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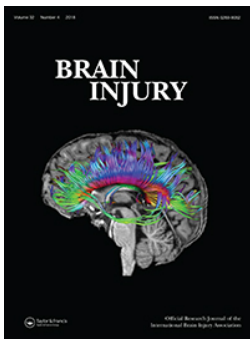
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Diffuse axonal injury after traumatic brain injury is a prognostic factor for functional outcome: a systematic review and meta-analysis

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ABSTRACT

Objective: To determine the prognosis of adult patients with traumatic brain injury (TBI) and diffuse axonal injury (DAI).

Methods: Online search (PubMed, Embase and Ovid Science Direct) of articles providing information about outcome in (1) patients with DAI in general, (2) DAI vs. non-DAI, (3) related to magnetic resonance imaging (MRI) classification and (4) related to lesion location/load. A reference check and quality assessment were performed.

Results: A total of 32 articles were included. TBI patients with DAI had a favourable outcome in 62%. The risk of unfavourable outcome in TBI with DAI was three times higher than in TBI without DAI. Odds ratio (OR) for unfavourable outcome was 2.9 per increase of DAI grade on MRI. Lesions located in the corpus callosum were associated with an unfavourable outcome. Other specific lesion locations and lesions count showed inconsistent results regarding outcome. Lesion volume was predictive for outcome only on apparent diffusion coefficient and fluid attenuation inversion recovery MRI sequences.

Conclusions: Presence of DAI on MRI in patients with TBI results in a higher chance of unfavourable outcome. With MRI grading, OR for unfavourable outcome increases threefold with every grade. Lesions in the corpus callosum in particular are associated with an unfavourable outcome.

Introduction

The prognosis of patients with traumatic brain injury (TBI) is complicated by the fact that outcomes highly depend on the location, the type and the severity of the injury. High-impact trauma with acceleration–deceleration forces, especially rotational acceleration, can lead to stretching and deformation of the brain tissue, resulting in diffuse axonal injury (DAI) (1), (2). In autopsy studies, DAI has been found in 100% of the fatal cases of severe TBI (Glasgow Coma Score (GCS) 3–8) (3). DAI has also been described in surviving patients with moderate or severe TBI DAI (4,5). The characteristic of deep petechial haemorrhages in DAI can be shown with magnetic resonance imaging (MRI) (6). In patients with mild TBI, white matter changes in predilection sites for DAI can be found with diffusion tensor imaging (DTI) (5).

Staging of DAI is based on a neuropathological study performed by Adams et al. (7). In vivo MRI is superior to computed tomography in visualization of DAI. Three stages can be distinguished on MRI: (1) visible lesions in the lobar white matter, (2) lesions in the corpus callosum and (3) lesions in the brainstem (6).

Literature is inconsistent regarding the prediction of outcome in TBI patients with DAI. One of the problems is the lack of a worldwide consensus on the definition and classification of DAI, and another problem is the heterogeneity of patients. TBI research is often done in patients with TBI of various severities, and patients with DAI are usually only a subgroup of the included patients. Conclusions regarding outcome prediction for patients with DAI may also be affected by other elements of study design, such as inclusion criteria, MRI field strength, performed sequences, and timing of the MRI. Therefore, results are difficult to compare; for example, one study reported that only stage 3 was related to an unfavourable outcome, whereas DAI stages 1 and 2 were not related to outcome (4). Conversely, another study found a good correlation of stages 2 and 3 with a vegetative state (8). Another study found that lesions in the genu of the corpus callosum were associated with unfavourable outcome after 1 year, although these lesions were not specified in the three-grade MRI rating scale (9). Because of these inconsistent results, predicting outcome in patients with TBI and DAI is a particular challenge in clinical practice.

Our main objective was to determine the functional prognosis, as measured with the Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale-Extended (GOSE), in adult patients with TBI and DAI. To ensure the most informed

answer, we performed a systematic review. This information can support clinicians in providing information to patients with DAI and/or their families, and it can support clinical decisions concerning treatment.

We firstly hypothesized that patients with a higher grading of DAI will have a more unfavourable outcome. Second, we hypothesized that outcome is related to lesion volume and location.

Methods

Search strategy

On 6 January 2015, an electronic database search was performed in PubMed, Ovid Embase and Science Direct. Synonyms for DAI were used as search terms, and MRI was added as a compulsory term. Finally, outcome was added, which could also be defined as prognosis, modified Rankin score, Glasgow Outcome Score or quality of life. The exact search syntaxes are presented in online supplementary table. No limitations were placed on the search. A reference check of the included articles was performed to ensure a complete selection of articles.

Selection criteria

Studies were included if they reported outcome (GOS/GOSE) in adult patients with TBI and DAI diagnosed by MRI [fluid attenuated inversion recovery (FLAIR), T2* gradient echo imaging (T2*GRE), susceptibility weighed imaging (SWI) or diffusion weighed imaging (DWI)], all magnetic field strengths. Since the definition of DAI is inconsistent in literature, we limited the inclusion of studies to DAI confirmed by MRI. By including the different sequences and MR field strengths, we still ensured a broad inclusion of studies describing outcome in patients with DAI.

Since DAI can occur after mild, moderate and severe TBI, we included all severities of TBI. Length of follow-up was no exclusion criterion, again to ensure the completeness of information. Besides, since TBI patients with DAI often also have other types of brain injury, this review included studies on patients with pure DAI, as well as studies on patients with DAI in combination with other types of TBI. Including studies on all patients with DAI provided complete and clinically relevant information about prognosis in these patients. However, articles were excluded if they described outcome of patients with TBI including patients with DAI, but did not provide outcome results for patients with DAI separately.

We only included peer reviewed, published articles in English, Dutch or German, no publication date was excluded. All research designs were included except review articles and case reports (<5 patients). Reviews were excluded to prevent bias by double count of a patient population, and case reports were excluded because the results can often not be generalized to a larger population. Studies performed only in children were excluded, and studies on adults and children in which outcome of adults could not be distinguished from outcome of children were excluded if the majority of patients was 16 years or younger.

Article selection

After filtering out duplicates, the titles and abstracts of the remaining articles were screened, using the following selection criteria: (1) patients with TBI and with DAI as diagnosed by MRI, (2) prognosis as outcome measure and (3) original data. Articles that fulfilled these criteria were retrieved, and full texts were assessed for inclusion or exclusion. Case reports (<5 patients included) and postmortem research were excluded. If several articles reported on the same patient population, the most relevant article concerning prognosis in patients with DAI was selected. In case of any doubt, the decision on in- or exclusion of articles was reached through discussion and mutual consensus (M.E. and G.R.).

Data collection and quality assessment

Of all the included articles, data were extracted using a standardized form. The following variables were collected: total number of patients, number of DAI patients, age, DAI grading, MRI: timing, field strength and used sequences, follow-up period, outcome for all patients and outcome for DAI patients.

The GOS is a 5-point scale for functional outcome, ranging from 1 = death to 5 = good recovery. The GOSE is an 8-point scale, ranging from 1 = death to 8 = good recovery (6,10). Both the dichotomized and, if available, the complete scores were extracted. We dichotomized the GOS and GOSE into favourable outcome (GOS 4–5 or GOSE 6–8) and unfavourable outcome (GOS 1–3 or GOSE 1–5). This dichotomization was chosen to include the maximum number of high-quality articles in the meta-analysis.

All studies were assessed for quality and risk of bias. For observational studies, no standardized system for quality control is available. We used the STROBE criteria to evaluate the quality of observational studies (11). STROBE is a list of 22 items, which should all be fully reported and comprehensively explained for the article to be of high quality. We scored each item 0 if it was not present or insufficient and 1 if present, hence a maximum of 22 points could be awarded. High quality was defined as a score of ≥19 with prospectively collected outcome measurements. The high-quality articles were included for meta-analysis.

Data analysis

The included articles were assigned to at least one out of four categories: (1) outcome of patients with DAI in the acute and subacute phase (including all the selected articles), (2) outcome in patients with TBI without DAI compared to patients with DAI (including only high-quality articles), (3) outcome of patients with DAI according to MRI grading (grade 1–3) (including only high-quality articles) and (4) outcome of patients with DAI according to other MRI scales, number or distribution of lesions (including all the selected articles).

Analysis according to categories 1–3 was prespecified. However, we found a number of articles that did provide information concerning DAI and prognosis but did not use the MRI grading Gentry et al. described (6). These articles

were described in a fourth category without statistical analyses.

Data were pooled if similar DAI descriptions and outcomes were reported. Articles not suitable for pooling were described.

Absolute risks and odds ratios (OR) and associated 95% confidence interval (CI) were collected. For pooled articles, an OR and associated 95% CI was calculated.

Statistical analysis was performed using IBM SPSS Statistics 19. A p-value of ≤ 0.05 was considered statistically significant.

Results

Of a total number of 902 articles found after entering the search syntax (446 PubMed, 392 Ovid Embase, 64 Science Direct), 164 duplicates were extracted, resulting in 738 remaining articles. Title and abstract screening reduced this number to 85 articles selected for full-text screening, which resulted in 30 relevant articles. A reference check of these 30 articles identified two additional articles, resulting in 32 articles being included in this review. Flowchart 1 describes the selection process and the reasons for exclusion.

The results for categories 1–3 are summarized in Table 1. Data extraction and quality assessment of the 32 included articles are presented in online supplementary table 4.

Outcome DAI in general

In this first category, all patients with DAI were included to determine the prognosis for this entire group of patients. Articles describing outcome in patients with DAI in the acute and subacute phase after injury were included, which resulted in 13 articles describing a total of 549 patients with a mean age of 33.5 years (4,9,12–22). DAI was present in 449 patients, and an unfavourable outcome was found in 38% ($n = 169$, 95% CI 0.33–0.42).

The field strength of the MR scanners differed: two studies used a 1.0 T scanner (19,23), two studies did not describe MRI field strength (15,17) and the other nine studies used a 1.5 T MR scanner.

One other study described outcome in patients with DAI; however, that study was not included in this analysis because it only included patients in a vegetative state ($n = 42$), in all of these patients DAI was present. None of them recovered from their vegetative state in the follow-up period of 12 months (8).

An imitation–inhibition test performed by Schroeter et al. showed that patients with DAI were impaired 3 years after trauma. The Stroop task was unaltered for these patients (24).

Outcome TBI with DAI versus TBI without DAI

In this category, we aimed to answer the question whether outcome differed between patients with DAI after TBI and
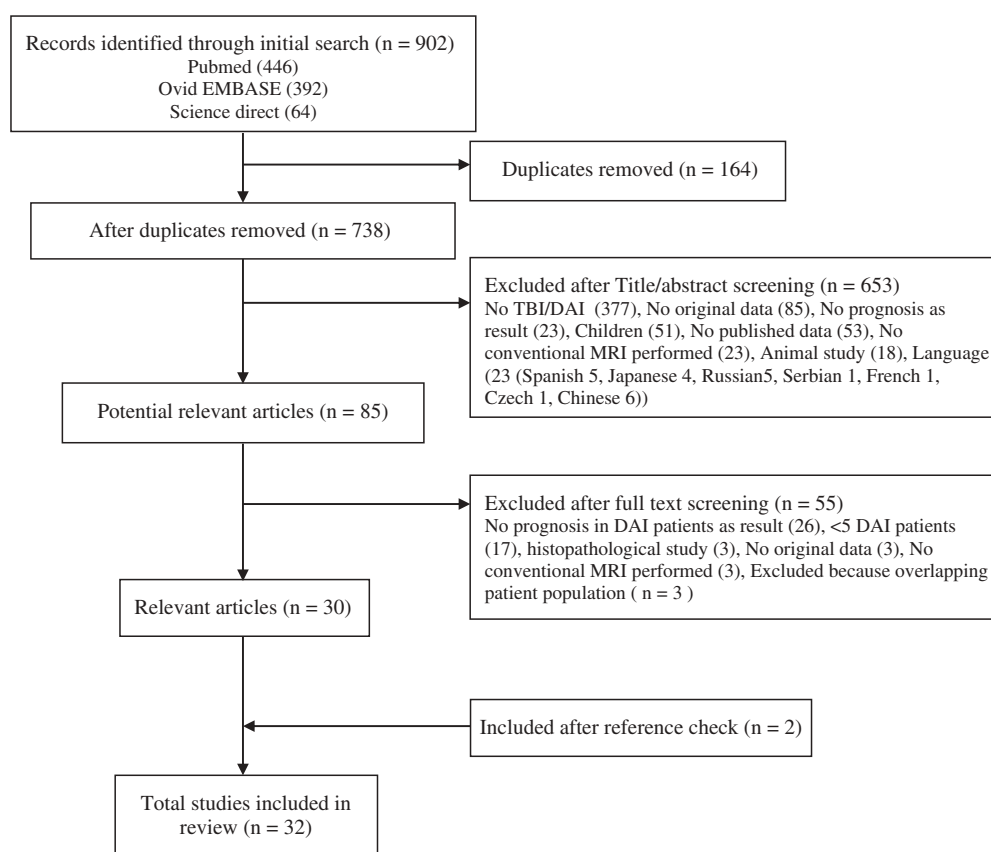
Flow chart 1. Article selection process.
TBI, traumatic brain injury; DAI, diffuse axonal injury; MRI, magnetic resonance imaging

Table 1. Summary of results.

	N	% favourable outcome (95% CI)	OR (95% CI)
DAI in general	395	52 (0.5–0.6)	–
TBI with DAI vs. TBI	– 64	83 (0.7–0.9)	2.9 (1.4–6.0)
without DAI	+ 141	62 (0.5–0.7)	
DAI according to MRI	1 88	83 (0.7–0.9)	2 vs. 1 3.3 (1.7–6.4)
classification	2 107	60 (0.5–0.7)	3 vs. 1 8.5 (4.0–18.0)
	3 63	37 (0.3–0.5)	3 vs. 2 2.6 (1.4–4.9)

N, number of patients; –, diffuse axonal injury absent; +, diffuse axonal injury present; 1, diffuse axonal injury grade 1; 2, diffuse axonal injury grade 2; 3, diffuse axonal injury grade 3; OR, odds ratios; 95% CI, 95% confidence interval; TBI, traumatic brain injury.

TBI patients without DAI. Articles comparing outcomes in patients with TBI and DAI versus patients with TBI but without DAI were scarce. Only two high-quality articles were found and included in the presented analysis (4,15). Three additional articles describing these outcomes were considered to be of low quality and were therefore not included in the analysis (16,18,25).

The high-quality articles described 141 patients with DAI and 64 patients without DAI. Mean age of patients was 30.5 years (range 5–71 years), and the mean follow-up time was 9 months (range 6–12). Of the patients with DAI after TBI, 38% had an unfavourable outcome compared to 17% of the patients without DAI after TBI. The OR for an unfavourable outcome for TBI patients with DAI versus TBI patients without DAI was 2.9 (95% CI 1.4–6.0).

Outcome DAI according to MRI classification

Five articles describing outcome in relation to MRI grading were of high quality and were therefore included in the analysis to determine the prognosis in relation to MRI grading (4,9,12,13,15). Three other articles also described outcome in relation to MRI grading, but due to their lower quality they were not included in the analysis (17,18,26).

The remaining five articles described a total of 258 patients with DAI. Grade 1 was seen in 88 patients, grade 2 in 107 patients and grade 3 in 63 patients. Mean age was 35.3 years, and the MRI was performed after a mean of 19.8 days. An unfavourable outcome was seen in 17% (95% CI 0.1–0.3) of patients with DAI grade 1, in 40% (95% CI 0.3–0.5) with DAI grade 2 and in 63% (95% CI 0.5–0.7) with DAI grade 3.

Table 2 presents the results of outcome related to the three grades. The OR for an unfavourable outcome gradually rises per DAI grade. A continuous OR was calculated. For each

step increase in DAI grade, the OR for an unfavourable outcome is 2.9 (95% CI 2.0–4.2).

Firsching et al. only reported mortality in patients with DAI in relation to MRI grading. One out of 32 patients with DAI grade 1 or 2 died and 8 out of 32 patients with DAI grade 3 died, resulting in an OR of 10.3 (95% CI 1.2–88.4) (27). It must be noted that this study only included patients with a severe TBI with GCS <8.

One other study on 15 patients with DAI grade 1 and 2 found no relation between MRI findings and the total scores on the working memory tests or the attention test (28).

Neither of these two articles could be included in the analyses because neither of them reported the GOS or GOSE. Another study by Chelly et al. (26) on 38 patients with DAI grades 1 and 2 could not be included in the analysis either since outcomes were not described for grades 1 and 2 separately.

Outcome DAI in relation to other MRI scales or distribution of lesions

Outcomes were also described in relation to other types of MRI grading or in relation to number, volume, or location of lesions. Pooling of the data provided by these studies was not possible because of the wide variation of classifications used.

Number of lesions

Several studies described lesion counts on different MRI sequences in relation to outcome. Five articles described a relation between number of lesions and outcome (21,26,29–31), and five other articles found no relation (32-35, 41). Therefore, this relation was not consistently proven throughout literature.

Lesion volume

The relation between lesion volume and outcome prediction was examined by applying several MRI sequences, mostly FLAIR and apparerant diffusion coefficient (ADC). Schaefer et al. found a correlation between volume of lesions on FLAIR, DWI and T2 spin echo and the modified Rankin scale score but they could not find this correlation for the volume of lesions on T2*GRE (29).

White matter DAI volumes in patients after moderate to severe TBI were found to be correlated with functional outcomes at 6-month follow-up. The greater the proportion of the brain volume affected by DAI, the poorer the GOSE scores. A greater lesion volume in the region of the internal/

Table 2. Lesion location and relation to outcome.

Location	Takaoka 2002	Schaefer 2004	Jeong 2010	Scheid 2010	Calvi 2011	Matsukawa 2011	Chelly 2011	Moen 2014
Corpus callosum	–	+	+	–	SL– ML+	+	+	+
Splenium	.	.	+	.	.	.	.	.
Genu	.	.	–	.	.	.	.	.
Basal ganglia	.	–	+	.	.	.	.	.
Brain stem	.	–	+	–	SL– ML+	.	–	+
Midbrain	.	.	.	–	.	.	.	.
Thalamus	.	-	+	.	.	.	.	+
GWM junction cerebrum	.	.	+	.	.	.	.	.

The included articles describing lesion location in relation to outcome regarding: corpus callosum, basal ganglia, brainstem, midbrain, thalamus and grey–white matter (GWM) junction in the cerebrum.
+, a relation between lesion location and outcome was found; –, no relation between lesion location and outcome was found; ., the mentioned lesion location is not described in the article. When distinction between a single lesion (SL) or multiple lesions (ML) was made, this is mentioned.

external capsule region predicted an unfavourable outcome (36). Unfavourable outcome was also predicted by the volume of lesions (MRI <4 weeks) in the corpus callosum, brainstem and thalamus after severe TBI (26). Another study found that global clinical outcome in early MRI was associated with the volume of non-haemorrhagic DAI lesions as well as with the number of DAI lesions (30).

Compared to controls, patients with DAI had significantly different mean ADC values in the peripheral grey and white matter, deep grey and white matter, and posterior fossa. Besides patients with an unfavourable outcome (GOS 1–3) had significantly higher mean ADC values in the deep white matter than patients with a favourable outcome (GOS 4–5) (20).

Location

The location of lesions has often been used as a classification and related to functional outcome. In Table 2, all described locations are summarized. Most studies focused on lesions in the corpus callosum (9,19,29,34,37–40) or other deep brain regions such as the basal ganglia (29,37) or the brainstem (29,37–39,41). Only lesions in the corpus callosum were consistently reported to have a relation with outcome. Six out of seven studies found this relation, in one of these studies only found a relation with outcome when there were multiple lesions in the corpus callosum (Table 2). No consistent relationship between prognosis and other locations of the lesions could be distilled from these articles.

In patients with hypopituitarism after trauma, more lesions were found in the body of the corpus callosum, in the basal ganglia, in the thalamus and in the and grey–white matter junction in the cerebrum structures. Injuries to these structures and hypopituitarism have a relation with an unfavourable outcome, but no definitive pathophysiological basis was found for a causal relationship between hypopituitarism and an unfavourable outcome (37).

Discussion

This systematic review of the literature aimed to summarize the current knowledge on the prognosis of TBI patients with DAI and to establish whether TBI patients with a higher grading of DAI have a more unfavourable outcome and whether outcome in these patients is related to lesion volume and location. Results of 32 included articles showed that the overall functional outcome of patients with DAI was unfavourable in 38%. The presence of DAI resulted in a threefold higher risk of an unfavourable outcome than in TBI patients without DAI: the risk for an unfavourable outcome also increased threefold for each increase in DAI grade. An unfavourable outcome was seen more often in patients with lesions in the corpus callosum, whereas for other locations this relation was inconsistent. The relation between lesion count and outcome was inconsistent as well as the relation between volume and outcome.

Comparison of patients with DAI and patients without DAI showed that the risk for an unfavourable outcome was almost threefold higher in patients with DAI. Overall, however, 62% of patients with DAI had a favourable outcome. Possibly the high percentage of favourable outcome in DAI

patients in general can be explained by the exclusion of patients with other brain injuries and of patients with a high risk of mortality. Among patients with DAI, a higher DAI grade resulted in a higher risk of an unfavourable outcome; nevertheless, it must be noted that a favourable outcome was found in 37% of patients with DAI grade 3. Therefore, the diagnosis of DAI, even grade 3, does not automatically imply an unfavourable outcome.

Contrary to our findings, Adams et al. only found a relation between DAI grade 3 and an unfavourable outcome (7). This difference in results is probably due to the difference between the MRI classification as defined by Gentry et al. and the histopathological grading used by Adams et al. According to the histopathological definition, DAI grade 1 comprises microscopical lesions either in the lobar white matter, the corpus callosum, the brainstem or the cerebellum. However, in the MRI classification, DAI grade 1 only comprises lesions in the cerebral hemispheres, whereas lesions in the corpus callosum are classified as DAI grade 2.

To represent everyday practice, articles were only included if DAI was diagnosed using a conventional MRI technique, whereas articles were excluded if diagnosis only involved DTI or functional MRI. This review focused on the relation between DAI and outcome, but outcome is also influenced by other factors such as pupillary response, GCS, duration of loss of consciousness, age and the presence of dysautonomia (9,26,31,34).

Patients with severe TBI were more likely to have DAI, and they also showed more severe DAI grades. Histopathological lesions in the lobar white matter, in the corpus callosum and in the dorsolateral aspects of the brainstem were related to an increased severity of trauma (7). DAI was diagnosed in 69% of patients with moderate TBI and in 89% of patients with severe TBI (41). DAI grade 3 was found more often in patients with severe TBI than in patients with moderate TBI (30% vs. 20%) (41).

We expected a higher number or volume of lesions to predict an unfavourable outcome, but this could not be confirmed due to inconstancies in the reported results. SWI is more sensitive for the detection of microbleeds than T2*GRE (42). However, the relation between DAI lesions detected with SWI and outcome is not clear. Only one of the included articles reported the use of SWI, but no relation between lesions detected with SWI and outcome was described (35).

Outcome is most often reported with a functional outcome measure, but other outcome measures such as cognitive impairment and quality of life are also relevant. In patients with pure DAI, all cognitive domains can be affected (33). However, a study on a cohort of patients with TBI demonstrated no relation between DAI and cognitive impairment (34). Perhaps this relation was not found because patients also had other intracerebral lesions which had more effect on cognition. Comparison of the studies was hampered by differences in the use of cognitive screening methods, follow-up period and presence of other types of brain injury.

None of the included articles reported patient-reported outcome measures, such as quality of life. Even though providing the patient's experience of outcome is becoming increasingly important.

Limitations

Despite the efforts to provide a complete summary of current literature, it is possible that relevant articles were missed in this review. We aimed to provide a complete overview of the literature by using several synonyms for DAI, MRI and outcome in the search, as well as cross-referencing the references of relevant articles. However, outcome measures in particular differ greatly between studies, and therefore we also included other terms such as 'outcome' and 'prognosis' in our search terms to prevent the missing of other outcome measures than GOS or GOSE (supplementary table). The different outcome measures and follow-up periods impaired the comparison of results.

Selection bias might have been caused by the fact that patients with moderate or severe TBI more often receive additional MRI scanning than patients with mild TBI. Only one article exclusively included patients with mild TBI, while patients with mild TBI were excluded in 13 of the included articles. As a result, patients with moderate to severe TBI and DAI are over-represented in this review. Patients with a more severe TBI are expected to have a less favourable outcome; therefore, this over-representation possibly resulted in a higher percentage of unfavourable outcomes. To reduce this bias in the results, we reported the analysis per DAI grade of the articles with a high STROBE score. An analysis which also included the articles with a lower strobe score resulted in similar risks for a favourable outcome.

The definition of DAI differs throughout all published articles. This review only included articles in which DAI was proven with MRI The MRI field strength and the used sequences differed between articles or were not described The use of an MRI with a lower field strength could have caused DAI lesions to be missed, which may have resulted either in a lower number of patients with DAI or in the attribution of a lower DAI grade. The MRI classification described by Gentry et al. is a widely used and accepted MRI scale, but other types of grading or MRI ratings were used as well (6).

Timing of the MRI after trauma varied from less than 24 h to 36 months, or was not mentioned. This may have influenced results since DAI lesions can disappear over time and haemorrhagic lesions may attenuate. The MRI should preferably be made within a few weeks after trauma in order not to miss valuable information (30).

The future

The results of this review demonstrate clearly that the presence of DAI after TBI is unfavourable in relation to functional outcome. However, the diagnosis of DAI alone is not sufficient to provide accurate prognostic information to patients or their families. DAI grading on MRI helps to indicate the odds of an unfavourable outcome. Other scoring methods than the three-graded Gentry classification have been insufficiently reported to incorporate these into everyday practice. An internationally accepted definition of DAI would facilitate comparison of research. Also, in clinical practice, predicting outcome in patients with DAI would benefit greatly from a prognostic model that includes an imaging scoring system, preferably in combination with clinical predictors.

In the future, predicting outcome may be based on other MRI sequences used to diagnose DAI, such as SWI and DTI. SWI is more sensitive to the number and volume of DAI lesions than the T2* GRE, but the relation of number or volume of DAI lesions on SWI was not proven in this review (43,44).

DTI is used to visualize and calculate white matter tracts (45). It is not yet clear which role DTI might play in everyday practice in the outcome prediction of patients with DAI. Most research on DTI has been done in patients with TBI in general, and results are often not specified for patients with DAI proven on conventional MRI (5,46–48). In patients with DAI grades 1 and 2, the distribution of white matter abnormalities correlated with the results of the neuropsychological tests of working memory and attention (28). Alterations in anisotropy along fibre tracts at predilection sites for DAI have been shown in patients with TBI when conventional MRI was unremarkable. The degree of fractional anisotropy was correlated to the discharge Rankin score (49). Future research should incorporate advanced imaging techniques in relation to neuropsychological impairments.

Conclusion

In patients with TBI and DAI confirmed with MRI, outcome is unfavourable compared to patients without DAI. When DAI is scored using the current MRI scoring system grades 1–3, the odds for an unfavourable outcome increase threefold with every grade.

The number or volume of DAI lesions was not found to predict outcome. As for the location, only DAI lesions in the corpus callosum predicted an unfavourable outcome.

Declaration of interest

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