Evidence for cellular damage in normal-appearing white matter correlates with injury severity in patients following traumatic brain injury
A magnetic resonance spectroscopy study

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Summary
Neuropsychological studies in patients who have suffered traumatic brain injury show that the eventual clinical outcome is frequently worse than might be predicted from using conventional (CT or T1/T2-weighted MRI) imaging. Furthermore, patients who have sustained an initial mild or moderate injury may show long-term disability. This implies that there may be abnormalities in areas of the brain that actually appear normal on conventional imaging. Proton magnetic resonance spectroscopy studies have shown that N-acetylaspartate and choline-containing compounds can provide measures of cellular injury. We report MRI and proton magnetic resonance spectroscopy studies of 19 head-injured patients performed once the patients were clinically stable (mean 11 days after injury, range 3–38 days). Proton magnetic resonance spectra were acquired from frontal white matter that on conventional MRI appeared normal. The brain N-acetylaspartate/creatine ratio was reduced [patients (mean ± standard deviation), 1.28 ± 0.25; controls, 1.47 ± 0.24; P = 0.04] and the choline/creatine ratio was increased (patients, 0.85 ± 0.18; controls, 0.63 ± 0.10; P < 0.001) compared with controls. When the severity of the injury was assessed using either the Glasgow coma scale or the length of post-traumatic amnesia, the increase in the choline/creatine ratio was significant even in the mildly injured group (P = 0.008 and P = 0.04, respectively). Furthermore, there was a significant correlation (P = 0.008) between the severity of head injury and the N-acetylaspartate/choline ratio. We conclude that there is an early reduction in N-acetylaspartate and an increase in choline compounds in normal-appearing white matter which correlate with head injury severity, and that this may provide a pathological basis for the long-term neurological disability that is seen in these patients.

Keywords: traumatic brain injury; magnetic resonance spectroscopy; injury severity; N-acetylaspartate; choline

Abbreviations: Cr = creatine; Cho = choline; GCS = Glasgow coma scale; MRS = magnetic resonance spectroscopy; NAA = N-acetyl aspartate; PTA = post-traumatic amnesia; STEAM = stimulated echo acquisition mode; TBI = traumatic brain injury; TE = echo time; TR = repetition time

Introduction
Traumatic brain injury (TBI) is a common cause of neurological damage and disability. Most patients with TBI suffer a mild injury with transient, if any, loss of consciousness. Despite this, significant numbers of these mildly injured patients have neuropsychological sequelae (King et al., 1997; Deb et al., 1998; van der Naalt et al., 1999). Conventional imaging (CT or T1/T2-weighted MRI) performed acutely after TBI is known to be abnormal in a significant number of patients (Jenkins et al., 1986; Yokota et al., 1991; Mittl et al., 1994). However, the correlation between abnormalities detected by early imaging and the neuropsychological outcome is weak (Wilson et al., 1988; Levin et al., 1992). This observation raises the possibility that regions around or at a distance from visible damage may be injured.

Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive technique which allows the detection of a localized metabolite profile. Several compounds can be identified by 1H-MRS in the brain, including N-acetylaspartate (NAA), a cellular amino acid considered to be a marker of
neuronal integrity, choline-containing compounds (Cho), total creatine (Cr), consisting of creatine and phosphocreatine, and lactate, which can accumulate in regions of anaerobic metabolism.

Recently, 1H-MRS has been applied in several studies of TBI (Choe et al., 1995; Ricci et al., 1997; Cecil et al., 1998; Friedman et al., 1998, 1999; Ross et al., 1998) and has demonstrated abnormalities in regions of normal-appearing brain. The relationship between injury severity and metabolic change, however, has not been reported previously.

Our aim was to investigate whether changes in these metabolite levels, assessed using 1H-MRS after acute TBI, were related to the severity of injury, and in particular if there were changes in normal-appearing white matter in patients with mild or moderate injury which might explain their long-term disability.

Methods

Patient population

Nineteen patients (mean age 37 years, range 18–66 years) admitted with a head injury were recruited from the Oxford Radcliffe Hospital. The patients were studied once they were clinically stable, with a mean delay from TBI of 11 days (range 3–35 days). The severity of the head injury was assessed in each patient using both the Glasgow coma scale (GCS) (Teasdale and Jennett, 1974) after resuscitation and the length of post-traumatic amnesia (PTA) (Russell, 1932). The GCS is an objective measure of the initial severity of injury obtained on admission to hospital, whereas the length of PTA is a subjective measure of global brain damage. There are clear correlations between GCS and PTA, but it is not unusual (e.g. Table 1, patient 8) to find prolonged PTA with minimal abnormality in the GCS (Wilson et al., 1994). Consequently, both methods were used to assess the patients and to categorize them into mildly, moderately and severely injured groups (Russell and Smith, 1961; Teasdale and Jennett, 1974). Eighteen normal control subjects with no significant previous history of head injury (mean age 36 years, range 23–70 years) were studied for comparison.

Ethical approval was obtained for the study from the central Oxford research ethics committee and informed consent was obtained from the patients or next of kin.

MRI/MRS examinations

Imaging and spectroscopy was performed using a 2 Tesla superconducting magnet (Oxford Magnet Technology, Eynsham, Oxon, UK) interfaced to a Bruker AVANCE spectrometer (Bruker Medical, Ettlingen, Germany) and a purpose-built quadrature head-coil. Conventional imaging consisted of an initial mid-line sagittal scout image followed by axial T1-weighted [gradient echo sequence, echo time (TE) 13 ms, repetition time (TR) 500 ms] and T2-weighted (fast spin echo sequence, TE 82 ms, TR 3000 ms) acquisitions. For the axial images, eight slices were obtained with a slice thickness of 5 mm and slice separation of 7.5 mm. In addition, the integrity of the blood–brain barrier was confirmed by the acquisition of a further T1-weighted sequence after the injection of gadolinium-DTPA.

Proton spectra were acquired from the white-matter tracts of the frontal lobes, after we had identified from the multislice axial images a voxel position which avoided any areas of T1 or T2 abnormality. Localization of the signal was performed using stimulated echo acquisition mode (STEAM) (Frahm et al., 1989a) (TE 30 ms, TR 3000 ms, mixing time 47 ms). Initial investigations used STEAM to define a 3 × 2 × 9 cm region, which was then subdivided into 3 × 2 × 1 cm voxels by incorporating 16 phase-encoded gradient steps (total number of averages 256) (Brown et al., 1982). As the total examination time proved to be at the limit of patient acceptance, later investigations employed single-voxel STEAM acquisition (voxel size 3 × 2 × 3 cm, number of acquisitions 128). Both methods used the same basic acquisition sequence and timing and so metabolite peak ratios were unaffected. This was confirmed in five control subjects, in whom there was <4% difference between the two methods. Water suppression was achieved using a chemical shift selective sequence (Haase et al., 1985). Pulse rate and oxygen saturation were monitored throughout the study.

Data analysis

The proton spectra were analysed off-line using the 1D Win-NMR software package (Bruker-Franzen Analytik, Bremen, Germany). Data were zero-filled, Lorentz–Gaussian- and Fourier-transformed, then phase- and baseline-corrected. The spectral peaks from NAA, Cr and Cho were fitted to Gaussian line shapes and integrated. Results are expressed in the following metabolite ratios: NAA/Cr, Cho/Cr and NAA/Cho. The Mann–Whitney U-test was used to compare these ratios between patient groups and controls and the Spearman rank test was used to correlate the severity of injury with the metabolite ratios.

Results

Demographic data from the patient population, including age, sex, days from TBI, GCS on admission, length of PTA, cause of injury and global MRI findings, are shown in Table 1. Considering the global MRI findings, eight patients had no evidence of any abnormality, contusions were present in seven, haematomas in five and diffuse axonal injury in two. Using the GCS to assign patients to groups, there were eight mildly, seven moderately and four severely injured patients, and using assessment of PTA there were six mildly, eight moderate and five severely injured patients (Table 1). Examples of typical data sets are shown in Fig. 1. Case 1 was a 27-year-old male cyclist studied 11 days after he had fallen off his bicycle whilst in a race. The GCS of the patient after resuscitation was 14 (mild) and the subsequent PTA
was 5–6 days (moderate). The $T_2$-weighted image showed a left frontal contusional haematoma. Localized spectroscopy was obtained posteriorly to the contusional haematoma in a region of normal-appearing white matter. No enhancement was visible in this area on the post-gadolinium $T_1$-weighted image. Case 2 was a 19-year-old male cyclist studied 13 days after a road-traffic accident. The GCS of the patient after resuscitation was 4 (severe) and the subsequent PTA was >1 month (severe). The $T_2$-weighted image shows a bifrontal haemorrhagic contusion. The spectroscopy voxel was localized to white-matter tracts, posterior to the contusion in the normal-appearing white matter, of the left frontal lobe. Compared with a spectrum obtained from a control subject from a similar region of normal-appearing white matter (Fig. 1), the most striking finding in both patients was the increase in the Cho/Cr ratio. In addition, in the severely injured patient there was a reduction in the NAA/Cr ratio. No lactate was visible in the spectra of either patient.

The metabolite ratios for NAA/Cr, NAA/Cho and Cho/Cr in controls and patients are given in Table 2. Considering the patients as a single group, there was a significant reduction in the NAA/Cr ratio (mean ± SD, 1.28 ± 0.25) relative to controls (1.47 ± 0.24, $P = 0.04$). This is in keeping with the marked reduction in NAA in the patients, assuming that the Cr level was stable. The Cho/Cr ratio was significantly increased in patients (0.85 ± 0.18) relative to controls (0.65 ± 0.09, $P < 0.001$), suggestive of an increase in Cho in patients after TBI. The NAA/Cho ratio was reduced in the patients (1.59 ± 0.43) compared with controls (2.28 ± 0.45, $P < 0.001$). This is likely to have been as a consequence of both the reduction in NAA and the increase in Cho.

The two measures of injury severity (GCS and PTA) relate to different aspects of TBI. Consequently, the data were analysed twice using grouping based on either measure. Considering the patients in groups who were mildly, moderately and severely injured, assessed using GCS, the NAA/Cr ratio was reduced in all three groups, but was significantly reduced only in the moderate and severe groups (mild $1.40 ± 0.23$, $P = 0.7$; moderate $1.25 ± 0.20$, $P = 0.04$; severe $1.11 ± 0.25$, $P = 0.02$) compared with controls. The Cho/Cr ratio was significantly increased in all three groups (mild $0.81 ± 0.16$, $P = 0.008$; moderate $0.86 ± 0.23$, $P = 0.01$; severe $0.91 ± 0.13$, $P = 0.007$) compared with controls. Considering the reduction in the NAA and the increase in Cho together, the NAA/Cho ratio was significantly reduced in all three groups (mild $1.80 ± 0.32$, $P = 0.006$; moderate $1.55 ± 0.49$, $P = 0.001$; severe $1.27 ± 0.39$, $P = 0.002$).

When the length of PTA was used to assign a patient to a mild, moderate or severely injured category, the NAA/Cr ratio was reduced compared with controls in all three groups, the difference being significant in the severe group (mild $1.33 ± 0.21$, $P = 0.2$; moderate $1.39 ± 0.16$, $P = 0.4$; severe $1.06 ± 0.25$, $P = 0.005$). The Cho/Cr ratio was increased in all three groups, significantly in the moderate and severe groups (mild $0.75 ± 0.11$, $P = 0.04$; moderate $0.84 ± 0.16$, $P = 0.005$; severe $0.98 ± 0.21$, $P = 0.003$) compared with controls. The NAA/Cho ratio was significantly reduced in all three groups (mild $1.84 ± 0.35$, $P = 0.03$; moderate $1.70 ± 0.28$, $P < 0.001$; severe $1.14 ± 0.43$, $P = 0.001$) compared with controls.

A significant negative correlation ($P = 0.007$, $r_s = −0.59$) was shown to exist between the NAA/Cr ratio and the GCS score for each patient, indicating that the loss of NAA in

### Table 1 Demographic data and imaging results in 19 patients after TBI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Time since TBI (days)</th>
<th>GCS</th>
<th>PTA (days)</th>
<th>Cause of TBI</th>
<th>Global MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>M</td>
<td>5</td>
<td>15</td>
<td>0.5</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>Bl inj</td>
<td>Chronic SDH</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>M</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>Fall</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>M</td>
<td>18</td>
<td>15</td>
<td>0</td>
<td>Fall</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>5</td>
<td>14</td>
<td>0.5</td>
<td>Fall</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>M</td>
<td>3</td>
<td>14</td>
<td>0.5</td>
<td>Fall</td>
<td>Contusion</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>3</td>
<td>14</td>
<td>2–3</td>
<td>Bl inj</td>
<td>Chronic SDH</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>M</td>
<td>11</td>
<td>14</td>
<td>5–6</td>
<td>BA</td>
<td>Contusional haematomata</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>F</td>
<td>18</td>
<td>11</td>
<td>4–5</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>M</td>
<td>11</td>
<td>11</td>
<td>4–5</td>
<td>Bl inj</td>
<td>Haemorrhagic contusion</td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>F</td>
<td>10</td>
<td>11</td>
<td>5–6</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>M</td>
<td>4</td>
<td>9</td>
<td>&gt;30</td>
<td>Fall</td>
<td>Contusion/previous SDH</td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>M</td>
<td>12</td>
<td>9</td>
<td>6–7</td>
<td>Fall</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>14</td>
<td>23</td>
<td>M</td>
<td>13</td>
<td>9</td>
<td>5–6</td>
<td>MVA</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>15</td>
<td>26</td>
<td>M</td>
<td>4</td>
<td>9</td>
<td>4–5</td>
<td>Fall</td>
<td>Contusion</td>
</tr>
<tr>
<td>16</td>
<td>33</td>
<td>M</td>
<td>15</td>
<td>7</td>
<td>15–20</td>
<td>Fall</td>
<td>DAI</td>
</tr>
<tr>
<td>17</td>
<td>41</td>
<td>M</td>
<td>35</td>
<td>6</td>
<td>&gt;30</td>
<td>Fall</td>
<td>Acute SDH</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>M</td>
<td>19</td>
<td>6</td>
<td>&gt;30</td>
<td>MVA</td>
<td>Haemorrhagic contusion/DAI</td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>M</td>
<td>13</td>
<td>4</td>
<td>&gt;30</td>
<td>MVA</td>
<td>Haemorrhagic contusion</td>
</tr>
</tbody>
</table>

BA = bicycle accident; Bl inj = blunt injury; DAI = diffuse axonal injury; MVA = motor vehicle accident; SDH = subdural haematoma.
Fig. 1 T2-weighted images and spectra obtained (from voxels as illustrated) in normal-appearing white matter in two patients and a control. All axial images were studied to ensure that the voxel did not include any area of abnormality identified on T1- and T2-weighted images.

Table 2 Values for the NAA/Cr, Cho/Cr and NAA/Cho ratios in the control subjects and mildly, moderately and severely injured patients [mean (standard deviation)]

<table>
<thead>
<tr>
<th></th>
<th>NAA/Cr</th>
<th>Cho/Cr</th>
<th>NAA/Cho</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.47 (0.24)</td>
<td>0.65 (0.09)</td>
<td>2.28 (0.45)</td>
</tr>
<tr>
<td>Patients</td>
<td>1.28 (0.25)*</td>
<td>0.85 (0.18)**</td>
<td>1.59 (0.43)**</td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.40 (0.23)</td>
<td>0.81 (0.16)**</td>
<td>1.80 (0.32)**</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.25 (0.20)*</td>
<td>0.86 (0.23)**</td>
<td>1.55 (0.49)**</td>
</tr>
<tr>
<td>Severe</td>
<td>1.11 (0.25)*</td>
<td>0.91 (0.13)**</td>
<td>1.27 (0.39)**</td>
</tr>
<tr>
<td>PTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.33 (0.21)</td>
<td>0.75 (0.11)*</td>
<td>1.84 (0.35)*</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.39 (0.16)</td>
<td>0.84 (0.16)**</td>
<td>1.70 (0.28)**</td>
</tr>
<tr>
<td>Severe</td>
<td>1.06 (0.25)**</td>
<td>0.98 (0.21)**</td>
<td>1.14 (0.43)**</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

Discussion

The principal findings of this study are that the NAA/Cr ratio is decreased and the Cho/Cr increased in normal-appearing white matter in patients after TBI. The reduction in the NAA/Cr ratio was significant in moderately and severely injured patients whilst the Cho/Cr ratio was significantly increased, compared with controls, in all patient groups. Furthermore, there was a significant correlation between the level of decreased NAA, increased Cho and severity of injury.
A reduction in NAA has been found previously in patients after TBI in both the grey matter (Ricci et al., 1997; Ross et al., 1998; Friedman et al., 1999) and the white matter (Choe et al., 1995; Cecil et al., 1998; Friedman et al., 1998; Ross et al., 1998), but these papers made no reference to the severity of injury. Furthermore, the previous studies have generally performed the MRS investigations in the later stages (6 weeks to several years) after TBI. An acute (within 1 day) reduction in NAA has only been described in patients with severe head injury in areas of visible contusion (Condon et al., 1998), and there was an early (within 1 month) reduction in NAA in a cohort of paediatric and adult patients (Ross et al., 1998). The present study performed the MRS investigation in the early stages after TBI, with a mean delay of 11 days after injury. Our results are in keeping with these previous studies in finding a reduction in the NAA levels in the early stages after TBI, but in addition there was a significant correlation of reduced NAA with the severity of head injury.

The anatomical area investigated for this study was normal-appearing white matter in one (or both) of the frontal lobes. Diffuse axonal injury in the lobar white matter tends to be primarily microscopic and hence undetectable using conventional neuroimaging techniques (Mittl et al., 1994). The reduction in NAA (reduced NAA/Cr ratio) in these areas was statistically significant in moderately and severely injured patients assessed using the GCS, and non-significantly reduced in the mildly injured patients. This is in keeping with substantial cellular injury in patients after TBI. The apparent reduction in NAA in these areas of normal-appearing white matter supports the hypothesis that regions of the brain remote from the focal lesion are involved in the pathology of head injury. This could result from shearing damage at the time of the impact, subsequent ischaemia or Wallerian degeneration of the axons that connect to the areas of focal damage. Wallerian degeneration has been regarded as the cause of the reduction in NAA level that has been found in white matter tracts at a distance from areas of pathology in stroke (Pendlebury et al., 1999) and multiple sclerosis (De Stefano et al., 1998).

NAA is known to be a mitochondrial product (Bates et al., 1996). Consequently, a reduction in NAA could be caused by impaired mitochondrial energy production rather than cellular loss (Bates et al., 1996). If reduced energy production is involved, it is unlikely to be a significant factor, as no lactate was present in the spectra of any of the patients. A previous study, using 1H-MRS (Condon et al., 1998), found lactate in some of the severely injured patients studied within 25 h of injury. In addition, previous work has shown that diffuse hypoperfusion, causing ischaemia, is a common feature only in the first few hours after TBI in severely injured patients (Bouma et al., 1992). Thus, it is possible that mitochondrial damage had occurred before we were able to study these patients.

In the current study, the apparent level of Cho in normal-appearing white matter was increased in patients and there was a significant positive correlation between this increase and the severity of injury. Previous studies have demonstrated an increase in Cho in the grey matter of patients in the chronic stages after TBI (Ricci et al., 1997; Friedman et al., 1998). The Cho peak consists of several compounds, the principle ones being phosphocholine and glycerophosphocholine, together with some free choline (Miller et al., 1996). The increase in Cho could be due to membrane degradation following cellular damage. However, significant cell disruption would be expected to be associated with abnormalities particularly on T2-weighted images, or with evidence of blood–brain barrier breakdown, neither of which was evident in the areas from which the 1H-MRS were acquired. Alternatively, the elevation in Cho could be consistent with an increase in membrane turnover similar to that found in tumours (McBride et al., 1995). An increase in membrane turnover may indicate the potential repair of cells within this area.

The Cho levels could also be affected by reduction in the activity of choline acetyltransferase, which has been reported in patients after head injury (Murdoch et al., 1998). High-resolution 1H-MRS of extracts of brain demonstrate that the Cho peak consists of free choline, phosphocholine and glycerophosphocholine (Miller et al., 1996). It is therefore possible that the observed difference between the ratios of patients and controls could be explained by changes in the activity of choline acetyltransferase.

Mildly and moderately injured patients account for the majority of those who suffer TBI. Several studies have shown that such patients have significant neuropsychological sequelae after TBI (King et al., 1997; Deb et al., 1998; van der Naalt et al., 1999). In our study, eight of the 14 patients...
with a mild or moderate injury had no evidence of abnormality on conventional MRI. However, there was a significant increase in the Cho/Cr ratio in the mildly and moderately injured groups and a significant reduction in the NAA/Cr ratio in the moderately injured group compared with the controls, confirming our hypothesis that white matter that appears normal on conventional imaging may show metabolic abnormalities when $^1$H-MRS is used. The relationship between the biochemical changes and the severity of injury provides a metabolic basis for the neurological disability seen in these patients. As discussed earlier, the mechanisms responsible for these abnormalities are currently unclear, but may provide a target for therapeutic intervention in the future.

The results used in this study were expressed on the assumption that Cr was present at a constant level. Cr is present in slightly higher concentrations in grey matter than in white matter (Pouwels and Frahm, 1998) and is relatively refractive to change. An alteration in Cr levels could not account for the decrease in the NAA/Cr ratio together with the increase in the Cho/Cr ratio. Alternatively, the apparent differences in the ratios in the patients and controls could be explained by a change in the relaxation properties of the metabolites in the patients. Trauma disrupts the normal cellular environment and thus could theoretically alter the $T_1$ and $T_2$ relaxation properties of the metabolites. This, in turn, would alter the apparent metabolite concentrations and hence the ratios. Assuming a $T_1$ value in the cerebral white matter of 1500 ms (Frahm et al., 1989b), it would not be possible to explain an increase in Cho by alteration of the $T_1$ or $T_2$ values. Furthermore, it would require a 55% increase in $T_1$ or a 55% decrease in $T_2$ to explain the reduction in NAA observed in this study, which is unlikely.

In conclusion, there are areas of the brain which appear normal on conventional MRI but which show significant $^1$H-MRS abnormalities. These results provide evidence of diffuse damage contributing to the pathology of head injury. These abnormalities are present in mildly, moderately and severely injured patients and there is a significant correlation between the severity of head injury and extent of abnormality in the $^1$H-MRS. The changes are consistent with widespread cellular injury (decrease in NAA/Cr) and abnormal membrane metabolism (increase in Cho/Cr).

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References


