Semiquantitative analysis of corpus callosum injury using magnetic resonance imaging indicates clinical severity in patients with diffuse axonal injury

M Takaoka, H Tabuse, E Kumura, S Nakajima, T Tsubuki, K Nakamura, A Okada, H Sugimoto

Objective: To evaluate the hypothesis that the extent of corpus callosum injury indicates the depth of shearing lesions in the central brain structure and therefore relates to the clinical severity of diffuse axonal injury.

Methods: A simple and objective procedure for semiquantitative analysis of magnetic resonance images (MRI)—the maximum signal intensity ratio (MSIR)—was employed prospectively in 21 patients with diffuse axonal injury but without apparent injury to the ventral pons. All were diagnosed using serial combination MRI scans of fluid attenuated inversion recovery (FLAIR) and T2* weighted gradient echo imaging during the initial two weeks after the injury. The signal intensity ratio between the two regions of interest—the corpus callosum and the normal appearing ventral pons—was calculated serially in mid-sagittal and parasagittal FLAIR image sections in each patient. The MSIR during the study period was determined as a semiquantitative index of corpus callosum injury in each patient. The correlations between MSIR and the duration of unconsciousness, Glasgow outcome scale at six months, and the presence of apparent midbrain injury were investigated.

Results: The mean (SD) MSIR value was 1.12 (0.18) at 7.4 (3.1) days after the injury (n = 21). MSIR correlated strongly with the duration of unconsciousness (n = 19, R² = 0.74, p < 0.0001), and was higher in patients with both an unfavourable GOS outcome (p = 0.020) and apparent midbrain injury (p < 0.001).

Conclusions: MSIR, which is a simple and objective procedure for semiquantitative analysis of corpus callosum damage in diffuse axonal injury, correlated with clinical severity. A high MSIR value may indicate the presence of concomitant midbrain injury.

Magnetic resonance imaging (MRI) studies over the past decade have clarified the imaging features of diffuse axonal injury and have proved invaluable in diagnosis. Furthermore, a clear correlation between clinical outcome and the depth of the diffuse axonal lesions in the central brain structures on MRI has been reported. However, the lesions of deep seated diffuse axonal injury are sometimes overlooked or underestimated because the detection of these lesions is unavoidably affected by the performance of the MRI device and by sequencing, time interval between the injury and the scan, and radiological interpretation. Thus discrepancies in MRI evaluation tend to occur between institutions and researchers as a result of methodological variations.

Corpus callosum injury is known to be a common component of diffuse axonal injury and serves as a diagnostic marker, because it is usually larger and more evident than other lesions on MRI. Theoretically, increasing rotational acceleration to the head causes centripetal extension of the shearing injury from the peripheral areas to the central brain structure. Confirming this, diffuse axonal injury severe enough to affect the brain stem has been found to amplify injury in peripheral areas such as the corpus callosum. We therefore hypothesised that the extent of corpus callosum injury on MRI indicates the depth of diffuse axonal lesions—particularly in conjunction with an associated upper brain stem injury—and so relates to the clinical severity of diffuse axonal injury. Our aim in this study was to evaluate this hypothesis prospectively, using a semiquantitative procedure for assessing corpus callosum injury with MRI.

METHODS

Patients
We enrolled 21 patients with diffuse axonal injury who had been admitted to the Osaka Prefectural Nakakawachi Medical Centre of Acute Medicine (NMCAM), level I trauma centre, between September 1998 and September 2000. At NMCAM, MRI was routinely performed within 24 hours after admission in unconscious patients with head injury who did not have evidence of an intracranial mass lesion on computed tomography (CT).

Patients with diffuse axonal injury fulfilled the following criteria:

- loss of consciousness from the time of injury that persisted beyond six hours;
- no cause of unconsciousness other than the primary brain injury;
- no apparent intracranial mass lesion on serial CT scans during the study;
- the presence of white matter injury on MRI.

All the patients had been admitted directly from the scene of an accident within an hour after sustaining their injuries, and had initial Glasgow coma scale (GCS) scores of 8 or less. None of the 21 patients had severe life threatening injuries to other organs.

During the study period, six additional patients with diffuse axonal injury were excluded from the investigation. Three were excluded because they needed emergency surgery for a splenic injury, an optic canal injury, and a pregnancy.
respectively. The other three were excluded because they had apparent pons injuries on MRI. In these latter patients, the signal intensity of the ventral pons was inappropriate as a control for calculating the signal intensity ratio, which is described later in detail.

Medical management
Medical management involved the prevention of respiratory complications and excessive hyperthermia. Artificial ventilation was initiated in patients who presented with decerebrate rigidity, and a tracheotomy was performed if necessary. Core temperature was kept under 38°C using cooling blankets or non-steroidal anti-inflammatory agents, or both. Although we used the minimum dose of midazolam or propofol necessary for the respiratory management, unnecessary continuous administration was strictly avoided. Administration of phenytoin or barbiturates to prevent seizures was also avoided during the study period.

MRI analysis
Our MRI protocol for diffuse axonal injury was as follows. Combination MRI scans using fluid attenuated inversion recovery (FLAIR) and T2\* weighted gradient echo (T2*) sequences were performed within 24 hours after the injury (day 0) and on days 1, 3, 7, and 14 after admission. All scans were obtained at 1.0 T (Siemens Magnetom Impact Expert). FLAIR images were obtained in the axial and sagittal planes using the following parameters:
- 9000 ms/119 ms/2200 ms (repetition time/echo time/time from inversion);
- flip angle 180°;
- matrix = 256 × 256;
- section thickness 7 mm, with a 2 mm gap;
- imaging time 5 minutes, 33 seconds.

T2* images were obtained in the same planes using the following parameters:
- 700 ms/26 ms (repetition time/echo time);
- matrix = 256 × 168;
- flip angle 20°;
- section thickness 7 mm, with a 2 mm gap;
- imaging time 4 minutes, 31 seconds.

The location and appearance of diffuse axonal lesions, especially in the corpus callosum and brain stem, were assessed by an attending neuroradiologist and two neurosurgeons, who were blinded to the clinical status of the patients.

Semiquantitative analysis of corpus callosum injury was performed with sagittal FLAIR image planes following a previously described procedure. Because absolute signal intensity measurements are potentially dependent on the position of the head surface coil and the amplifier gain of the image reconstruction circuitry, we used the relative signal intensity of the corpus callosum compared with the normal appearing ventral pons as the indicator of corpus callosum injury.

The signal intensity ratio between the corpus callosum and ventral pons was obtained from sagittal FLAIR image planes in the following manner (fig 1). Two regions of interest (ROI) were generated by tracing the contours of the cross sections of both the corpus callosum and the ventral pons on the monitor display. The mean signal intensity of each ROI was measured using MRI console software. The signal intensity of the corpus callosum was then divided by that of the ventral pons (corpus callosum/pons) to correct for the difference in imaging factors between the respective slices. This operation was conducted for midsagittal and bilateral parasagittal slices, in which the anatomical structures of both the corpus callosum and the ventral pons were clearly discriminated. Signal intensity ratios (SIR) for these three slices were averaged, after which the maximum SIR value in the serial examinations of each patient was determined (MSIR). A reference SIR value was also obtained from six healthy volunteers during the study period.

Clinical assessment
Clinical severity was assessed in each patient according to the duration of unconsciousness and the outcome. The duration of unconsciousness was defined as the time lapse until simple orders were obeyed with the eyes opening spontaneously. Simple orders, such as “open your mouth and stick out your tongue,” “clench and loosen your hand,” and “flex and extend your knee,” suggest the recovery of cognitive acuity to verbal stimuli. Note that unconsciousness may encompass a state of wakefulness (opened eyes) associated with a total lack of cognitive function, which sometimes accompanies a persistent vegetative state. Two consulting neurosurgeons confirmed the duration of unconsciousness in each patient. Motor paresis was identified on detailed neurological examination.
The outcome was determined at six months after the injury according to the Glasgow outcome scale, as follows: 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, mild or no disability. For statistical comparison, patients with a GOS score of 4 or 5 were classified as having a favourable outcome, and those with scores of 1, 2, or 3 as having an unfavourable outcome. Each survivor participated in a personal follow up interview, either by visit or by telephone.

Statistical analysis
All values are expressed as mean (SD). Statistical analysis was performed using the Mann–Whitney U test and Pearson’s correlation coefficient. Significance was assigned when the probability (p) value was less than 0.05. The data were analysed using Stat View (Abacus Concepts Inc).

RESULTS
Patient characteristics
The clinical profiles of the 21 patients are summarised in table 1. Twenty patients were injured in motor vehicle accidents. The remaining patient was a pedestrian injured in a railway accident. Ages at the time of injury ranged from 5 to 65 years, and five patients were children aged 15 or younger.

Midazorom or propofol was given continuously in 10 patients, but not for more than 72 hours. Although six patients required artificial ventilation beyond a week because of prolonged unconsciousness, no severe complications occurred. None of the patients died but two were in a vegetative state at six months after the insult. The other 19 patients recovered consciousness within six weeks. Mean (SD) duration of unconsciousness in the patients who recovered was 12.2 (11.6) days, ranging from one to 42 days. Although not shown in table 1, the duration of unconsciousness in the patients with favourable outcomes was significantly shorter than in those with an unfavourable outcome (8.4 (8.9) v 22.8 (12.5) days, p = 0.014, n = 19).

MRI findings
The serial combination MRI scans in each patient showed at least one injury in three separate areas—the cerebral lobar white matter, the corpus callosum, and the dorsolateral quadrants of the midbrain. These are common lesions of diffuse axonal injury and are known as the shearing injury triad. The distribution of the lesions in the 21 patients was classified according to whether they were present in the corpus callosum or the dorsolateral midbrain (table 2). An apparent injury on MRI in either of these regions was detected in 16 patients, while neither was present in five; eight patients had only corpus callosum injury, and the other eight had both corpus callosum and dorsolateral midbrain injuries. None of the patients had only a midbrain injury—midbrain injury was always combined with corpus callosum injury.

The location and appearance of the lesions in the 16 patients with apparent corpus callosum injury were as follows.

Statistical comparison
Table 1 shows that the mean duration of unconsciousness was significantly shorter in patients with an unfavourable outcome (8.4 (8.9) v 22.8 (12.5) days, p = 0.014, n = 19).

Table 2 Magnetic resonance imaging findings in 21 patients with diffuse axonal injury

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury in corpus callosum/midbrain</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Midbrain only</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Corpus callosum and midbrain</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Injury to MSIR interval (days)</td>
<td>7.40</td>
<td>(3.13)</td>
</tr>
<tr>
<td>MSIR</td>
<td>1.12</td>
<td>(0.18)</td>
</tr>
<tr>
<td>SIR of healthy volunteers (n=6)</td>
<td>0.91</td>
<td>(0.02)</td>
</tr>
</tbody>
</table>

Values are n or mean (SD). MSIR, maximum signal intensity ratio between corpus callosum and ventral pons; SIR, signal intensity ratio between corpus callosum and ventral pons.

Correlation between MSIR and clinical manifestations
In 19 patients who recovered consciousness within six months, MSIR correlated strongly and positively with the duration of unconsciousness (R² = 0.74, p < 0.0001, n = 19) (fig 3). The MSIR values in the two vegetative patients were 1.35 and 1.52.

At the six months follow up, MSIR was significantly higher in patients with an unfavourable outcome than in those with

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T2* imaging is particularly useful for confirming the diagnosis of diffuse axonal injury, as small haemorrhages are accentuated by the magnetic susceptibility effect. In this study, haemorrhagic foci in the corpus callosum were clearly identified in T2* images immediately after the injury, and remained essentially unchanged through the study period. Yanagawa and colleagues reported that the total number of traumatic brain lesions detected by T2* imaging correlated with the duration of unconsciousness. In our study, however, there was no relation between T2* findings in the corpus callosum and clinical severity, because of the low sensitivity for non-haemorrhagic lesions (which were usually much larger than haemorrhagic foci). In contrast, the FLAIR image is considered to provide good visualisation of the entire extent of diffuse axonal injury. In a preliminary study, we found that the signal intensity of the corpus callosum on a FLAIR image increased relative to lesion enlargement, while T2* findings remained unchanged.

The sensitivity of the FLAIR image depends strongly on the temporal relation between the injury and the scan. It has been suggested that the best time to perform MRI in patients with diffuse axonal injury is between three and seven days after the trauma, because cellular necrosis and oedema are maximal at that time. In our study, high intensity lesions in the corpus callosum on FLAIR images—often surrounding the haemorrhagic foci—showed progressive enlargement over a few days or a week. These lesions diminished or sometimes disappeared on repeated MRI scans in the subacute phase. Tokutomi and colleagues suggested that these high intensity lesions represent oedema. This was the reason why the signal intensity ratio in patients with corpus callosum injuries usually increased in the initial phase of injury, peaking approximately one week after the insult. Similar findings are sometimes observed with brain stem injuries, while being less evident than in the corpus callosum.

A limitation of this study using FLAIR was the relatively long interval between the injury and the day of MSIR. Eight patients recovered consciousness before the MSIR occurred, all of whom had low values (below 1.02) and a favourable outcome. In these patients, MSIR was significant in predicting the outcome but not the duration of unconsciousness. On the other hand, all six patients with high MSIR values (above 1.20) had concomitant midbrain injuries and prolonged unconsciousness (more than three weeks). Recently, new imaging techniques—such as diffusion weighted imaging and magnetisation transfer imaging—were reported to be superior to the FLAIR image for the early detection of traumatic white matter lesions. Further investigation is necessary to establish quantitative criteria using these techniques.

Before the advent of neuroimaging, the characteristics of diffuse axonal injury were defined by Adams et al and Gennarelli et al from a histopathological viewpoint. Their experimental studies suggested that centripetal extension of a shearing injury into the brain stem caused prolonged unconsciousness. Furthermore they emphasised the importance of injury to the corpus callosum and dorsolateral midbrain, and described diffuse axonal damage in the cerebral hemispheres. The coexistence of these two injuries was considered to represent the most severe histological grade in fatal human cases. This concept is now applicable to MRI findings in vivo.

Visualisation of corpus callosum injury on MRI indicates that a shearing force of sufficient degree to produce a widespread diffuse axonal injury has occurred. Recent reports by Kampfl and colleagues—who performed detailed analyses of the anatomical location and frequency of lesions—provided evidence that a combination of lesions in the corpus callosum and the dorsolateral upper brain stem was a highly significant MRI feature in post-traumatic vegetative states associated with diffuse axonal injury. Gentry et al reported an increased incidence of brain stem lesions in cases of corpus callosum...
injury, and suggested that impairment of consciousness in the latter might reflect inapparent damage to the brain stem or the hemispheric white matter. Extensive callosal injury raises the possibility of upper brain stem injury, whether or not it is visible on MRI. In our study, eight of the nine patients with extensive corpus callosum injuries had associated midbrain injuries and showed greater clinical severity, suggesting a close relation between these two injuries.

Although we did not determine the role of axonal injury distribution in the development of unconsciousness, corpus callosum injury on its own may not be the direct cause.

In conclusion, the importance of observing corpus callosum injury in cases of diffuse axonal injury lies in the fact that these injuries serve as an indicator of other possible lesions, particularly in the brain stem, which may be responsible for unconsciousness.24

REFERENCES

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