Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome

Clinical article

TORIL SKANDSEN, M.D.,1,3 KJELL ARNE KVISTAD, M.D., PH.D.,2,4 OLE SOLHEIM, M.D.,1,5 INGRID HAAVDE STRAND, M.D.,4 MARI FOLVIK, M.D.,4 AND ANNE VIK, M.D., PH.D.1,5

Departments of 1Neuroscience and 2Circulation and Imaging, Norwegian University of Science and Technology (NTNU); and Departments of 1Physical Medicine and Rehabilitation, 3Diagnostic Imaging, and 4Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Object. In this prospective cohort study the authors examined patients with moderate to severe head injuries using MR imaging in the early phase. The objective was to explore the occurrence of diffuse axonal injury (DAI) and determine whether DAI was related to level of consciousness and patient outcome.

Methods. One hundred and fifty-nine patients (age range 5–65 years) with traumatic brain injury, who survived the acute phase, and who had a Glasgow Coma Scale (GCS) score of 3–13 were admitted between October 2004 and August 2008. Of these 159 patients, 106 were examined using MR imaging within 4 weeks postinjury. Patients were classified into 1 of 3 stages of DAI: Stage 1, in which lesions were confined to the lobar white matter; Stage 2, in which there were callosal lesions; and Stage 3, in which lesions occurred in the dorsolateral brainstem. The outcome measure used 12 months postinjury was the Glasgow Outcome Scale–Extended (GOSE).

Results. Diffuse axonal injury was detected in 72% of the patients and a combination of DAI and contusions or hematomas was found in 50%. The GCS score was significantly lower in patients with “pure DAI” (median GCS Score 9) than in patients without DAI (median GCS Score 12; p < 0.001). The GCS score was related to outcome only in those patients with DAI (r = 0.47; p = 0.001). Patients with DAI had a median GOSE score of 7, and patients without DAI had a median GOSE score of 8 (p = 0.10). Outcome was better in patients with DAI Stage 1 (median GOSE Score 8) and DAI Stage 2 (median GOSE Score 7.5) than in patients with DAI Stage 3 (median GOSE Score 4; p < 0.001). Thus, in patients without any brainstem injury, there was no difference in good recovery between patients with DAI (67%) and patients without DAI (66%).

Conclusions. Diffuse axonal injury was found in almost three-quarters of the patients with moderate and severe head injury who survived the acute phase. Diffuse axonal injury influenced the level of consciousness, and only in patients with DAI was GOSE score related to outcome. Finally, DAI was a negative prognostic sign only when located in the brainstem. (DOI: 10.3171/2009.9.JNS09626)

Key Words • craniocerebral trauma • diffuse axonal injury • magnetic resonance imaging • Glasgow Outcome Scale • treatment outcome • cohort study

TRAUMATIC brain injury is characterized by a complex and heterogeneous pathology. Brain damage may occur from different primary lesions, such as hematomas, cortical contusions, and DAI, as well as from secondary cellular processes.24 The axonal injury results from the stretching and deformation of the brain tissue caused by angular or rotational acceleration-deceleration forces.8 Diffuse axonal injury has microscopic and macroscopic characteristics, and the latter may be absent in milder cases. Three grades of DAI have been described by Adams et al.1 based on their neuropathological studies: Grade 1 DAI denotes widespread, microscopic axonal damage in any location; in Grade 2 DAI there are additional focal abnormalities in the corpus callosum; and in Grade 3 DAI, focal lesions in the rostral brainstem are also found. From these early studies, DAI was noted in one-third of all fatal cases. However, using newer techniques to visualize the axonal damage, DAI has been almost universally demonstrated in fatal TBI.9

Magnetic resonance imaging of DAI has shown hemorrhagic and nonhemorrhagic lesions in the white matter in the hemispheres, corpus callosum, and rostral brainstem, compatible with the neuropathological characteristics of this type of injury,11 and a modified staging has been used in imaging studies. Stage 1 represents a pattern of traumatic lesions confined to lobar white

Abbreviations used in this paper: DAI = diffuse axonal injury; FOV = field of view; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale–Extended; HISS = Head Injury Severity Scale; IQR = interquartile range; MOI = mechanism of injury; TBI = traumatic brain injury.
Diffuse axonal injury in head injury: occurrence and outcome

matter, whereas in Stages 2 and 3, lesions are depicted in the corpus callosum and brainstem, respectively. The prevalence of DAI detected with MR imaging has not been studied often in consecutive head-injured patients, and will depend on the sensitivity of the MR imaging sequences, selection of patients, and time between injury and scan.

The association between DAI detected by MR imaging and outcome has not been established. It has been argued that DAI may be a common cause of poor outcome and the mechanism most likely to be responsible for many of the cognitive deficits resulting from moderate to severe TBI. Yet studies are lacking comparing outcome in groups of patients with TBI with and without DAI. Several studies have shown an association between the number or volume of lesions and outcome, whereas others have failed to do so.

Stage 3 DAI, or brainstem injury in general, has been associated with a poor outcome in adults as well as in children and adolescents. However, the importance of MR imaging–detected Stage 1 (lesions confined to the hemispheres) or Stage 2 (callosal lesions) DAI is less clear because studies have yielded conflicting results.

The aims of this study were to describe the frequency and staging of DAI depicted with early MR imaging in consecutive patients with moderate to severe head injury admitted to a neurosurgical department. Furthermore, we wanted to relate the findings to the GCS score and to global patient outcome.

**Methods**

**Patient Population**

This MR imaging study included 106 patients in whom MR imaging was performed during the first 4 weeks after TBI. All patients were admitted to the neurosurgical department at St. Olavs Hospital in Trondheim, Norway. This hospital is the only Level I trauma center in a region of 660,000 inhabitants, and due to centralized treatment policy, the data regarding the severe head injuries are population-based. The patients had moderate to severe head injury according to HISS criteria.

Between October 2004 and August 2008, 182 individuals ranging in age from 5 to 65 years were admitted with moderate to severe head injury and were registered. Six additional admitted patients did not consent or were not registered for various reasons; of 23 who died during the acute phase, 21 died from the head injury, and 2 from other injuries. Of the 159 survivors, 108 (68%) had an MR imaging examination within 4 weeks postinjury, of which 2 were excluded due to poor quality. Reasons for not undergoing an examination with MR imaging within 4 weeks were: medical contraindications in 10 patients; logistical reasons in 27 patients, most often early transfer to other hospital; premorbid cerebral injuries in 11 patients; and refusing the MR imaging examination in 3 patients.

**Magnetic Resonance Imaging**

Magnetic resonance imaging was performed on a 1.5-T Siemens Symphony or Siemens Avanto MR imaging system (Siemens Medical) at the study hospital. Six patients were examined using a similar MR imaging system at a neighboring hospital. The scan protocol consisted of 5 different imaging methods:

1. Sagittal turbo spin echo T2-weighted imaging: 20 slices, TR 4300 msec, TE 110 msec, echo train length 14, number of excitations 4, FOV 23 cm, bandwidth 130 Hz, acquisition time 2:28 (minutes:seconds), matrix 291 × 512, pixel size 0.6 × 0.7 mm.
2. Sagittal, transverse, and coronal T2-weighted FLAIR imaging: 24 slices, TR 9000 msec, TE 109 msec, TI 2500 msec, number of excitations 4, FOV 23 cm, bandwidth 130 Hz, acquisition time 2:44, 2:26, and 2:26, matrix 291 × 512, pixel size 0.6 × 0.7 mm; fat saturation was used.
3. Transverse T2*-weighted gradient echo imaging: 24 slices, TR 830 msec, TE 25.8 msec, number of excitations 4, FOV 21 cm, bandwidth 80 Hz, acquisition time 2:52, flip angle 20°, matrix 291 × 512, pixel size 1.0 × 0.8 mm.
4. Transverse spin echo T1-weighted imaging: 24 slices, TR 430 msec, TE 7.8 msec, number of excitations 4, FOV 23 cm, bandwidth 130 Hz, acquisition time 3:44, matrix 291 × 512, pixel size 0.9 × 0.9 mm.
5. Diffusion weighted imaging: single-shot, spin echo planar imaging sequences with 19 slices of 5-mm section thickness (TR 3300 msec, TE 110 msec, number of excitations 4, FOV 23 cm, bandwidth 1240 Hz, acquisition time 1:44), obtaining baseline images (b = 0 second/mm²) and varying diffusion gradient strength along each of 3 orthogonal directions (b = 500 and 1000 second/mm²). Diffusion trace maps were computed from the isotropic diffusion image and were used to estimate the apparent diffusion coefficient.

**Imaging Analysis**

Two experienced neuroradiologists (K.A.K and M.F.) reported the imaging findings by consensus based on visual inspection, in accordance with predefined variables. Diffuse axonal injury was classified into Stage 1, 2, or 3 (Table 1; Fig. 1). Lesions in the cerebral cortex were defined as contusions.

For evaluation of reliability, 31 cases were selected according to identification number only (blind to data) from the ascending list of cases. These cases were scored by a third neuroradiologist who was blinded to clinical information and previous classification. Lesions were classified according to presence and staging of DAI.

**Computed Tomographic Imaging**

The CT scans were reviewed by a radiologist (I.H.S.) and classified as worst (highest CT score) according to the Marshall CT classification and presence of traumatic subarachnoid hemorrhage, including intraventricular hemorrhage.

**Demographic and Injury-Related Variables**

Demographic variables included sex, age, and preinjury problems. Preinjury problems were present if substance abuse, or neurological or psychiatric conditions affected daily functioning at the time of injury. Injury-
related variables were MOI, CT findings, lowest observed GCS score (recorded at or after admittance, or before intubation in cases of prehospital intubation), moderate (GCS score 9–13) or severe (GCS score ≤ 8) head injury, and pupillary abnormalities. The GCS score may be falsely low due to nonhead injury factors; that is, intoxication or major nonhead trauma. Accordingly, those patients whose mental condition had returned to normal during the first 24 hours and whose initial low GCS score could be explained by other factors were diagnosed with mild head injury and excluded. Likewise, those patients whose GCS score rose to 9–13 during the first 24 hours and whose initial low GCS score could be explained by other factors were upgraded from initially severe to moderate.

Outcome Assessment

Global outcome was assessed 12 months postinjury by telephone or personal contact, using the structured interview for the GOSE. To reduce the potential error associated with the telephone setting, relatives or caregivers also provided information in two-thirds of the cases, and the best source of information was used (based on the judgment of the authors). One of the 159 patients eligible for MR imaging was lost to follow-up at 12 months, and in that case, 6-month outcome results were used. The GOSE score was dichotomized into “good recovery” (GOSE Score 7 or 8) and “disability” (GOSE score ≤ 6). Individuals with good recovery had resumed a preinjury level of occupational and social function, although complaints may have been present, and even affected daily life (GOSE Score 7). Another point of dichotomization was between “poor outcome” (GOSE score ≤ 4) or “favorable outcome” (GOSE Score 5–8; individuals independent in daily activities).

Statistical Analysis

Patient demographics and injury characteristics are presented as percentages, mean ± SD, median with IQR (25–75%), or range. The GCS and GOSE scores were analyzed using nonparametric tests due to lack of normal distribution of data. We used the Kruskal-Wallis test for analysis of medians in > 2 groups, followed by the Mann-Whitney U-test. The chi-square test was used for comparison of proportions. The Student t-test was used for comparisons of mean age. The relationship between GCS and GOSE scores was explored using the Spearman rank correlation test. The relationship between DAI and outcome was analyzed using multiple logistic regression with GOSE dichotomized into “good recovery” or “disability” as the dependent variable and DAI and age as covariates. An interrater reliability analysis was performed using the linear-weighted Kappa statistic to determine consistency among raters. We adopted the Altman guidelines in which κ values < 0.20 are considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and > 0.81 very good.

Available case analysis was used for the analyses of the variables with missing data, which never exceeded 5 cases. The precision of the estimates was assessed with 95% CIs. All tests were considered statistically significant at p < 0.05. The statistical analyses were performed using the statistical software SPSS for Windows, version 16.0 (SPSS Inc.) and StatXact 8 (Cytel Inc.).

**TABLE 1: Magnetic resonance imaging–based classification of DAI**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>traumatic lesions confined to the lobar white matter or cerebellum only</td>
</tr>
<tr>
<td>2</td>
<td>traumatic lesions in the corpus callosum, w/ or w/o lesions in the lobar white matter</td>
</tr>
<tr>
<td>3†</td>
<td>traumatic lesions in the brainstem in areas typical of DAI (dorsolateral quadrant of the upper brainstem, superior cerebellar peduncles) w/ or w/o lesions in the lobar white matter or corpus callosum</td>
</tr>
</tbody>
</table>

* Signal loss compatible with microbleeds (in the gradient echo sequence) or increased signal intensity compatible with tissue edema (in the FLAIR sequences).
† In cases with unilateral superficial brain stem lesions, the lesion was interpreted as a contusion rather than DAI.

![Examples of the 3 stages of DAI using FLAIR MR images.](image_url)
Diffuse axonal injury in head injury: occurrence and outcome

Informed Consent

The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services approved the study. Written informed consent was obtained from the patient or, for individuals underaged or incapacitated, their next of kin. Permission was obtained from the Norwegian Directorate of Health to use data from the deceased without consent from their next of kin.

Results

Patient Characteristics

One hundred and six patients were examined within 4 weeks postinjury (median 8 days, range 1–26 days, IQR 4–14 days). In the remaining 53 patients, MR imaging was performed later or not performed. In patients not examined with early MR imaging, mean age was significantly higher and a higher proportion reported preinjury problems (Table 2). For injury-related variables, no significant differences were found. The 21 patients who died of the head injury are presented separately.

Occurrence of DAI

Diffuse axonal injury was found in 76 patients (72%) and 1 or several contusions were found in 77 (73%). Only 3 patients had no parenchymal lesions, and 2 of these 3 had an epidural hematoma. A combination of DAI and other lesions (contusions and hematomas) was found in 50%. A pattern of “pure DAI” was noted in 23 patients (22%). In all 6 cases of skiing accidents, pure DAI was reported. Patients with DAI lesions were significantly younger, had more severe injuries, and were more frequently injured in traffic accidents than patients without DAI. The frequency of an evacuated mass lesion was also significantly lower in patients with DAI (Table 3).

In patients with severe head injury, a significantly higher frequency of DAI (90%) was found compared with patients with moderate head injury (56%; p = 0.001). A combination of DAI and other lesions was also more common in patients with severe head injury (67%) than in those with moderate head injury (33%; p = 0.001).

Staging of DAI

Twenty-one patients (28%) had Stage 1 DAI, 34 patients (45%) had Stage 2 DAI, and 21 patients (28%) had Stage 3 DAI. In patients with Stage 2 DAI, 94% also had lobar white matter lesions (as in DAI Stage 1). In patients with Stage 3 DAI, 90% also had visible lesions in the lobar white matter (as in Stage 1 DAI) and 90% in the cor-

<table>
<thead>
<tr>
<th>Variable†</th>
<th>MRI Performed W/in 4 Wks</th>
<th>p Value</th>
<th>Early Death From Injury‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>106</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>mean age in yrs (± SD)</td>
<td>28 ± 15.9</td>
<td>38 ± 17.3</td>
<td>0.001</td>
</tr>
<tr>
<td>preinjury problems</td>
<td>13 (12)</td>
<td>18 (34)</td>
<td>0.003</td>
</tr>
<tr>
<td>MOI</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>traffic accident</td>
<td>56 (53)</td>
<td>22 (42)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>fall</td>
<td>37 (35)</td>
<td>24 (45)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>other</td>
<td>13 (13)</td>
<td>7 (13)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>median GCS score (IQR§)</td>
<td>9 (6–12)</td>
<td>8 (4.25–12)</td>
<td>0.44</td>
</tr>
<tr>
<td>HISS category</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>49 (46)</td>
<td>29 (55)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>moderate</td>
<td>57 (54)</td>
<td>24 (45)</td>
<td>0</td>
</tr>
<tr>
<td>pupillary dilation</td>
<td>12 (11)</td>
<td>8 (15)</td>
<td>0.48</td>
</tr>
<tr>
<td>traumatic SAH on CT</td>
<td>60 (57)</td>
<td>32 (60)</td>
<td>0.49</td>
</tr>
<tr>
<td>Marshall CT classification</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (14)</td>
<td>10 (19)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>47 (44)</td>
<td>25 (47)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>13 (12)</td>
<td>3 (6)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>IV</td>
<td>6 (6)</td>
<td>1 (2)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>V (evacuated mass lesion)</td>
<td>23 (22)</td>
<td>13 (25)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>VI</td>
<td>2 (2)</td>
<td>1 (2)</td>
<td>8 (38)</td>
</tr>
<tr>
<td>median GOSE score (IQR)</td>
<td>7 (5–8)</td>
<td>7 (5–8)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

* All results given as number of patients (%) unless otherwise stated. Abbreviation: SAH = subarachnoid hemorrhage.
† For some variables, 1–3 cases had missing data.
‡ Not included in the statistical analyses.
§ IQR = (25th percentile–75th percentile).
T. Skandsen et al.

pus callosum (as in Stage 2 DAI). There were no cases of Stage 3 DAI without other DAI lesions (either lesions in the corpus callosum or in the lobar white matter).

Glasgow Coma Scale Score and DAI

The median GCS score was 9 (IQR 7–10.25) in 22 patients with pure DAI and significantly lower than in 27 patients without DAI (median 12, IQR 11–13; p = 0.001). The GCS score was correlated with outcome (GOSE score) in patients with DAI (r = 0.47; p = 0.001), whereas no such correlation was found in patients without DAI (r = 0.03; p = 0.89). Furthermore, in the patients without DAI, median GCS scores were similar in 9 patients who were disabled (median 13, IQR 9–13) and in 20 patients who had good recovery at 12 months (median 12.5, IQR 11.25–13).

Mass Lesions and DAI

Twenty-three patients underwent operations involving evacuation of a mass lesion, and 52% of these had DAI. Coexistence of DAI was demonstrated in 5 (33%) of 15 patients with an evacuated epidural hematoma, and in 5 (83%) of 6 patients with an evacuated subdural hematoma.

Outcome and DAI

Outcome data were available for 105 patients. One

had died of an unrelated event before any follow-up data was obtained. Patients with DAI had a median GOSE score of 7, and patients without DAI had a median GOSE score of 8, but the difference did not reach significance (Table 3). The median GOSE score was significantly lower in patients with Stage 3 DAI than in patients with Stage 1 or 2 DAI (Table 4). However, no significant difference in GOSE score was found between patients with Stage 3 DAI and patients 1 or 2 DAI. In the entire MR imaging cohort, 17 patients (16%) had a poor outcome, and 16 of these had DAI. As a result, significantly more patients without DAI (97%) experienced a favorable outcome than patients with DAI (79%; p = 0.036).

To determine whether outcome in patients with DAI could be attributed to the subgroup of patients with Stage 3 DAI, we examined cases without any kind of brainstem injury and compared cases with (46 patients) and without DAI (30 patients). In patients without brainstem injury, no difference in GOSE score was found between patients with DAI (7.5, IQR 6–8) and patients without DAI (8, IQR 5.5–8; p = 0.7). Furthermore, a good recovery was found in 67% of patients with DAI and in 66% of patients without DAI (p = 1.0). Finally, because mean age was higher in the patients without DAI, thus representing a possible confounder, we also conducted a multivariable logistic regression analysis of the patients without brainstem injury. After this analysis, greater age was found to be significantly associated with disability, whereas DAI was not (Table 5).

 Interrater Reliability

The interrater reliability of the staging of DAI in 31 cases was very good with a weighted linear χ of 0.84 (95% CI 0.67–1.00; Table 6).
Diffuse axonal injury in head injury: occurrence and outcome

**TABLE 5: Association between DAI and disability in patients without brainstem injury**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>No. W/ Disability* (%)</th>
<th>Unadjusted OR</th>
<th>Adjusted OR†</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>30‡</td>
<td>10 (33)</td>
<td>1.0</td>
<td>1.0</td>
<td>referent</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>46</td>
<td>15 (33)</td>
<td>0.9</td>
<td>1.7</td>
<td>0.5–5.7</td>
<td>0.3</td>
</tr>
<tr>
<td>age</td>
<td>75</td>
<td></td>
<td>1.07</td>
<td>1.03–1.11</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* GOSE Score 1–6.
† Adjusted for age.
‡ Outcome data only available for 29 cases.

**Discussion**

In this prospective cohort study, we found that almost three-quarters of all patients had some degree of DAI, and very often in combination with contusions or hematomas. The level of consciousness was lower in patients with DAI, and only in patients with DAI was GCS score related to outcome. Moreover, DAI was a negative prognostic factor only when located in the brainstem.

To our knowledge, no such study has previously been conducted. Several prospective studies have used MR imaging in consecutive patients and present outcome data, but these may not be suitable for comparison for different reasons. Gentry\(^\text{¹⁰}\) made a substantial contribution to our current knowledge on the distribution of traumatic lesions depicted by MR imaging in head injury, but the MR imaging modalities available at that time were less sensitive. Pierallini et al.\(^\text{²³}\) found a correlation between FLAIR lesion volume and outcome, but MR imaging was performed late. Carpenter and colleagues\(^\text{⁶}\) and Firsching et al.\(^\text{⁶}\) performed MR imaging early in consecutive patients, but did not study DAI specifically. Finally, in a recent study Lagares and associates\(^\text{³⁶}\) found a prevalence of DAI comparable to our findings, but they did not report how patients were selected for MR imaging.

**Occurrence and Staging of DAI**

We found a high frequency of patients with lesions compatible with DAI. Diffuse axonal injury has been shown to be a common type of primary lesion,\(^\text{¹¹}\) but the prevalence of DAI has rarely been reported in survivors of TBI.

In severe head injury, DAI was found in almost every case. This finding corresponds with the results of neuropathological studies, showing DAI in almost all fatal cases.\(^\text{⁸}\) Among the patients with moderate head injuries, 56% were diagnosed with DAI. This finding might not be expected, given the widespread belief that patients with DAI usually present with deep coma,\(^\text{³⁸}\) and that in less severe cases, MR imaging results will often be normal.\(^\text{³⁸}\)

The prevalence of DAI found in the present study may, to some degree, overestimate the true prevalence of DAI in moderate and severe head injury, because the patients who were not examined using MR imaging were somewhat older and more often injured by falls, indicating a higher proportion of focal injuries. We also included only patients ≥ 65 years of age. In older patients, the incidence of DAI would probably be different. Our hospital serves as a Level I trauma center for the whole region and as a local hospital for a part of the region as well. Regarding severe head injury, our data are population-based and representative (of all patients with severe head injury in a region of our country) because almost all patients were registered. However, we cannot exclude that a few patients, without mass lesion, may not have been transferred to the neurosurgical department despite having a severe injury. The findings in the moderately injured patients may also be biased by a selection of patients with hematomas or contusions for transportation from the local hospital to the regional trauma center.

**Glasgow Coma Scale Score**

Patients with DAI had lower GCS scores than patients with other lesions. This fact is in accordance with the observations of Salazar et al.\(^\text{²⁵}\) that in focal lesions, unconsciousness was often of short duration or not observed at all. However, the injuries in this study were penetrating injuries. Interestingly, we found that in patients with DAI, a low GCS score was negatively related to outcome, but not in patients with other lesions only. To our knowledge, this discrepancy has not previously been reported, and this fact could partly explain why the correlation between GCS score and outcome has been weak in some studies.\(^\text{⁷}\) Furthermore, this discrepancy demonstrates that in more focal injuries, prognostic factors other than the GCS score need to be evaluated.

**Mass Lesions and DAI**

One-third of patients who had an epidural hematoma evacuated also had DAI lesions, and in patients who underwent operations involving evacuation of a subdural hematoma, coexistence of DAI was very common. This is important information for neurosurgeons, because both the mass lesion and DAI may contribute to the reduction of consciousness observed in these patients.

**Diffuse Axonal Injury and Relation to Outcome**

As a whole, patients with DAI had a worse outcome...
with a higher proportion of poor outcomes. A poor outcome was rare in patients without DAI. The patients with Stage 3 DAI, however, demonstrated a very high rate of disability, and when cases with brainstem injuries were removed from the analysis, patients with DAI did not show a worse outcome. We infer from these results that the worse outcome initially found in patients with DAI most likely is explained by the worse outcome found in cases with Stage 3 DAI. Consequently, the present study indicates that the mere presence of DAI lesions is not a negative prognostic factor if DAI is not affecting the brainstem. This may be in contrast to the common belief, as recently stated in a review, that “DAI is a common cause of poor outcome.”

Unquestionably true, but this view might be balanced by the fact that DAI is also frequent in patients who recover well.

Also surprising was the fact that we found no significant difference in outcome between Stage 1 and Stage 2 DAI, and a good recovery was common in both groups. In a frequently cited study, Kampfl et al. found that callosal injury and brainstem injury both independently predicted permanent vegetative state in 80 severely injured patients. They did not apply FLAIR or gradient echo MR imaging, however, and direct comparison of their results is difficult because they did not report the number of patients with Stage 2 DAI only. Furthermore, permanent vegetative state is a rare outcome after TBI, and thus, their sample is highly selective and not representative of the majority of patients with traumatic callosal lesions.

In the present study, in general, patients with Stage 3 DAI also had lesions in the corpus callosum and the hemispheres, and those with Stage 2 DAI also had lesions in the hemispheres. Thus, our results support the Ommaya and Gennarelli model with successive involvement of more central and deeper brain structures as the load of impact increases. However, our data regarding outcome in Stage 1 and 2 DAI do not support an understanding of a linear increase in clinical severity that might be inferred from the neuropathological grading.

Study Limitations

Limitations of the study are those associated with the lack of a standardized procedure for detection and classification of MR imaging lesions. The MR images were reviewed by 2 experienced neuroradiologists, and any disagreement was resolved by consensus. Ideally, the radiologists should have been blinded to clinical information. In the present study, this was not possible due to required cooperation with neurosurgeons during treatment of the patients. Thus, we performed an analysis of interobserver agreement in a subset of the patients, and the \( \kappa \) value indicated sufficient reliability of the procedure.

Moreover, FLAIR lesions tend to attenuate over time, and it would have been preferable if the time from injury to imaging was equal in all cases and performed even earlier. This is not possible in a clinical cohort due to medical and logistic reasons. Thus, we cannot exclude the possibility that some nonhemorrhagic lesions may have been missed in patients examined close to 4 weeks after injury.

There were several strengths to the study. The sample size was relatively large compared with many other MR imaging studies. Furthermore, the prospective data collection assured reliable injury-related data and also a comprehensive overview of all eligible patients. The very high participation rate in the database and a loss to follow-up near 0 were also strengths of the study.

Conclusions

We conducted a prospective study of early MR imaging findings, with emphasis on DAI and outcome in a fairly representative sample of neurosurgical patients with moderate and severe head injuries who survived the acute injury phase. We used a clinical approach with visual inspection of the MR imaging results to study the frequency of DAI in typical head injuries treated in neurosurgical departments. Diffuse axonal injury was found in more than half of the patients with moderate injuries, and in 9 of 10 patients suffering a severe injury. Diffuse axonal injury was also found in nearly half of the patients who underwent operations for mass lesions. An unexpected finding was that GCS score was related to outcome only in patients with DAI. This finding indicates that in subgroups of patients with head injury, prognostic factors may act differently, and this fact might be important in the design of future studies. Diffuse axonal injury lesions in the brainstem were associated with a worse outcome. Otherwise, DAI, or a location in the corpus callosum, was not a negative prognostic factor.

Disclosure

Drs. Skandsen and Solheim have received a research grant from the liaison committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology—Dr. Skandsen during the whole study period, and Dr. Solheim during the period of manuscript preparation.

Acknowledgments

The authors thank Jana Rydland for review of the MR imaging scans in the reliability analysis, Beate Holmqvist Karlsen and Brit Sørum for participation in the management of the database and the GOSE interviews, Kent Geran Moen for his work with the data files, residents at the neurosurgical department for collection of some of the injury-related variables, and the staff at the MR imaging unit for their cooperation with the MR imaging examinations.

References

5. Carpentier A, Galanaud D, Puybasset L, Muller JC, Lescot T, Boch AL: Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect “in-
Diffuse axonal injury in head injury: occurrence and outcome

visible brain stem damage” and predict “vegetative states.” J Neurotrauma 23:674–685, 2006

Accepted September 14, 2009.
Please include this information when citing this paper: published online October 23, 2009; DOI: 10.3171/2009.9.JNS09626.
Address correspondence to: Toril Skandsen, M.D., Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway N-7006. email: toril.skandsen@ntnu.no.