8]. Another study [11] verified that the increased Cho/Cr ratio was associated with the increased cell number induced by inflammatory reaction. In the present study, Cho/Cr ratio was increased in the frontal lobe on the injured side in the control group, which may be induced by local inflammatory response during surgery.

Among spectra, the Cr peak is third highest in normal brains, as revealed by MRS. Cr contains creatine and phosphocreatine, and a small amount of r-aminobutyric acid, lysine, and glutathione. Cr is a reserve of high-energy phosphate compounds and is a buffer for ATP and ADP [7]. Cr content is stable in the brain, and is commonly used as an internal reference. After brain injury, Cr concentration can diminish [12], but the degree of decrease is small. In this study, the relative ratio of metabolite to creatine was used for assessment. High-performance liquid chromatogram can be used to quantitatively determine

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actual concentrations of metabolites, or to determine the actual concentration by calculating the area under the peak of the metabolite spectral line, so as to assess the degree of TBI. Nevertheless, brain edema after TBI and individual differences in brain function will affect the actual test results. Therefore, we did not detect the actual concentration.

Lac is the product of anaerobic glycolysis, and can indirectly indicate hypoxia. MRS can show the increased Lac level and increased Cho level, as well as decreased NAA and Cr levels in TBI patients, suggesting obvious hypoxia after TBI, and indicating that the injury was severe and irreversible [13]. If increased Lac levels were not observed, the prognosis was good [13]. In this study, Lac peak continued to rise within 24 h after injury in the moderate and severe TBI groups, and the increase was most significant in the severe TBI group, suggesting that Lac peak level was positively associated with the degree of injury. A previous study [14] confirmed that appearance or increase of Lac peak was associated with increased metabolic energy requirement in the brain. For the treatment of TBI, a personalized treatment program not only can reduce the treatment cost, but also can improve therapeutic efficacy, reduce the incidence of long-term complications, and improve clinical prognosis [15].

Conclusions

In this study, [1]H-MRS was used to measure the characteristics of metabolite changes within 24 h after TBI. MRS can detect the abnormal changes in the brain after TBI earlier than with conventional MRI. Different pathological metabolic states induced by different degrees of injury and different neurological impairment scores suggest that MRS has a value in judging the severity of TBI. This provides a strong basis for the early development of personalized treatment program.

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