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ORIGINAL REPORT

BRAIN PATHOLOGY AFTER MILD TRAUMATIC BRAIN INJURY: AN EXPLORATORY STUDY BY REPEATED MAGNETIC RESONANCE EXAMINATION

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Objective: **To explore brain pathology after mild traumatic brain injury by repeated magnetic resonance examination.**
Design: **A prospective follow-up study.**
Subjects: **Nineteen patients with mild traumatic brain injury presenting with Glasgow Coma Scale (GCS) 14–15.**
Methods: **The patients were examined on day 2 or 3 and 3–7 months after the injury. The magnetic resonance protocol comprised conventional T1- and T2-weighted sequences including fluid attenuated inversion recovery (FLAIR), two susceptibility-weighted sequences to reveal haemorrhages, and diffusion-weighted sequences. Computer-aided volume comparison was performed. Clinical outcome was assessed by the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), Hospital Anxiety and Depression Scale (HADS) and Glasgow Outcome Scale Extended (GOSE).**
Results: **At follow-up, 7 patients (37%) reported ≥ 3 symptoms in RPQ, 5 reported some anxiety and 1 reported mild depression. Fifteen patients reported upper level of good recovery and 4 patients lower level of good recovery (GOSE 8 and 7, respectively). Magnetic resonance pathology was found in 1 patient at the first examination, but 4 patients (21%) showed volume loss at the second examination, at which 3 of them reported < 3 symptoms and 1 ≥3 symptoms, all exhibiting GOSE scores of 8.**
Conclusion: **Loss of brain volume, demonstrated by computer-aided magnetic resonance imaging volumetry, may be a feasible marker of brain pathology after mild traumatic brain injury.**

Key words: mild traumatic brain injury; brain concussion; magnetic resonance imaging; Rivermead Post-Concussion Symptoms Questionnaire; Glasgow Outcome Scale Extended.

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INTRODUCTION

Traumatic brain injury (TBI) is a global health problem and one of the most common causes of impaired function and disability, accountable for huge human and economic costs (1). The majority, 70% or more of patients with TBI, have a mild traumatic brain injury (MTBI) with a reported annual incidence of 100–300 per 100,000 inhabitants in Western countries (2). In Sweden, approximately 15,000 patents are admitted to hospital with a diagnosis of MTBI every year, most with a history of an uncomplicated brain concussion with brief loss of consciousness (LOC) and/or amnesia, presenting with a Glasgow Coma Scale (GCS) score of 15 and no clinical or radiological signs of brain injury (3). An increasing proportion of these patients have undergone an acute computed tomography (CT) and been discharged if this and their neurological condition have proven normal. Thus, head CT is now part of standard acute management of adults with MTBI.

Most patients with a MTBI have a favourable outcome (4), something that may be true even when the MTBI is complicated by intracranial haematoma and the need for neurosurgical management (5). There is, however, a subgroup of patients reporting problems that may impact on their social activities and work abilities for 3 months or longer post-injury (6). The labelling, definition, frequency and main determinants of such problems have been studied and debated for a long time and are still subject to debate (7, 8). There is evidence that factors associated with an increased risk for a poor outcome include advanced age (7, 9), female gender (9), psychiatric illness (10, 11), pre-morbid or co-morbid physical problems (11), associated injuries (7, 11) and litigation (4). In contrast, the impact of the brain injury itself after MTBI remains unclear over the longer term. Previous studies have demonstrated that head CT pathology is not a strong predictor of outcome with regard to symptoms or global function according to the Glasgow Outcome Scale Extended (GOSE) (7, 9). Consequently, there is a need for studies utilizing other methods to detect disordered brain structure and function in this area. Magnetic resonance imaging (MRI) is a more sensitive radiological method than CT.

TBI may cause not only focal damage with oedema and haemorrhage, but may also cause widespread damage to microcirculation and nerve cells, known as diffuse axonal injury (DAI) (12). MRI is more accurate in identifying DAI (13, 14). Animal studies have shown that even minimal haemor-

rhages can be detected by MRI immediately after haematoma inception (15). It has also been proven that minimal blood products remain in the brain for at least 7 months and can be visualized by MRI (16). Intracellular oedema in ischaemic injuries can be visualized by MRI as early as 1.5–2.5 min after blood circulation has stopped (17).

Human MRI studies have demonstrated clinically significant DAI after moderate or severe TBI, and its relation to clinical outcome according to the Glasgow Outcome Scale (GOS) (18). Some studies have also demonstrated that DAI may be visualized in patients with MTBI (13, 14), but the prevalence and clinical significance of MRI pathology remain to be clarified. Thus, although these studies demonstrate that DAI may be observed in patients with MTBI, further studies are needed to explore the optimal MRI methods and timing to visualize DAI after MTBI, in order to evaluate its clinical impact.

Another approach in this area is taken in follow-up studies using volume change as an indicator. Repeated MRI has demonstrated a loss of brain volume after TBI, but most of these studies include patients with all degrees of severity (18–20). Some have demonstrated a correlation between volume loss and acute lesion (18) or length of coma (20) and the correlation between atrophy and unfavourable outcome according to GOSE (19). Corresponding studies of patients specifically with MTBI are scarce. In a study of 18 patients diagnosed with brain concussion, Schrader et al. (21) found no MRI pathology on either the acute or follow-up MRI. In contrast, Hofman et al. (22) reported MRI pathology in the acute phase in 12 out of 17 patients, exhibiting atrophy at follow-up after 6 months. However, no correlation between atrophy and the results of cognitive tests could be observed.

While previous studies with small materials provide evidence that MRI may reveal brain pathology in patients exposed to MTBI, there is an obvious need to conduct further studies to explore the prevalence and clinical impact of such pathology, as well as the optimal MRI technique and timing. The aim of this study was to explore intracranial pathology after MTBI, using repeated MRI and computer-aided analyses of brain volume changes, in a prospective study.

MATERIAL AND METHODS

During the period April 2008 to October 2011, 22 subjects were recruited from the Emergency Unit of a University Hospital. The recruitment rate was low because some eligible patients declined to participate, and because the recruitment process was restricted to certain time-periods and days of the week. Inclusion criteria were: age 16–65 years, head trauma within the preceding 24 h with a loss or alteration of consciousness for not more than 30 min, and a GCS score of 13–15 at examination in the Emergency Unit, but otherwise normal findings at a neurological examination. Exclusion criteria were: a previous brain injury, any other neurological or psychiatric disorder causing ongoing disability or treatment, as well as substance abuse and other accompanying injuries needing special treatment. Three of the participants did not undergo the second MRI and were, therefore, excluded, resulting in a final study sample of 19 subjects. MRI, neurological examination and assessment with the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), and the Hospital Anxiety and Depression Scale (HADS) were performed at day 2 or 3 after the injury. Follow-up at 3 months or later included MRI, neurological examination and assessment with RPQ, the Rivermead Head Injury Follow-Up Questionnaire (RHIFUQ), HADS and GOSE.

The local medical ethics committee approved the study plan and all patients received oral and written information about the study and gave their informed consent. No financial incentives were offered.

Radiological methods

Computed tomography. Head CT was not included in the study protocol, but was performed on the day of injury in all except 3 patients, as a part of a post-MTBI standard management procedure.

Magnetic resonance imaging. All magnetic resonance (MR) examinations were performed with the same MR imager, operating at 1.5 T, and using the same imaging protocol. Transverse images were obtained with a T2-weighted spin echo (SE) sequence and a T2-weighted FLAIR sequence, using a slice thickness of 5 mm, an interslice gap of 0.5 mm, and a pixel size of 0.90×1.0 mm. A sagittal 3D series with a T1-weighted gradient echo sequence using a slice thickness of 1.0 mm and a pixel size of 0.90 × 0.90 mm was also obtained, as well as a coronal 3D series with a T2-weighted FLAIR sequence using a slice thickness of 3 mm and a pixel size of 1.3 × 1.3 mm. Two susceptibility-weighted sequences were used. The first sequence was a T2*-weighted gradient echo sequence (FLASH) using repetition time (TR) 500 ms, echo time (TE) 14 ms and a flip angle of 30º. Slice thickness was 3 mm, the interslice gap 0.3 mm and pixel size 0.9 × 0.9 mm in transverse series and 5 mm, 0.5 mm, and 0.9 × 0.7 mm, respectively, in coronal series. The second sequence was a 3D susceptibility-weighted imaging (SWI) sequence taken in a transverse plane using TR 49 ms, TE 40 ms, a flip angle of 15º, a slice thickness of 1.5 mm and a pixel size of 1.1 × 0.9 mm. SWI images were further reconstructed with a minimal intensity projection technique in the form of 12-mm thick transverse slices without gaps, and as transverse and coronal slices using the same slice thicknesses and interslice gaps as in the FLASH images. Diffusion-weighted imaging (DWI) was performed in 3 directions, using a SE echo planar technique with TR 4,600 ms, TE 89 ms, a slice thickness of 5 mm, a pixel size of 1.2 × 1.2 mm and b values of 0 s/mm^2 and 1000 s/mm^2. Trace images and apparent diffusion coefficient (ADC) maps were used for analyses.

All CTs were reviewed and all MR images visually analysed by a single experienced neuroradiologist who did not know the patient's outcome. The T1-weighted 3D series were also analysed with the help of a computer-aided volume comparison method developed from already existing ideas on voxel-based morphometry (23). It works by registering the first MRI of the patient to the second MRI using affine transformations, i.e. transformations that preserve straight lines and ratios of distances between points lying on a straight line. Once the two volumes are properly aligned, the program subtracts the first MRI (assumed to be the fixed-volume, or base) from the volume created by the registration. The result is another volume that indicates which voxels have changed the most according to the subtraction values.

Outcome measures

Rivermead Post-Concussion Symptoms Questionnaire. The RPQ (24) is a questionnaire designed to measure the severity of symptoms following mild or moderate traumatic brain injury. The RPQ comprises 16 items asking the patient about the degree of experienced headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed/tearful, feeling frustrated/impatient, forgetfulness, poor concentration, slowed-down thinking, blurred vision, light sensitivity, double vision, and restlessness over the previous 24 h compared with before the head injury. The items are rated on a 5-point scale, with the response alternatives: 0 = not experienced at all, 1 = no longer a problem, 2 = a mild problem, 3 = a moderate problem, and 4 = a severe problem. According to results from an earlier study on RPQ with Rasch analysis, in which we found multidimensionality and category dysfunction, we chose to not report

differentiated scores or sum scores (25).We used a report of 3 or more symptoms at 3 months to indicate persistent problems, in accordance with prior suggestions (26, 27).

Hospital Anxiety and Depression Scale. The HADS was developed to assess states of anxiety and depression (28) and consists of 14 items with ratings ranging between 0 and 3. The scale allows calculation of sub-scores to estimate the level of anxiety and of depression. A sub-score of 0–6 corresponds to an absence of anxiety/depression, 7–10 to mild-moderate anxiety/depression, and > 10 to a state of severe anxiety/depression.

Rivermead Head Injury Follow-Up Questionnaire. The RHIFUQ was developed to assess outcomes on activity and participation levels after mild to moderate brain injury. Changing ability to perform different activities for 10 items is rated 0–4 on the following scale: 0 = no change, 1 = no change but more difficult, 2 = a mild change, 3 = a moderate change, 4 = a very marked change. The scale has evidenced adequate reliability and validity to assess outcome after mild to moderate TBI (29).

Glasgow Outcome Scale Extended. The GOSE (30) is an ordinal 8-level scale assessing global outcome after TBI: 1 = dead, 2 = vegetative state, 3 = lower severe disability, 4 = upper severe disability, 5 = lower moderate disability, 6 = upper moderate disability, 7 = lower good recovery, and 8 = upper good recovery. The GOSE covers aspects of personal care and social functioning and has demonstrated good inter-rater reliability and content validity (31). The GOSE has been shown to be more sensitive to change after mild to moderate TBI in comparison with the GOS (32).

Statistics

This exploratory study reports frequencies, proportions, median and mean values. For RPQ and RHIFUQ, ratings were dichotomized into ratings in 2 ranges, 0–1 vs 2–4.

RESULTS

Demographic and injury data are summarized in Table I. Age ranged from 17 to 63 years (mean 34, median 28 years) and 12 out of 19 subjects were women. The mean and median educational years were 12 (range 9–18 years). Pre-injury morbidity was reported by 7 patients (4 with chronic pain, 2 with prior depression with no current need for treatment, and 1 with diabetes, renal failure and liver cirrhosis). Seventeen patients presented a GCS score of 15 and 2 exhibited a score of 14. The estimated duration of loss of unconsciousness ranged from 0 to 15 min (median approximately 1 min) and the estimated post-traumatic amnesia (including both retrograde and antegrade traumatic amnesia) ranged from 0 to 600 min (median 15 min). Routine neurological examinations revealed no impairments either at 2–3 days after MTBI or at follow-up.

Table I. *Demographic and injury data of the study sample*

	n
Gender	
Men	7
Women	12
Working status	
Working full-time	7
Working part-time	5
Studying	5
Retirement	1
Other	1
Cause of accident	
Fall	10
Traffic accident	6
Other	3
GCS at emergency unit	
GCS 14	2
GCS 15	17

GCS: Glasgow Coma Scale.

Computed tomography

No cranial or intracranial changes consistent with a recent trauma could be seen in 15/16 patients examined with CT. In one patient, there was a very slight suspicion of a minimal amount of subarachnoid blood or calcification in one parietal sulcus.

Magnetic resonance imaging

The first MRI was performed on day 2 in 3 cases and on day 3 in 16 cases. The second MRI was performed after 3–7 months (with a mean of 4.4 months). The first examination revealed pathology related to a recent trauma in one patient (patient 1), the same patient who had uncertain subarachnoid blood on CT. His left hippocampus was oedematous with an increased T2 signal intensity (Fig. 1a–b) and mixed, both increased and decreased, diffusion. At follow-up, that hippocampus had shrunk

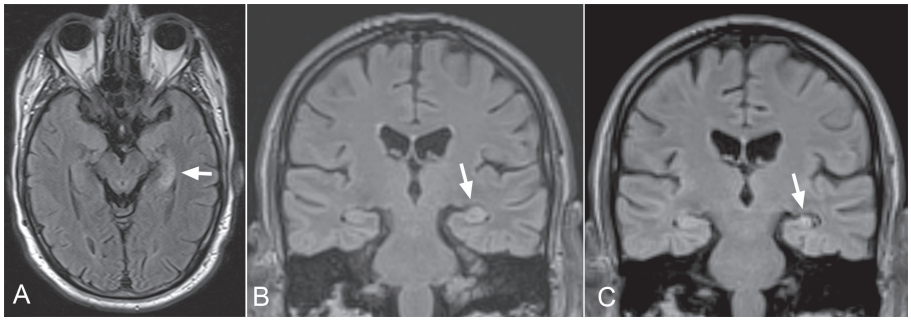

Fig. 1. Patient with hippocampal injury (patient 1). In the first examination, the left hippocampus (arrow) is oedemic: it is enlarged and shows high T2 signal intensity. (A) Axial and (B) coronal slices with a fluid attenuated inversion recovery (FLAIR) sequence. (C) In the second examination, the left hippocampus is shrunken and has a high T2 signal intensity.

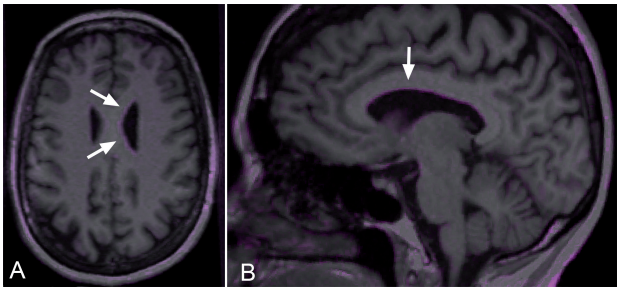

Fig. 2. Volume loss in the corpus callosum demonstrated by the computer-aided volume comparison method (patient 2). Volume loss is marked by red colour in the roof of the left lateral ventricle. (A) Axial image. (B) Sagittal image.

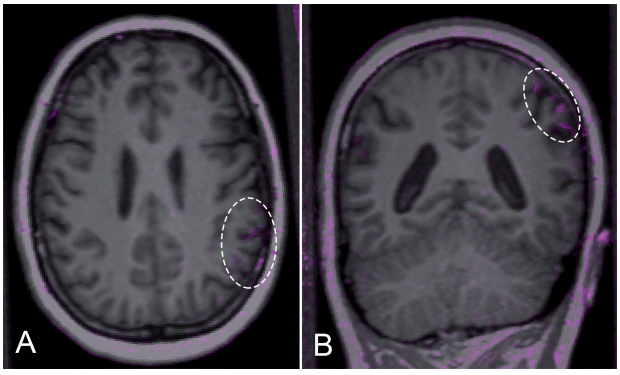

Fig. 3. Volume loss in left parietal gyri (patient 3). (A) Axial image. (B) Coronal image.

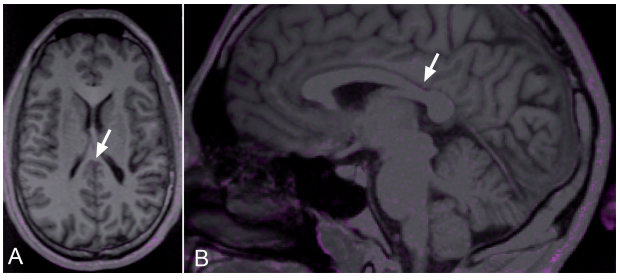

Fig. 4. Slight focal widening between the corpus callosum and the posterior cingulum (patient 4). (A) Axial image. (B) Sagittal image.

and showed a high T2 signal intensity (Fig. 1c) and high diffusion. No visually detectable changes had developed during the follow-up in the other 18 patients. The computer-aided volume comparison revealed mild focal substance loss in 3 additional patients. In the first of them (patient 2), the loss of parenchyma was localized in the corpus callosum (Fig. 2), while in the second patient (patient 3), it was localized in some gyri in the left lower parietal lobe (Fig. 3). In the third patient (patient 4) a slight focal, but bilateral, sulcal widening between the corpus callosum and the posterior cingulum was found (Fig. 4). In 14 patients, the computer-aided method did not detect any loss of substance. In two cases, the co-registration of the two examinations was suboptimal and the results could not be interpreted. One of these two patients was the patient with the hippocampal injury (patient 1) and visible substance loss described above.

Symptoms according to Rivermead Post-Concussion Symptoms Questionnaire

During the first assessment (2 or 3 days after the injury), 17 of the patients (89%) reported ≥3 symptoms. At follow-up, 7 patients (37%) reported ≥3 symptoms. The most common symptoms on both occasions were headache and fatigue.

Hospital Anxiety and Depression Scale

States of anxiety and depression are shown in Table II. The two patients with severe anxiety and/or mild to moderate depression at follow-up also reported a significantly greater number of lasting symptoms (8 and 16 remaining symptoms in RPQ, respectively) compared with a mean number of symptoms of 1.82 (median 1) in the other patients. The two patients with previous episodes of depression reported no anxiety or depression either at first investigation or at follow-up.

Rivermead Head Injury Follow-Up Questionnaire

At follow-up, 14 of the patients reported no change regarding activity and participation according to RHIFUQ, 4 reported changes in 1–3 items and 1 reported changes in 8 of the 11 items. There was a correlation between scoring a high number of changes in RHIFUQ and a high number of remaining symptoms, as well as having severe depression at follow-up.

Glasgow Outcome Scale Extended

At follow-up, 15 patients had a GOSE score of 8 and 4 had a GOSE score of 7.

Relationship of the magnetic resonance imaging findings and outcome

The patient with the hippocampal changes in the acute phase and at follow-up (patient 1) reported 4 symptoms (dizziness, nausea, fatigue and poor memory) in the first RPQ, but only 1 symptom (fatigue) at follow-up. The patient with a loss of parenchyma around the roof of the left lateral ventricle (patient 2) reported 8 symptoms (headaches, nausea, sleep disturbance, fatigue, irritability, frustration, poor memory and longer to think) in the first RPQ and 1 symptom (headaches)

Table II. *States of anxiety and depression according to the Hospital Anxiety and Depression Scale (HADS)*

	Ratings		
	None *n*	Mild to moderate *n*	Severe *n*
Anxiety			
Examination 1	17	0	2
Examination 2	13	3	2
Depression			
Examination 1	15	3	1
Examination 2	18	1	0

at follow-up. The patient with a volume loss in the left lower parietal lobe (patient 3) reported 13 symptoms (headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, longer to think and restlessness) in the first RPQ and 6 symptoms (headaches, noise sensitivity, sleep disturbance, irritability, poor memory and double vision) at follow-up. The patient with a slight focal sulcal widening between the corpus callosum and the posterior cingulum (patient 4) reported 6 symptoms (headaches, dizziness, nausea, fatigue, irritability and depression) in the first RPQ, but no remaining symptoms at follow-up. None of them reported any anxiety or depression according to the HADS at follow-up.

Patient 1 with the hippocampal injury reported change in 2 out of 10 items regarding activity and participation according to RHIFUQ, while patients 2–4 reported no changes. All 4 patients reached upper level of good recovery according to the GOSE (i.e. score 8). Data regarding patient 1–4 are summarized in Table III.

DISCUSSION

This exploratory study included patients who fulfilled established criteria for MTBI and exhibited a typical response pattern with respect to long-term outcome. MRI, according to a study protocol that included DWI and two susceptibility-weighted sequences, revealed one trauma-related abnormality in the acute stage and at follow-up 3–7 months later. The computer-aided analyses of volume changes showed the loss of brain parenchyma in 3 additional patients. In total, the MR examinations detected atrophic changes in 4 patients. It should be pointed out that the study sample was small and the findings cannot be generalized. Data in the literature in this respect are scarce and inconsistent, but some previous reports indicate that an even more limited MRI protocol than that applied here (14, 33) may reveal traumatic pathology after MTBI. The interpretation of our observations will be discussed first with regard to the characteristics of the study sample and then with regard to the MRI methodology.

Study participants appear to be representative of the milder MTBI spectrum with regard to age and presentation of symptoms (2, 6, 27). We observed a certain occurrence of anxiety and depression, which are recognized, common co-morbidities or outcomes related to MTBI (10). Although the study design does not allow any conclusions to be drawn, interestingly, anxiety/depression according to HADS correlated with remaining symptoms according to RPQ and with activity and participation according to RHIFUQ. A somewhat larger proportion of women than expected (2, 27) participated, which may reflect a random effect, or that women perhaps are more prone to accept participation in studies that may be perceived as demanding. In fact, our study required not only an early visit after the injury, but also a later follow-up visit; both included not only clinical assessments but also MR examinations. The higher proportion of women may have increased the frequency of symptom-reporting at follow-up (10, 27). However, the small sample size does not allow any conclusions to be drawn on gender effects.

The majority of participants were examined by routine acute CT. Only one patient had uncertain trauma-related pathology, while the remaining 15 were uncomplicated in that respect. This finding is in accordance with a frequency of CT pathology to be approximately 5% in the mild part of the MTBI severity

Table III. *Characteristics of patients with signs of brain atrophy*

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	54	53	45	24
Gender	Male	Female	Female	Male
Cause of accident	Traffic	Fall	Fall	Traffic
GCS	15	15	15	15
LOC, min	2	<5	5–10	<1
RPQ 1, symptoms, first occasion, *n*	4 – dizziness, nausea, fatigue, poor memory	8 – headaches, nausea, sleep disturbance, fatigue, irritability, frustration, poor memory, longer to think	13 – headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, longer to think, restlessness.	6 – headaches, dizziness, nausea, fatigue, irritability, depression
RPQ 2, symptoms, second occasion, *n*	1 – fatigue	1 – headaches	6 – headaches, noise sensitivity, sleep disturbance, irritability, poor memory, double vision	0
HADS 1 anxiety/depression at first occasion	No anxiety/no depression	No anxiety/no depression	No anxiety/mild depression	No anxiety/no depression
HADS 2 anxiety/depression at second occasion	No anxiety/no depression	No anxiety/no depression	No anxiety /no depression	No anxiety/no depression
RHIFUQ, variables with limited ability, *n*	2 – harder to keep standard of housing, work is tiring	0	0	0
GOSE	8	8	8	8

GCS: Glasgow Coma Scale; LOC: loss of consciousness; RPQ: Rivermead Post-Concussion Symptoms Questionnaire; HADS: Hospital Anxiety and Depression Scale; RHIFUQ: Rivermead Head Injury Follow-Up Questionnaire; GOSE: Glasgow Outcome Scale Extended.

spectrum (9, 34). However, congruent with earlier studies (7, 9), all had favourable outcomes according to GOSE.

The time increments chosen for the early and late MRI were carefully considered, taking into account the results of previous studies and clinical experience. The first time-point, i.e. on days 2 or 3 post-injury, was considered optimal in order to detect any oedema or haemorrhage, which may not be visible at the day of injury, but which may evolve during the initial days post-injury and also may wear off within 1 week. The late time-point, i.e. at 3 months or longer post-injury, would allow for atrophy to develop and be visualized. In addition to conventional sequences, MRI comprised DWI and two blood-sensitive sequences to capture early signs of DAI (35).

Earlier studies have reported the presence of MRI pathology after MTBI even in patients with normal head CT (13, 33). Compared with the present study, these studies probably included more severely injured patients at trauma centres or neurosurgical units presenting with GCS range of scores 13–15. In one study on patients with MTBI and GCS 13–15, microhaemorrhages were found in 1 of 20 patients (36). In the present study we also found pathology in 1 patient in the form of oedema at an acute stage. Some previous studies that applied both early (within 7 days after injury) and late (3–8 months) MRI demonstrated the development of atrophy after TBI (18, 19, 22) and that such atrophy may be correlated with early MRI pathology. Several of these earlier reports are based on studies of small samples and have also included participants with more severe TBI. Furthermore, the time between injury and MR examinations varies between studies and, thus, the interpretation of these data is difficult (37). The results of two specific MTBI studies are inconsistent. In a study of 17 subjects with GCS 13–15, Hofman et al. (22) reported atrophy in the form of increased ventricle-to-brain ratio, in patients (n 12) with acute MRI pathology. In contrast, Schrader et al. (21) found no atrophy or any other pathology in 18 patients diagnosed with concussion. It may be speculated that reasons for the discrepancy between these two studies include the use of a weaker MR-imager (1.0 T) and less severely injured patients in the study by Schrader (21). Interestingly, our study demonstrated volume loss in some patients within the mild MTBI spectrum. However, all these 3 studies comprised only small study samples and do not allow any firm conclusions to be drawn. Our study shows that post-traumatic volume loss can be minute, and that advanced methods are accordingly needed to detect them.

Regarding the inconsistency of data on brain pathology according to MRI after MTBI, it may not be surprising that the relationship between such pathology and clinical presentation is poorly understood. Previous studies demonstrating brain atrophy or other pathology according to MRI observed no significant correlation with cognitive functions (22, 33). Levin et al. (33) reported unintelligible differences between individuals with regard to the site of lesions and the patterns of neuropsychological findings. Another study observed a correlation between atrophy and unfavourable GOSE outcome; however in that study, only 3 out of 25 participants exhibited a mild TBI (19). In our study sample, we did not identify any obvious correlation between the location of brain pathology and number or types of symptoms, other disability or GOSE score at follow-up.

The main findings of our study must be interpreted with caution because of the small study sample and use of a new *computer-aided analysis of volume changes*. However, our study is one of the most comprehensive to date with regard to the number of participants and examining the same patients at a standardized early and late point in time after MTBI.

Further analysis of our data will include diffusion tensor imaging (DTI) results. DTI has been reported to be more sensitive than other MRI methods in detecting MTBI pathology (36, 37). Correlations have been reported between DTI pathology and cognitive function (38, 39) and clinical outcome (40). However, findings are not unequivocal regarding fractional anisotropy (FA) as an indicator in white matter injury (38, 40), and it remains unclear if DTI pathology is representative of DAI (41). The analysis of DTI data is difficult and the repeatability may be low.

Obviously, further studies are needed to clarify the role of brain pathology on MTBI outcome. There is increasing evidence that factors other than injury factors, such as pre-morbid or co-morbid illnesses or conditions, are at play (4, 6, 7, 9–11). Even though some factors offer targets for meaningful intervention to prevent and treat long-term problems after MTBI, the evidence in this respect is not very strong (34). Thus, there is a need for more effective intervention models, and a better understanding of the role of disordered brain structure and function seems crucial. Recent studies provide consistent evidence that CT pathology is not a strong predictor of outcome after MTBI (7, 9, 11), something which highlights the need for studying methods that are sensitive to pathology not detected by CT. The results of our study indicate a potential contribution of advanced MR examinations in patients within the milder spectrum of MTBI, and points to the need for further studies to uncover both structural and functional pathology.

Study limitations

This study was designed as an exploratory study to find out if MR methodology in repeated examinations may reveal pathology in patients with MTBI. The study sample was small, study participants were recruited from one emergency unit and only during restricted time-periods. Thus, the occurrence of the findings cannot be generalized to a larger MTBI population. Time to follow-up varied from 3 to 7 months after the injury, and this may have had an impact on both MR findings and clinical data at follow-up. However, participants exhibited symptoms and activity limitations similar to what is known from previous studies (4), and the findings may guide further studies in the area. Although we intended to include patients within the whole MTBI GCS spectrum, most participants had a GCS score of 15, and none had a score of 13, which reflects that the milder forms of MTBI are more frequent (42). Interestingly, all patients with signs of brain atrophy had a presenting GCS score of 15, indicating that the MR method used here may be

a relevant method in studies of these patients, which form the largest subgroup of patients with MTBI (42). The software used in volume comparisons is new and under further development. The software results might, in some cases, have been biased by the registration process, especially in cases where the patient's position changed significantly from one MRI to the other. Therefore, the volume comparison failed in two patients in our study. In summary, the results of this study are only suggestive and do not lend themselves to any generalization.

Conclusion

These findings indicate that patients with MTBI may have minor organic injuries that are not detectable by conventional radiological methods, which may be possible to visualize using more advanced methodology. The loss of brain volume after MTBI may be a sensitive MRI marker of traumatic brain pathology. Further studies are needed to clarify the prevalence of such pathology and of its clinical meaning.

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