Mild Traumatic Brain Injury

Studies on outcome and prognostic factors

MARIANNE LANNSJÖ
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Abstract

Objectives: To explore the prevalence and structure of self-reported disability after mild traumatic brain injury and the impact of traumatic brain pathology on such outcome.

Material and methods: In study 1-3, symptoms data were collected by use of Rivermead Post-concussion Symptoms Questionnaire (RPQ) and data on global function by use of Glasgow Outcome Scale Extended (GOSE) from 2602 patients at 3 months after MTBI. RPQ data were subject to factor and Rasch-analyses Head CT data from 1262 patients were used in a prediction analysis that also included age and gender. In study 4, MRI and symptoms data were collected at 2-3 days and at 3-7 months follow-up after MTBI in 19 patients. Global function was assessed at follow-up by use of the Rivermead Head Injury Follow-Up Questionnaire (RHIFUQ) and GOSE.

Results: I. Most respondents reported no remaining symptoms but 24% reported ≥3 and 10% ≥7 remaining symptoms. The factor analysis demonstrated that all symptoms are correlated but also identified subgroups of symptoms. II. Rasch-analysis of RPQ showed disordered category function, local dependency of items, poor targeting of persons to items and indications of 3 or more dimensions. There was no differential item functioning. III. Head CT pathology with no need for acute intervention was observed in 52 patients (4%) but was not associated with either frequency of remaining symptoms or global outcome at 3 months post injury. Female gender and age over 30 years were associated with less favourable outcome with respect to symptoms and GOSE. IV. Post-acute MRI indicated trauma-related pathology in one patient and follow-up MRI indicated loss of brain volume in 4 patients.

Conclusions: A substantial proportion of patients with MTBI report remaining problems at three months after MTBI. RPQ is useful but not optimal to assess symptoms outcome after MTBI and calculation of a total sum score is not recommended. Female gender and older age are negative prognostic factors while brain pathology according to CT has no effect on self-reported outcome. Loss of brain volume after MTBI according to MRI may be a sensitive marker of traumatic brain pathology and deserves further studies.

Keywords: Rehabilitation, Mild Traumatic Brain Injury, Rivermead Post-concussion Symptoms Questionnaire, Rasch-analysis, prediction, outcome, head CT pathology, Magnet Resonance Imaging

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To my family
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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Picture on the front cover by Rebecka Lannsjö
Abbreviations

CT Computed Tomography
DAI Diffuse Axonal Injury
DIF Differential Item Functioning
DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition
DWI Diffusion Weighted Imaging
GCS Glasgow Coma Scale
GOS Glasgow Outcome Scale
GOSE Glasgow Outcome Scale Extended
HADS Hospital Anxiety and Depression Scale
ICD-10 International Statistical Classification of Diseases, Tenth Revision
LOC Loss of consciousness
MNSQ Mean Square
MR Magnet Resonance
MRI Magnetic Resonance Imaging
MTBI Mild Traumatic Brain Injury
OR Odds Ratio
PCD Post Concussion Disorder
PCS Post Concussion Syndrome
PTA Post Traumatic Amnesia
RHIFUQ Rivermead Head Injury Follow Up Questionnaire
RPQ Rivermead Post Concussion Symptoms Questionnaire
SBU Swedish Council on Technology Assessment in Health Care (Statens beredning för medicinsk utvärdering)
SWI Susceptibility Weighted Imaging
TBI Traumatic Brain Injury
Introduction

Traumatic brain injury (TBI) is a common condition and patients with TBI are managed in a variety of health care settings including departments of rehabilitation medicine. The TBI is commonly classified as mild, moderate or severe depending on the clinical presentation in the emergency room. Patients with mild TBI (MTBI) are most often discharged with a diagnosis of brain concussion (S06.0) according to the ICD10. Accordingly, persisting symptoms after mild injuries are often diagnosed as post-concussional symptoms.

Historically, the term concussion has been used since centuries and is still used in clinical practice and also commonly used in the sports medicine literature. The term MTBI has been increasingly used since the TBI severity grading system based on the Glasgow Coma Scale (GCS) was introduced in 1974 (1). There is no consensus on a universal definition of MTBI or concussion and this is a matter of on-going debate. Although the criteria according to the definitions of both MTBI and brain concussion comprise transient signs and symptoms of altered brain function, the definitions differ with regard to the upper and lower limits of such disturbances. In addition, modern brain imaging has added questions about how to classify the condition for a patient, who fulfils the clinical criteria for MTBI or concussion but where computerized brain tomography (CT) or magnetic resonance imaging (MRI) demonstrates traumatic, structural or functional abnormalities (2). In this thesis, the term MTBI is used and the definition proposed by the American Congress of Rehabilitation Medicine was applied (see further below, page 17).

Overall, traumatic Brain Injury is one of the most common causes of impaired function and disability corresponding to huge human and economic costs (3, 4). According to most studies, 70% or more of patients with TBI, have a Mild Traumatic Brain Injury (MTBI). The reported annual incidence of MTBI is 100-300 per 100,000 inhabitants in western countries (5, 6). Most of these present with a GCS score of 15 (7, 8), i.e. are fully awake and oriented at first examination after the injury. Until recently, around 15,000 patients were admitted to in-hospital observation after MTBI each year in Sweden (9). During the last decade, this number has decreased (10) when CT examination has been introduced for the acute triage (11).

Most patients with MTBI experience a favourable prognosis and outcome (12). However, a proportion present with post-concussional problems during
months or years after the injury (13-15). The labelling, definition, frequency
and main determinants of such problems have been studied and debated over
a long period of time and are still subject to further debate (2, 13, 16, 17).
Thus, this is an area where further studies are needed not only to reach con-
sensus on definitions but in order to understand how to manage these pa-
tients in the health care system.

One major challenge relates to the “case definition”, i.e. what symptoms
and signs that characterise a clinically relevant, poor outcome after MTBI.
E.g., suggested criteria according to ICD10 (18) are based on self-reported
symptoms while the DSM IV (19) for a post contusional condition also re-
quires that cognitive impairments are demonstrated by neuropsychological
testing. However, the interpretation of both symptoms and such test data is
subject to many problems.

Another challenge relates to the impact of traumatic abnormalities
demonstrated by CT or MRI. In patients with the mildest form of MTBI,
presenting a GCS score of 15, CT demonstrates intracranial pathology in
around 5% (20, 21) but the impact of such abnormalities on the long-term
outcome has not been demonstrated. While previous studies have demon-
strated that older age (22-27), female gender (28-32), premorbid physical
problems (33), neck-injury or other on-going pain problem (34), psychiatric
illness or depression (35, 36), co-morbidities as fractures and other extra-
cranial injuries (27, 33), financial incentives and litigation (12, 37) may be
associated with poor outcome, the role of the brain injury itself has been
unclear. Therefore, while there are now evidence-based guidelines for the
acute management of patients with MTBI, there is still a lack of such guide-
lines to prevent or treat long-term problems after MTBI.

The challenges indicated above are the background for the studies in this
thesis.

Symptoms after MTBI

The number of persisting symptoms reported after MTBI varies between
studies, and the validity of three or more symptoms has not been demon-
strated, even if some studies indicate a correlation between the number and
intensity of symptoms and other measures of disability (14, 38, 39). Several
studies have demonstrated that symptoms reported after MTBI are not spe-
cific but are also reported after extra-cranial trauma (40), low back pain (41),
whiplash disorder (42), as well as in healthy subjects (43, 44). However, it
has been suggested that some symptoms or constellations of symptoms
might be more specific for MTBI (45). The lack of symptom specificity is
considered to be an argument against the concept of a unitary condition, i.e.
a post-concussional syndrome (12, 13, 40, 44, 46, 47). It also has been re-
ported that multiple symptoms after MTBI are rare (48) but data in this respect are scarce.

One aim of this project is to examine the prevalence of remaining symptoms three months after the onset of MTBI with regard to the number and intensity of symptoms by using data from a large national cohort, the so-called Octopus Study.

Assessment of self-reported data

In order to study the self-reported outcome after MTBI, reliable measuring instruments are needed. In studies of people’s attitudes, feelings, behaviour, health, etc. different types of questionnaires are used. These questionnaires often have a response scale, such as a Likert scale or another rating scale with ordered categories. To be able to perform mathematical operations, such as summing numerals, a scale is required to feature equidistance between adjacent numerals and a zero point (that could be unique for the particular unit of measure), which is not the case for ordinal data (49). Rating scale categorizations should be well-defined, mutually exclusive, univocal and exhaustive (50).

Variables present in an individual, for example independence, pain, balance, fatigue, depression and knowledge cannot be measured directly. They are usually assessed by measuring related behaviours, defined by standardized items. The homogeneity of the different items and proportionality of raw counts to measure, may only be postulated (51).

Since the analyst is always uncertain as to the exact manner in which a particular rating scale may be used by a particular sample, an investigation of the functioning of a rating scale is always preferable. One way to analyse the construct of a rating scale is by performing a factor analysis. Together with other statistical and psycho-linguistic tools, a Rasch-analysis also provides an effective framework within which to verify, and at best improve, the functioning of rating scale categorization (52).

When using questionnaires, the type of method’s chosen has an impact on the results. Using a structured interview for Glasgow Outcome Scale Extended (GOSE), increases the test-retest and interrater reliability (53, 54). Male athletes reported a higher frequency of symptoms when the interviewer was a woman (55). Nolin et al described a higher reporting of remaining symptoms when using a check-list compared to an open question (56). Even when healthy students were asked which symptoms to expect after MTBI, a check-list or structured interview resulted in a higher degree of reported symptoms compared to an open question (57). These findings are important to have in mind when analysing data from questionnaires.
Rivermead Post-concussion Symptoms Questionnaire (RPQ)

The Rivermead Post Concussion Symptoms Questionnaire (RPQ) (58) is designed to measure the severity of symptoms following mild or moderate traumatic brain injury. The RPQ has been shown to measure post-concussion symptom severity reliably in terms of test-retest and interrater reliability for total and individual symptom scores (38, 58). This questionnaire takes into account the high prevalence of background symptoms by asking the patients not only if symptoms are present, but also to rate the intensity of each of 16 symptoms as compared to the period preceding the MTBI.

Two previous studies (60, 61) have examined aspects of the structure of symptoms reported by patients after a MTBI by use of RPQ. In a confirmatory factor analysis using structural equation modelling (SEM), Potter et al (60) tested a single factor model that would reflect PCS as a unitary syndrome, in addition to a model of cognitive, somatic and emotional factors, as proposed by Smith-Seemiller et al (45). While the one-factor solution was rejected by the factor analysis, there was some support for separable constellations of cognitive, emotional and somatic symptoms.

The other study by Eyres et al (61) examined the construct of the RPQ through Rasch-analysis of data from a sample with prior head injuries of varying severity. The Rasch-analysis is another approach to elucidate the construct and usability of instruments with ordinal data, which has been proven valuable not least in a rehabilitation context (51). A Rasch analysis examines how data conform to the model, in contrast to the traditional approach whereby the model is used to explain the data (52, 62). It is a probabilistic model specifying that a reasonable uniform level of randomness must exist throughout the data (62). Eyres et al (61) found significant deviations from the expectations of the Rasch Model, and that half of the 16 RPQ items displayed disordered thresholds. Removal of the first three items (headache, dizziness and nausea) with very large residuals improved the overall fit. The resulting 13-item scale exhibited unidimensionality as did the three removed items combined, indicating that the RPQ comprises two different constructs. These two constructs did only partially correspond to the factors identified in the study by Potter et al (60) and argued against summation of RPQ scores from items belonging to each of the two constructs. Thus, there is a need for further evaluation with regard to the interpretation of data provided by the RPQ.

Therefore, one aim of this project is to examine symptom structure and the construct of the RPQ by use of a homogenous study sample consisting of data derived from a large national cohort of patients (the Octopus study).
Impact of head CT pathology

The significance of organic brain damage on the long-term outcome after MTBI is far from fully understood and is still subject to debate (2, 17). Evidence-based guidelines for the acute management of patients with MTBI, based on several large studies (63-65), specify criteria for the routine use of head CT as part of the diagnostic set up (66). Af Geijerstam et al have shown that acute head CT allows safe and cost-effective triage of this large MTBI population (67). Although there is strong evidence that some 5% of those with MTBI and GCS 15, have non-surgical, intracranial traumatic abnormalities according to head CT (20, 21), data on the impact of such abnormalities on the clinical course and long-term outcome are scarce.

Two recent studies indicate that demographic and other variables (27, 33) are stronger predictors than CT pathology but more conclusive evidence is needed to advance our understanding of the key determinants of poor outcome after MTBI.

Therefore, one aim of this project is to examine relations between traumatic CT scan abnormalities and symptoms as well as global function at three months after MTBI by use of data from a large national cohort (the Octopus study).

DAI in MTBI

Although a head CT is the common clinical method, MRI can in most aspects offer a more sensitive examination (68-70). TBI may cause not only focal damage with oedema and haemorrhage but also diffuse widespread damage to microcirculation and nerve cells – Diffuse Axonal Injury (DAI) (71, 72).

Recent human MRI studies have demonstrated clinically significant DAI after moderate or severe TBI capable of predicting outcome according to the Glasgow Outcome Scale (GOS) (69, 73, 74). Some previous studies have also demonstrated that DAI may be visualised in patients with MTBI by use of MRI (70, 75, 76) but the prevalence and clinical significance of DAI after MTBI remains to be clarified. Thus, although these studies demonstrate that DAI may be demonstrated in patients with MTBI, further studies are needed to explore the optimal MRI sequences and timing to visualise DAI after MTBI in order to explore its clinical impact in these patients.

Another approach in this area is taken in follow-up studies using volume change as an indicator. Some studies have demonstrated a loss of brain volume in patients after TBI by use of repeated MRI:s (73,77-79). Most studies included patients with all degrees of severity demonstrating a correlation between volume loss and acute DAI volume (73) or length of coma (79) and that atrophy correlates to unfavourable outcome according to GOSE (78).
Corresponding studies of patients with MTBI are scarce. Two separate earlier studies showed different results (80, 81). Schrader et al found no pathology on MRI (80) either on the acute or follow-up MRI. In contrast, Hofman et al (81) reported MRI pathology in about half of the 21 participants but there was no correlation between atrophy and cognitive test data.

While previous studies provide evidence that MRI may reveal brain pathology in patients who have been exposed to MTBI, there is an obvious need of further studies to explore the prevalence and clinical impact of such pathology as well as the optimal MRI design and timing.

Therefore, one aim of this project is to explore signs of DAI and brain volume loss according to advanced MRI methods, as well as the clinical impact on disability at three months after MTBI in a prospective study of patients with MTBI.
The overarching aim of this project is to expand the knowledge on long-term outcome after Mild Traumatic Brain Injury (MTBI) and the impact of a traumatic brain lesion on this outcome. The specific aims are as follow:

1. Examine the prevalence of remaining symptoms at three months after MTBI with regard to number and intensity of symptoms by using data from a large national cohort.
2. Examine symptom structure and the construct of the RPQ by using data from a large national cohort.
3. Examine relations between traumatic head CT abnormalities and symptoms, as well as global function at three months after MTBI by use of data from a large national cohort.
4. Explore signs of DAI and brain volume loss according to advanced MRI methods, as well as the clinical impact on disability at three months after MTBI in a prospective study of patients with MTBI.
Materials and methods

Definition of Mild traumatic Brain Injury (MTBI)

In this thesis, the term Mild Traumatic Brain Injury (MTBI) is used and the definition developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (82) was applied. According to this definition, a patient with MTBI has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: any loss of consciousness maximum 30 minutes, any loss of memory for events immediately before or after the accident with maximum 24 hours of posttraumatic amnesia (PTA), any alteration in mental state at the time of the accident but having GCS 13-15 after 30 minutes. Included in the studies were patients representing the largest subgroup of patients with MTBI, i.e. those presenting with a GCS score of 15 (study I-III) or 14 and 15 (study IV). While the GCS is used internationally, some hospitals in Sweden use the Swedish Reaction Level Scale (RLS) (83). A GCS score of 15 or 14 corresponds to a RLS score of 1 or 2 respectively.

Materials

Data from a national multi-centre study of MTBI – “Octopus”, Studies 1-3.

In 2000, The Swedish Council on Technology Assessment in Health Care (SBU) reported a need for further studies comparing the traditional policy to observe patients with a MTBI/brain concussion in the hospital as compared to performing an acute brain CT after which the patient would be discharged to his home if this examination revealed no intracranial pathology (11). The report initiated a national multi-centre randomized controlled trial (“Octopus”), which reported equivalent medical outcome according to a non-inferiority analysis (67). During the May 2001 to January 2004 time period, 39 out of 75 Swedish Emergency Departments participated in the “Octopus Study”. Participating departments represent hospitals of all sizes and all parts of the country and correspond to the geographical distribution of the Swedish population. Pa-
tients with MTBI aged 6 years or older were recruited to the study. Eligibility criteria included a history of head trauma within the last 24 hours, confirmed or suspected loss of consciousness (LOC) and/or amnesia, normal neurological examination and a Glasgow Coma Scale (GCS) score of 15 without any associated injuries requiring admission. Exclusion criteria were any of following: Loss of consciousness (LOC) >30 minutes, posttraumatic amnesia (PTA) > 24 hours, other significant physical injury or major neurological disorder, including previous significant head injury. A total of 2,602 individuals were recruited to the study. All those eligible received oral and written information and gave their written consent, whereas the consent of children was obtained from a parent or accompanying caregiver.

Three months after visiting the Emergency Department, participants were sent questionnaires (with a follow-up reminder sent two weeks to non-respondents) about their needs of daily assistance, work or study ability, duration of sick-leave, consumption of medications, change in leisure time activities and social life, in addition to interpersonal problems. The questionnaire also included the Rivermead Post Concussion Symptoms Questionnaire (RPQ). Depending on the reporting in the questionnaires, a score in Glasgow Outcome Scale Extended (GOSE) was calculated by the research nurses using the GOSE interview. Questionnaires were received from 2,523 participants (97 %) and the frequency of missing data was less than 1.5% for each of the 16 items and 3% for the total RPQ.

Study 4
During the time period April 2008 to February 2012, 22 subjects were recruited from the Emergency Department of the University Hospital at Uppsala. Inclusion criteria were: age 16-65 years, MTBI diagnosis according to an actual head trauma with loss or altered consciousness for less than 30 minutes, a GCS score of 13-15 and a normal neurological examination. Exclusion criteria included an earlier brain injury, neurological or psychiatric illness, substance abuse or other accompanying injuries needing special treatment. MRI, neurological examination and assessment by means of RPQ and Hospital Anxiety and Depression Scale (HADS) was performed during day two or three after the injury. After at least three months, an MRI follow-up, neurological examination and assessment with RPQ, Rivermead Head Injury Follow-Up Questionnaire (RHIFUQ), HADS and GOSE were performed. Three participants did not perform the second MRI and were therefore excluded, resulting in a study sample of 19. A head CT was not included in the study protocol but was performed on 16 of 19 participants. No financial incentives were offered. The local Medical Ethics Committee approved the study and all patients received oral and written information about the study and gave their informed consent.
Assessment instruments

Rivermead Post-concussion Symptoms Questionnaire (RPQ)

A Swedish version of the RPQ (after forward-backward translation) was used in the studies. The RPQ (58) consists of 16 items asking the patient about the degree to which the following symptoms had been experienced over the preceding 24 hours compared to the situation before the head injury: headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. Symptoms are assessed on a five-point scale with the following response alternatives: not experienced at all (Category 0), it is no longer a problem (Category 1), a mild problem (Category 2), a moderate problem (Category 3), and a severe problem (Category 4). The total RPQ score is the sum of a subject’s score for each of the 16 items. In the original RPQ study, category 1 was not included in the total score. The total score was then based on category 2, 3 and 4 combined ratings. Thus, the lowest possible total score was 0 (if subjects answered “not experienced at all” on all items) and the highest score was 64 (if the subject answered “severe problems” on all items). RPQ has demonstrated validity and reliability in studies using classical test theory (59, 84).

Glasgow Outcome Scale Extended (GOSE)

The Extended Glasgow Outcome Scale (GOSE) (85) was developed to address the limitations of the original Glasgow Outcome Scale (GOS), including the use of broad categories that are insensitive to change and difficulties with reliability due to lack of a structured interview format. The GOSE extends the original five GOS categories to eight. The eight categories are: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery. A structured interview was provided to improve the reliability of ratings and using the instrument to enable good interrater reliability and content validity to be demonstrated for the GOSE (53). Compared to the GOS, the GOSE has been shown to be more sensitive to change in mild to moderate TBI (54). In study 2, GOSE was categorised into two classes; 1 to 6 and 7 to 8.

HADS

The Hospital Anxiety and Depression Scale (HADS) was developed in order to detect states of anxiety and depression (86). The scale consists of 14 items assessed from 0-3. The total score is divided into two parts - anxiety and
depression – and the severity of these conditions can be calculated. In each part a score of 0-6 means no anxiety/depression, 7-10 mild to moderate anxiety/depression and >10 severe anxiety/depression.

RHIFUQ
The Rivermead Head Injury Follow Up Questionnaire (RHIFUQ) was developed to assess outcome on activity- and participation levels after mild and moderate brain injury. It consists of ten items with response alternatives scored 0-4. It has shown adequate reliability and validity for mild and moderate brain injuries. (38)

MRI
All examinations were performed using the same MR imager operating at 1.5 Tesla and were analysed by an experienced neuroradiologist unaware of patient outcomes. The MRI protocol included conventional T1- and T2-weighted sequences including FLAIR, and also two susceptibility-weighted (SWI) sequences to reveal haemorrhages, diffusion weighted (DWI) sequences and volumetry using a computer-aided comparison method. SWI is reported sensitive to haemorrhage resulting from DAI (87). DWI is capable of detecting DAI lesions not seen on conventional MRI (88) and is mostly applicable on grey matter. Trace images and apparent diffusion coefficient (ADC) maps were used for analyses.

Statistics
Study 1
Descriptive statistics, frequencies, proportions, median and mean values were used to describe symptoms data. For some of the analyses, symptoms were dichotomised into no symptoms (ratings 0 and 1) versus some symptoms (ratings 2, 3 and 4). The significance level was set to 5 % (p<0.05). Spearman's rank correlation analysis was used to explore correlations between symptoms and structural equation modelling (SEM) was performed by use of several fit indices to explore if data were compatible with one or more factors.

Study 2
The Rasch-analysis is a mathematical measurement model developed by Danish mathematician Georg Rasch (89) and uses a statistical approach to
measure human performance, attitudes and perceptions (51). In the Rasch model, cumulative raw scores, achieved by a person across items or by an item across persons, are transformed into linear continuous measures of ability (for persons) and difficulty (for items) (51). The model is probabilistic, i.e. the easier the item, the more likely it will be passed, and the more able the person, the larger the probability that he or she will pass a difficult item, compared with a less able person (90). Applying this to a symptom questionnaire as RPQ, the latent variable will correspond to a continuum of persons with increasing problems related to symptoms and a dispersion of items along that continuum with symptoms from common to rare.

Since it was assumed that thresholds would differ for each item, the Partial Credit Model (91) was applied. In order to test the unidimensionality of RPQ, the following aspects were analysed: Category function, local dependency, uniform differential item functioning by age and gender, principal components analysis of the residuals, item and person fit, in addition to targeting by analysing item and person measures.

Study 3
A binary logistic regression analysis was performed with results presented as odds ratios (OR) with 95% confidence intervals and p-values. The Type III analysis was used to evaluate the significance of the variables included in the statistical model. Associations between variables were checked with Spearman rank correlation and log linear models. The significance level was set to 5 % (p<0.05).

Study 4
Descriptive statistics, frequencies, proportions, median and mean values were used to describe symptoms data. For some descriptions, ratings in RPQ and RHIFUQ were dichotomised into 0-1 versus 2-4.
Results

Prevalence and structure of symptoms after mild traumatic brain injury in a national cohort - paper 1

The study sample consisted of the 2,523 participants (97%) from the Octopus Study that responded to the RPQ questionnaire three months after their MTBI. A total of 1,488 were male (59%) and 1,035 female (41%). The mean age was 31 years, while the median age was 22 (range 6-96) years. In total, 56% (1,411) of respondents reported no remaining symptoms, 24% (615) reported three or more symptoms and 10% (259) reported seven or more symptoms, see table 1. Most frequently reported symptoms were fatigue, reported by 23%, headaches (22%), and dizziness (16%). The least frequent symptom was double vision (2%).

Table 1. Proportion of patients reporting 0-7 or more symptoms (scoring 2-4). Missing data 3%.

<table>
<thead>
<tr>
<th>Number of symptoms</th>
<th>Frequency (valid %)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>56</td>
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<tr>
<td>1</td>
<td>10</td>
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<tr>
<td>2</td>
<td>7</td>
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<td>5</td>
<td>2</td>
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<td>6</td>
<td>3</td>
</tr>
<tr>
<td>≥3</td>
<td>24</td>
</tr>
<tr>
<td>≥7</td>
<td>10</td>
</tr>
</tbody>
</table>

There was a positive relation between the number of remaining symptoms and the intensity of these symptoms; the higher the number of remaining symptoms, the higher the intensity.

All symptoms exhibited strong positive interrelations and there was strong support for a single or two factor solution. Fit indices were only slightly weaker for three and four factor solutions. In the three factor solution, the factors were labelled as somatic, cognitive and emotional consistent with previous studies (45, 60). In a four-factor solution, the fourth factor included visual and auditory symptoms.
In summary, our study of a national cohort of MTBI patients shows that a significant minority reports multiple symptoms that persist at three months post injury and that there is a strong common factor for all RPQ symptoms, as well as subgroups of symptoms.

Internal construct validity of the Rivermead Post-concussion Symptoms Questionnaire - paper 2

The study sample was the same as in study 1. Of 2,523 questionnaires, 2,508 were subjected to the Rasch-analysis. Of the respondents, 59% were male and 41% female. The mean age was 31 years (median age of 22) with a range of 6-96.

Categories did not work in a consistent manner; however collapsing Categories 1 and 2 yielded ordered thresholds. Local dependency of items was present and two item pairs were combined. There was no differential item functioning by gender or age. The Rasch Factor explained 47.7% of the variance and the first contrast explained 12.4% of the unexplained variance (eigenvalue 1.7). Further analysis indicated three or more dimensions. The person reliability was 0.71 and the person separation index was 1.56. The person measure had a mean of -2.16 showing poor targeting of persons to items, which is illustrated in figure 1.

![Figure 1. Map of persons and items along the latent variable. Persons are ordered according to measure on the left hand side. X=75 persons and .=1-74 persons. A value of -5 indicates a low degree of experience of problems with symptoms and a value of 2 indicates a high degree. The items are ordered by measure on the right hand side with the most highly rated items on top. A value of -1.01 indicates that the item is more frequent than an item with a value of 1.59.](image-url)
According to this Rasch-analysis of data from a representative MTBI sample, the RPQ may not be optimal for this population. Even after reducing the number of categories and collapsing items with local dependency, unidimensionality was not reached, which argues against summation of a total score. However, the scale is unbiased for gender and age.

Does head CT scan pathology predict outcome after Mild Traumatic Brain Injury? - paper 3

The study material originated from the participants in the Octopus study that were randomized to head CT and discharge (1,316). Excluding those who did not fulfil head CT (24) and those with irrelevant pathologic findings on head CT (30) resulted in a study sample of 1,262. There were 751 men (60%) and 511 women (40%), with a mean age of 30 years (the median age was 21 and the age range 6-94). Relevant or suspiciously relevant pathologic findings on acute head CT were observed in 52 patients (4%).

Outcomes were measured with regard to remaining symptoms according to RPQ and with global function as assessed by GOSE. Unfavourable outcomes after three months were defined as having \( \geq 3 \) remaining symptoms and as belonging to GOSE 1-6. Of the participants, 279 (22%) had \( \geq 3 \) remaining symptoms and 101 (8%) belonged to GOSE 1-6.

The results of the binary logistic regression analysis were presented as odds ratios (OR) for having an unfavourable outcome. Patients aged over 30 reported less favourable outcomes with respect to both symptoms and GOSE as compared to patients in younger age groups. Men reported better outcomes than women with regard to symptoms with OR 0.64 (0.49-0.85) for three or more symptoms and with regard to global function with OR 0.60 (0.39-0.92) for GOSE 1-6. Traumatic pathology on head CT in the acute setting had no association with either frequency of remaining symptoms or assessed GOSE level after three months.

Clinical outcome and brain pathology after MTBI – an exploratory study by repeated MR examinations – paper 4

The study sample consisted of 19 participants, 7 men and 12 women, with a mean age of 34 (median age of 28, age range 17-63). Causes of accidents ranged from falls (10), traffic accidents (6) and other (3). Seventeen participants had a GCS score of 15 and two had GCS 14. The estimated unconsciousness mean was 2 minutes (range 0-15) and the estimated amnesia median was 15 minutes (mean 115, range 0-600 minutes). Sixteen participants
underwent head CT on the day of injury and minor trauma related pathology was found in one patient.

The participants with severe anxiety and/or mild to moderate depression at follow-up (two participants in total) also reported a significantly greater amount of remaining symptoms.

The first MRI was performed on day two or three, while the second MRI was performed after 3-7 months (mean 4.4 months). One patient evidenced trauma related pathology at both investigations. The computer aided volume comparison detected mild focal substance loss in three additional patients. The four patients with significant pathologic findings did not have any common characteristics regarding acute injury markers or clinical outcome at follow-up. They all reported Upper Level of Good Recovery according to GOSE (GOSE 8) at follow-up.
Discussion

The findings presented in this thesis will be discussed first with regard to the methods and design of the four studies and thereafter with regard to the answers to the specific questions posed. Further, comments will be made on the potential usefulness of the findings for clinical practice and further studies in this area.

The first three studies (I-III) were all based on data from a national cohort study, which primarily was designed to compare two acute management protocols with regard to medical safety – the Octopus Study. However, that study also provides data for in-depths studies of outcomes and the assessment of those outcomes. Major strengths of the Octopus Study include its large population base and prospective design, as well as the extraordinary low attrition rate at follow up. The fourth study (IV) was defined as exploratory. Primarily the intention was to achieve a larger sample size than turned out to be possible within the framework of the study setting and study time. However, the study provides some new data on brain pathology according to MR examinations.

At the beginning of these studies, the same question were asked as in many previous studies, i.e. how common are symptoms and everyday problems after MTBI? The main reasons for posing these questions were that no previous study had been based on such a comprehensive and complete data set from well-defined MTBI patients. Furthermore, clinical presentations may change over time and between countries and detailed information on the prevalence of patients with high numbers of reported symptoms are scarce and inconsistent. As expected, most patients with MTBI who were presenting a GCS score of 15 had a favourable prognosis with regard to symptoms and everyday life performance at three months post injury. However, one fourth reported ≥3 symptoms, and according to GOSE, about one tenth reported problems at this point in time after the injury with regard to global function in everyday life. Interestingly, one tenth reported 7 or more symptoms, with the intensity of symptoms growing with higher numbers of remaining symptoms. Overall, these findings are consistent with most previous studies but offer new and strong evidence with respect to the largest subgroup of patients with MTBI, i.e. those presenting a GCS score of 15 and who are diagnosed with a brain concussion according to the ICD10. Regarding the high incidence of MTBI (5, 7), the observed frequency of post-
concussion problems corresponds to a huge number of patients with such problems and indicates that current clinical management is insufficient.

It has been recognized for long that symptoms reported after MTBI are not specific but are also reported by healthy people (43), patients with chronic pain (45, 93,94), in addition to patients with depression (95, 96). Some previous studies indicate that post-concussion symptoms may aggregate in somatic, cognitive and emotional factors (45, 60) and that the constellations of those symptoms may be specific to MTBI (60). Therefore, a factor analysis according to RPQ was used to analyze the structure of symptoms in the large national cohort of patients of patients with MTBI and a GCS score of 15. The factor analysis of RPQ demonstrated one common factor but also provided support for the hypothesis that somatic, cognitive, emotional and audio-visual symptoms may be differentiated. This finding principally corresponds to earlier studies performing factor analysis of RPQ data from smaller and more heterogeneous study samples (45, 60) and offers an interesting approach for studying the relationship between symptoms and brain pathology, as applied in study III (predictive value of head CT pathology), and other disabilities. Further studies, relating baseline factors to outcome in terms of subgroups of symptoms, might help to clarify mechanisms behind persistence of symptoms and guide intervention studies.

Although the RPQ has been used extensively in this area, data on the internal construct of the scale are scarce, which is why a Rasch-analysis was performed. The findings of the Rasch-analysis did not clearly correspond to the observation in the factor analysis of a factor that is common to all symptoms. The Rasch-analysis demonstrated at least three dimensions, occurrence of local dependency and that scale categories were not functioning optimally. The findings of the Rasch-analysis were partly in line with an earlier study by Eyres et al (61) but showed increasing signs of multi dimensionality. RPQ was originally designed to be used to assess the outcomes of mild and moderate traumatic brain injuries (58). Thus, one reason why the data in the present study did not fit to the Rasch-model may be that the study sample was relatively homogenous and only comprised patients within the mild spectrum of MTBI. For this group of patients, reducing scale categories and items might improve the functioning of the scale; however, further studies are required to demonstrate this hypothesis.

An important aim of this project was to explore prognostic factors for MTBI outcomes. We used symptoms reporting according to RPQ and global function according to GOSE to assess clinically relevant outcomes. Although the GOSE only offers broad categories of outcomes, it has shown good reliability and validity in assessing outcomes after traumatic brain injury (53) and is also considered adequate to assess outcomes after MTBI (54). Cognitive functions according to neuropsychological testing were not included in the outcome protocol, although such testing would have been valuable. However, neuropsychological testing is not a part of routine follow-up
and would have required considerably greater resources. Furthermore, there is evidence from several previous studies that a potential decline in cognitive test performance after MTBI is transient (12) and the interpretation of subtle impairments may be difficult. There is also a lack of evidence so far of any correlation between deficits in neuropsychological testing and unfavourable self-reported outcomes or degrees of remaining symptoms (97).

In the present study, head CT pathology showed no impact on self-reported outcomes three months after the injury in patients with MTBI and a GCS score of 15. The incidence of 4% CT pathology is in accordance to previous studies (20). The demonstrated lack of an impact of head CT pathology on self-reported outcomes after MTBI is in good agreement with findings in recent studies (27, 33) and adds strong evidence with regard to the largest subgroup of patients with MTBI. Similarly, the study provides strong evidence that such factors as higher age and female gender are associated with less favourable outcomes. The credibility of these findings is supported by the Rasch-analysis findings that RPQ was unbiased for gender and age. Earlier studies have also shown that higher age is a risk factor for obtaining a poor prognosis (12, 25, 27). In contrast, earlier studies of the impact of gender are less consistent with both reports of no relationship to symptoms outcome (12l, 33) and reports of women reporting more remaining symptoms (29). Previous studies have demonstrated other prognostic factors, e.g. other health problems (28, 30, 59, 94, 98), as mentioned in the Introduction. Although not all factors are available for specific interventions, all factors have to be considered in the rehabilitation process.

A major focus in the search for factors that may have an impact on the post MTBI outcome, has been to find methods to expose an “organic brain injury”, and the new imaging methods continuously inspires new studies. MRI has proven to be more sensitive than CT to reveal pathology after a traumatic brain injury (69, 99). Although there is a growing body of evidence related to MRI findings after MTBI, most studies have included only a few patients and the results are not consistent.

Our study, in which the MRI study protocol included DWI and two susceptibility weighted sequences, revealed only one trauma-related abnormality in the early post-acute stage. However, a new computer-aided analysis of volume changes indicated loss of brain parenchyma in totally 4 out of 19 patients at follow-up, indicating that volume loss may be a sensitive marker of brain pathology after MTBI. Atrophy is a recognised consequence of moderate and severe traumatic brain injury (77, 79, 100) but data from patients with MTBI are scarce and two recent studies present diverging findings, i.e. either observed atrophy (81) or its absence (80). Further, reports on the relationship between atrophy and outcome are scarce (73) and findings inconsistent. Correlations between atrophy and injury markers as DAI volume (73), length of loss of consciousness (77) and Post Traumatic Amnesia (PTA) (73) have been reported. A study of patients with heterogeneous inju-
ry severity reported a correlation between atrophy and unfavourable outcome according to GOSE (78). In contrast, no correlation between atrophy and cognitive deficits could be found in a study of patients with MTBI (81). Thus, new imaging methods offer increasing opportunities in this area and there is indeed a need for additional studies that may help to identify structural and functional pathology after MTBI. Any pathology identified must be related to relevant clinical variables. Thus, clinical research in the MTBI field should strive to further develop this area.

Limitations: As discussed, cognitive testing was not included in the study protocols and would have been of interest. The results of Studies I-III are only valid for patients within the mild spectrum of MTBI (i.e. presenting a GCS score of 15) and may not be generalized to the entire MTBI group. The design in Studies I and III did not allow controlling neither for other relevant baseline factors, for example, psychosocial conditions or co-morbidities, nor for intervening events or other types of interventions during the follow-up period. In the MRI study (Study IV), the study sample was too small to draw any strong conclusions and the results must be considered to be only indicative.

Conclusions: Most patients with MTBI experience a favourable outcome regarding remaining symptoms and global function, but a significant minority report multiple symptoms and impaired global function three months after the injury. The RPQ may need to be modified to be optimal in assessing the outcome of symptoms after MTBI and the calculation of a total score is not recommended when the current version is applied. Head CT pathology that does not require neurosurgery has no impact on self-reported outcome after MTBI, while female gender and older age increase the risk for poor outcomes. The explorative study on MRI pathology using the new methodology indicates that the loss of brain volume after MTBI may be a sensitive MRI marker of traumatic brain pathology. The observations in this thesis highlight the need for improved clinical management protocols in patients with MTBI, in the addition to the need for clinicians during the follow-up to consider the role of co-morbidities and psychosocial factors rather than minor head CT abnormalities, as well as the need for further studies to clarify the role of a traumatic brain disorder in patients who suffer long-term problems post MTBI.
References


Sammanfattning på svenska

Patienter med lätt traumatisk hjärnskada får oftast diagnosen hjärnskakning och handläggs av många olika aktörer i sjukvården. Hjärnskakning är vanligt förkommande med en incidens på ca 100-300/100.000 invånare och är i västvärlden. För flertalet är det kliniska förloppet gynnsamt men en betydande andel får kvarstående besvär, som hindrar dagliga aktiviteter. Trots ett stort antal tidigare studier finns fortfarande flera frågetecken både beträffande förekomst och typ av kvarstående besvär och beträffande förekomst och betydelse av strukturell hjärnskada för prognosen. Behovet av bättre kunskap i dessa avseenden är angelägen för att kunna utveckla bättre interventionsmodeller än dagens och detta var utgångspunkten för projektet.

För att säkert kunna mäta grad av kvarstående symtom behövs tillförlitliga frågeformulär. Rivermead Post-concussion Symptoms Questionnaire (RPQ) är ett vanligt använt sådant bestående av en lista av 16 olika symtom graderade med en 5-stegsskala. Syftet är att mer strukturerat kunna beskriva antal och grad av symtom efter hjärnskakning. Hur väl RPQ fungerar för detta ändamål är dock oklart.

För att analysera konstruktionen av RPQ och hur väl det passar för patienter med hjärnskakning genomfördes både en faktoranalys (studie 1) och en Rasch-analys (studie 2) av RPQ. Faktoranalysen visade att symtomen korrelerar till varandra som helhet vilket talar för att RPQ är ett bra frågeformulär just för hjärnskakning, men man kunde också se 4 olika grupper av symtom – kroppsliga, kognitiva, emotionella och syn/hörsel relaterade. Raschanalysen visade en något annan bild i form av att RPQ inte bestod av en dimension och att de 5 skalstegen inte hade en bra spridning. Två par av symtom som var för lika kunde identifieras och man såg inte någon bra spridning av antal och grader av symtom i patientgruppen som undersöks. Ett positivt fynd var emellertid att RPQ fungerar lika oavsett kön och ålder. Sammantaget bedöms RPQ inte vara optimalt men ändå användbart vid hjärnskakning och kan sannolikt förbättras genom att man minskar antalet symtom och skalsteg, men det måste först undersökas i nya studier. Man kan dock inte rekommendera beräkning av en totalsumma baserat på patientens skattnings av symptomintensitet.

Även om flera tidigare studier har undersökt förekomsten av besvär efter lätt traumatisk hjärnskada finns oklarheter, som motiverade en fördjupad undersökning av symptom och funktionsnivå i en stor grupp av patienter från hela Sverige. Analysen omfattade uppgifter från 2602 patienter vid 3 måna-
der efter skadan där bortfallsfrekvensen för svarsformulären var endast 3%. Andelen män var 59% och medianåldern var 22 år (spridning 6-96 år). De vanligaste symptomen enligt skattningarna i RPQ var trötthet (23%), huvudvärk (22%) och yrsel (16%). 56% hade inga symptom alls, 24% hade 3 eller fler symptom och 10% hade 7 eller fler symptom. Ju fler symptom man hade desto högre intensitet hade också symptomen.

För att undersöka faktorer som har prognostisk betydelse för utfallet (studie 3) analyserades data från den del av patientgruppen i studie 1 som hade randomiserats till att genomgå undersökning med akut CT skalle, vilket var 1262 patienter. Ogynnsamt utfall efter 3 månader definierades som att ha 3 eller fler kvarstående symptom enligt RPQ respektive att ha nedsatt funktion i vardagsaktiviteter i form av skalsteg 1-6 enligt skalan Glasgow Outcome Scale Extended (GOSE). CT-skalle undersökningarna visade skador i 52 fall (4%), främst i form av svullnad och/eller blödning. 23% av patienterna hade 3 eller fler kvarstående symptom och 8% hade ogynnsamt utfall gällande vardaglig funktion. Skador på CT skalle visade sig inte ha någon prognostisk betydelse. Däremot hade patienter under 30 år ett mer gynnsamt utfall både vad gäller symptomförekomst och vardaglig funktion jämfört med de över 30 år. Män rapporterade bättre utfall än kvinnor både vad gäller symptomförekomst och vardaglig funktion.

Hjärnskakning kan alltså orsaka skada i form av svullnad eller blödning, vilket kan ses på CT undersökning. Tidigare studier har visat att man också kan få diffusa skador på mikrocirkulation och nervceller och för detta är Magnetkameraundersökning (MRI) en mer känslig metod än CT. I studie 4 ingick 19 patienter med hjärnskakning, 7 män och 12 kvinnor med medianålder 28 (spridning 17-63 år). Studieprotokollet omfattade MRI, klinisk undersökning och insamling av data angående symptom och funktion i dagliga livet vid två tillfällen, efter 2-3 dagar respektive efter 3-7 månader. En av patienterna hade patologiska fynd på MRI både vid första undersökningen i form av svullnad i hippocampusregionen och vid uppföljningen i form av atrofi. Vid jämförelse av hjärnvolymen mellan undersökningarna med en data-baserad metod fann man en liten volymminskning hos ytterligare 3 patienter. Dessa totalt 4 patienter med atrofi efter hjärnskakning var inte lika på något sätt vad gäller symptomförekomst eller vardaglig funktion vid uppföljningen. Några statistiska beräkningar gjordes inte på grund av det låga antalet patienter men volymminskning bedöms kunna vara en markör för hjärnpåverkan efter hjärnskakning. Mer forskning behövs både i form av större studier och med avancerade hjärnavbildningsmetoder men också för att undersöka vilken betydelse fynden har för utfallet i form av såväl fysiskt och psykiskt mående som aktivitetsförmåga.

Resultaten i dessa studier visar att (1) en betydande andel av personer som drabbats av hjärnskakning har kvarstående besvär tre månader efter skadan, (2) den vanligt använda RPQ skalan kan förbättras, (3) hjärnskada som påvisas med datortomografi men inte kräver neurokirurgisk behandling.
inte påverkar besvärbilden tre månader efter skadan medan högre ålder och kvinnligt kön ökar risken för sådana besvär och (4) nya MR-metoder kan användas för att påvisa förlust av hjärnsubstans. Resultaten pekar också på behovet av förbättrade uppföljningsprogram efter dessa skador och belyser flera viktiga områden för fortsatta studier.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.