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Moderate and Severe Traumatic Brain Injury

Magnetic Resonance Imaging Findings,
Cognition and Risk Factors for Disability

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Moderate og alvorlige hodeskader
MR-funn, kognisjon og risikofaktorer for funksjonshemming

Moderate og alvorlige hodeskader omfatter pasienter med ytre skade mot hodet og tydelig påvirket bevissthet i akuttfasen. Dette er en sammensatt pasientgruppe der resultatet varierer fra død eller alvorlig funksjonshemming til fullstendig restitusjon. Det eksisterer få studier der man over tid har fulgt en fullstendig kohort av pasienter uten stort frafall.
Formålet med studiene i denne avhandlingen var å studere funksjon hos en fulltallig gruppe av personer som 3-8 år tidligere var behandlet for alvorlig hodeskade ved St. Olavs Hospital. Videre ønsket vi å etablere en pasientdatabase for forskning innen moderat og alvorlig hodeskade ved St. Olavs Hospital. Med utgangspunkt i den ville vi, i denne avhandlingen, spesielt studere MR funn i tidlig fase etter hodeskaden samt grad av kognitiv reduksjon etter tre måneder.

Avhandlingen består av fire delarbeider.

I artikkel I studerte vi forekomsten av funksjonshemming, arbeidsuførhet og epilepsi blant 94 personer (1-88 år), 3 til 8 år etter at de ble behandlet for alvorlig hodeskade. Et hovedfunn var at bare 1/3 hadde fått en alvorlig funksjonshemming etter skaden, slik at de trengte personhjelp i dagliglivet. Det var også i denne gruppen vi fant de fleste tilfellene av epilepsi. Derimot hadde ca 2/3 falt ut av det ordinære skole- og arbeidsliv. Bevissthetstilstand fire uker etter hodeskaden kunne i noen grad forutsi dette.
Artikkel II og III omhandler en gruppe på 106 pasienter fra pasientdatabasen som hadde fått utført MR undersøkelsene i løpet av de fire første ukene. Alle unntatt én pasient hadde tegn til skade i hjernevevet, og ca 70 % hadde diffus aksonal skade. Diffus aksonal skade medførte mer påvirket bevissthet rett etter skaden, men var ikke i seg selv forbundet med dårligere funksjon ett år etter. Ved dobbeltsidig skade i hjernestammen var det stor fare for alvorlig funksjonshemming etter skaden. Skader sentralt i hjernen var en negativ prognostisk faktor hos pasienter med alvorlig hodeskade, men ikke hos de som hadde moderat hodeskade. Alder var en svært viktig negativ prognostisk faktor ved moderat hodeskade.
Artikkel IV beskriver kognitiv funksjon tre måneder etter hodeskaden hos 63 personer med hodeskade sammenliknet med friske personer. Som gruppe hadde de med hodeskade redusert kognitiv funksjon, særlig på tester som krevde hurtig bearbeidelse av informasjon. Redusert kognitiv funksjon ved 3 mnd var også relatert til det å ha plager eller funksjonshemming ett år etter skaden. På den annen side presterte mange i pasientgruppen normalt bedømt ut i fra de normene som brukes i klinisk arbeid. Nesten halvparten av de med normal funksjon hadde plager eller funksjonshemming relatert til hodeskaden ved ett års oppfølging. Dette aktualiserer spørsmålet om hvorvidt vanlige nevropsykologiske tester er sensitive nok for å evaluere effektene av hodeskader.

Foreword

During my work for fifteen years in the field of brain injury rehabilitation, I have got many questions. How is it going to be? Is this problem typical? Or expected?

Questions came from our patients, but also their families, other professionals, lawyers, the Court and insurance companies. And through my work, I gathered experience.

But, inevitably, I collected my experience to a large extent from the individuals who I saw most, and those were person who struggled and who in periods needed much support from our specialized rehabilitation facility. And thus, without really knowing, my view of traumatic brain injury became biased.

Through the Head Injury Project, we have had the unique possibility to get in touch with *all* the persons that were treated for moderate and severe head injuries at this hospital for a long time period. This has increased our understanding of the consequences of head injury. It has shown us a great variation in outcomes, and also that many of those who sustain a traumatic brain injury recover well or cope well with the effects of the injury.

Hopefully, in the years to come, we may be able to answer the questions from our patients and those around them more precisely and, more important; improve our services.

I am deeply grateful to all those who consented to participate in the project; our patients and their families. Their trust and effort made this possible.

Thanks!

Acknowledgements

Table of contents

ABBREVIATIONS

TBI	Traumatic brain injury
HI	Head injury
TBIMS	Traumatic Brain Injury Model System (American database)
WHO	World Health Organization
GCS	Glasgow coma scale
HISS	Head injury severity scale
VS	Vegetative state
MCS	Minimally conscious state
PTA	Posttraumatic amnesia
MRI	Magnetic resonance imaging
DAI	Diffuse axonal injury
CT	Computed tomography
FLAIR	Fluid attenuated inversion recovery
ADC	Apparent diffusion coefficient
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
GOS	Glasgow outcome scale
GOSE	Glasgow outcome scale extended
IMPACT	International Mission for Prognosis And Clinical Trial; database of traumatic brain injury which contains the complete dataset from most clinical trials and organized epidemiologic studies conducted over the past 20 years.
PTE	Posttraumatic epilepsy
ICF	International Classification of Function, Disability and Health
ERP	Event related potentials
EEG	Electroencephalography

LIST OF PAPERS

PAPER I

Global outcome, productivity and epilepsy 3-8 years after severe head injury.

The impact of injury severity.

Toril Skandsen Tom Ivar Lund Nilsen, Oddrun Fredriksli, Anne Vik
Clin Rehabil 2008;22:653-62.

PAPER II

Prevalence and impact of diffuse axonal injury in patients with moderate and

severe head injury: a cohort study of early magnetic resonance imaging findings

and 1-year outcome.

Toril Skandsen, Kjell Arne Kvistad, Ole Solheim, Ingrid Haavde Strand, Mari Folvik,
Anne Vik
J Neurosurg 2009. Oct 23. [Epub ahead of print]

PAPER III

Prognostic Value of Magnetic Resonance Imaging in Moderate and Severe Head

Injury. A Prospective Study of Early MRI Findings and One Year Outcome

Toril Skandsen, Kjell Arne Kvistad, Ole Solheim, Stian Lydersen, Ingrid Haavde
Strand, Anne Vik
Submitted

PAPER IV

Cognitive Impairment Three Months After Moderate and Severe Traumatic

Brain Injury. A prospective follow-up study.

Toril Skandsen, Torun Gangaune Finnanger, Stein Andersson,
Jan Ference Brunner, Stian Lydersen, Anne Vik
Submitted

SUMMARY

Traumatic brain injury (TBI) is a diagnosis comprising a heterogeneous group of patients. A TBI may be categorized as mild, moderate or severe depending on the level of consciousness after the trauma. It is generally accepted that individuals with moderate and severe TBI may experience long-lasting disability, but the frequency and magnitude of cognitive impairments or disabilities are not well described in neurosurgical cohorts that also include moderate injuries. Furthermore, there are few prospective, longitudinal follow-up studies describing early MRI findings.

The objective was to describe early MRI findings as well as the short-term and long-term consequences in samples of individuals with moderate and severe head injury. Furthermore, we sought to study risk factors for disability and epilepsy. We aimed at emphasizing a clinical approach, regarding methods as well as interpretation of results.

Two populations were studied, both including individuals with head injury that had been admitted to St. Olavs University Hospital. One population comprised all patients with severe head injury who had been treated at St. Olav Hospital from 1998-2002. The next population comprised all patients who have been treated with moderate and severe head injuries at St. Olavs Hospital from October 2004 to July 2009. From the latter population two samples were studied: first, a sample of 106 individuals (5-65 years) who had been examined with MRI within four weeks post-injury and second, a sample of 63 individuals (13-65 years) who had been tested with neuropsychological tests 3 months post injury. Control participants in the latter study were 48 healthy individuals, matched for gender, age and years of education.

In the MRI studies, we found that all but one of the patients had visible, traumatic lesions in the brain parenchyma. It was common to find a combination of contusions and diffuse axonal injury (DAI). DAI was very common, and was found in 90 % of patients with severe TBI and in 56 % of those with moderate injury. Patients with DAI had more severely disturbed consciousness as measured with the Glasgow Coma Scale (GCS) acutely after the accident. Only in patients with DAI, was the GCS score related to outcome. DAI was negatively related to outcome only when located in the brain stem.

Brain stem injury was found in 46 % of patients with severe head injury, but also 14 % of the patients with moderate TBI.

The individuals with TBI performed worse than healthy volunteers in most cognitive domains. We used the 5th percentile of the normative data as cut-off for impaired test score, and having ≥ 2 impaired test scores out of a selection of nine tests as definition of cognitive impairment. Doing so, we found that 43 % of the individuals with moderate TBI and 65 % of those with severe TBI had cognitive impairment. Cognitive impairment was associated with disability or complaints affecting daily life at 12 months post-injury. Yet, a substantial proportion of those with normal cognitive performance reported disability or complaints at the time of testing (69 %) or at 12 months follow-up (43 %). Thus, the sensitivity of the tests to a recent TBI or their ecological validity was rather low.

Two thirds of the individuals who survived a severe head injury, and virtually all with moderate head injury, experienced a favourable outcome, that is either no, minor or moderate disability, and independency of others in daily activities. In the first population of severe TBI, however, only one third could participate in paid work or ordinary education more than three years after the injury.

In both populations we found that approximately one third of those who survived severe TBI, experienced long lasting, severe disability, as measured with the extended Glasgow outcome scale. Severe disability was strongly predicted by bilateral brain stem injury on the MRI scan and being in a minimally conscious state or vegetative state 4 weeks post-injury, the latter also being a strong risk factor for epilepsy.

CHAPTER 1   GENERAL INTRODUCTION

1.1 Incidence and mortality

The incidence of traumatic brain injury (TBI) differs among countries [19] as there are variations regarding frequency of traffic accidents, safety in work places and transportation, frequency of assaults and gun shots in the civilian society and, not least, participation in war with the increasing incidence of blast injuries [84]. Consequently, incidence figures from the US, as well as from some of the large developing countries, are of limited relevance to us in Norway.

Tagliaferri et al. performed a meta-analysis on the incidence of TBI in Europe [150]. They derived an overall rate of hospitalized plus fatal TBI of 235 /100 000 pr year. Only some studies reported severity distribution, again with large variations, and thus the incidence of moderate and severe head injuries is not well known.

When we started our data collection in 2004, Norwegian epidemiological research in the field of TBI had mainly been focusing on mild TBI, with the exception of a study of the epidemiology of hospital treated head injury from the northern Norwegian counties [66]. Concurrent with our studies, similar data have been published from other regions, and these are reviewed in section 5.1.5 of this thesis.

Traumatic brain injury is the most common cause of death following trauma [39], which in turn is among the major causes of deaths among young people. For patients with severe head injury admitted alive to hospital, the mortality from the head injury is 25-40 %, depending on whether all age groups are included, and whether patients admitted alive, but with signs of herniation and no hope of survival are included. Mortality from TBI is probably decreasing. From the Traumatic Coma Data Bank, mortality after severe TBI (age 16-65) was 39 % in 1984-87, versus 27 % in 1988-96 [87].

1.2 Definitions and classifications of Head injury and Traumatic brain injury

1.2.1 Head injury and Traumatic Brain Injury

The term Head Injury (HI) defines a trauma to the *head*, not necessarily the brain, although inevitably, that is the case with increasing severity of the HI. Thus, HI encompasses not only brain trauma, but also scalp lesions and cranial fractures, and the HI diagnosis may be used without evidence of loss of consciousness or altered brain function.

A standard diagnosis of traumatic brain injury (TBI), used in the large cohort in the USA, Traumatic Brain Injury Model System (TBIMS, described in section 1.8.3) is: "external mechanical force causing damage to *brain tissue* as evidenced by loss of consciousness, post-traumatic amnesia, or objective neurological findings that can be reasonably attributed to TBI on physical or mental status examination, with or without skull fracture".

All the patients in our studies have clear evidence of mechanical forces acting upon the head as well as disrupted brain function in relation to the trauma, and the terms "Head injury" and "Traumatic brain injury" are both applicable.

1.2.2 Mild, moderate and "definite" injury

The WHO's Task Force on Mild TBI (2004) identified inconsistency in the definition of Mild TBI across studies, typically regarding whether they included cases of Glasgow coma scale (GCS) score of 13 or not [21]. The Task Force recommended that a TBI was mild if GCS score was 13–15 after 30 minutes post-injury, loss of consciousness lasted for less than 30 minutes and post-traumatic amnesia for less than 24 hours.

However, there is a trend in the field of neurosurgery to classify patients with GCS score 13 as moderate head injury as the rate of complications and need for neurosurgical intervention is higher than when GCS score is 14-15 [104, 134].

The term "definite TBI" has also been introduced as synonymously with the moderate-severe TBI spectrum. Some authors have proposed to include TBI cases with intracranial lesions detected by neuroimaging in definite TBI [88]. This would

represent a change in the most common criteria for mild TBI, since traditionally, pathology detected by neuroimaging has not been taken into account. However, there is a move towards developing also the patho-anatomical characteristics into new classification systems [149].

1.3 Measurement of injury severity

1.3.1 The Glasgow Coma Scale (GCS)

This scale from 1974 was developed to assess depth of coma and impaired consciousness [152]. It is based on the observed response to stimuli regarding motor responses, verbal performance and eye opening. Although not primarily intended to be a system to grade head trauma severity, most TBI severity scales are based upon the GCS. The GCS scores range from 3 (no responses to painful stimuli) to 15 (fully alert and oriented patient). It has also been shown that in moderate and severe TBI the motor score alone may be used; with similar, or even better properties than the full scale [89, 153].

1.3.2 The Head Injury Severity Scale (HISS)

HISS is a two dimensional scale based on (a) injury severity assessed with the Glasgow Coma Scale Score (GCS) and (b) presence or absence of complications appropriate for the severity category [144]. The scale is widely adopted, and is used in the Scandinavian guidelines for management of HI. The scale defines cases with GCS score 13, or loss of consciousness (LOC) $\geq$ 5 minutes as moderate head injury. In order to comply with common terminology, we chose *not* to use the concept of "serious head injury" further subdivided into "severe; GCS score 5-8" or "critical; GCS score 3-4" in the HISS, but rather use the term "severe head injury " or "severe TBI" for all patients with GCS score 3-8.

1.4 Clinical phases during recovery

During recovery from TBI, several clinical phases with disturbed consciousness are recognized; from coma towards a fully alert and oriented state [114]. Typically,

each phase is longer than the preceding phase, and thus, recording duration of the clinical stages may provide professionals with valuable prognostic information.

Fig 1.4.1. Traumatic Brain Injury - clinical phases during recovery

Coma   Coma

(Vegetative state)

Minimally conscious state → Posttraumatic amnesia

Gradual improvement of cognitive functions
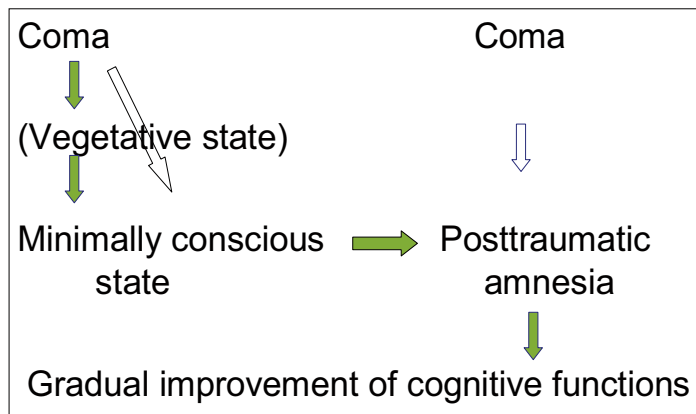
Figure 1.4.1 illustrates the clinical course of recovery of normal consciousness in TBI. The direct transition from coma to posttraumatic amnesia, depicted to the right, illustrates the less severe cases, where the vegetative state and the minimally conscious state may not be present as distinct clinical phases.

1.4.1 Vegetative state

The vegetative state (VS) is a mental state defined by absence of awareness about self or environment [79]. It is distinct from coma by presence of eye opening. Brain stem functions are usually preserved, and thus reflexes may be elicited that mimic responsive behaviour [7]. In the Glasgow outcome scale extended (GOSE), the GOSE score 2 is assigned to patients in VS. The diagnosis VS may be considered permanent 12 months after TBI [1]. Contrary to the belief of many laymen, and probably also some health professionals, permanent vegetative state appears to be an uncommon outcome after TBI [101].

20

1.4.2 The minimally conscious state

A definition and diagnostic criteria for the minimally conscious state (MCS) were published by Giacino et al. in 2002 [52]. MCS is a disorder of consciousness, characterized by inconsistent, but clearly discernible, behavioural evidence of consciousness, and MCS can be distinguished from coma and VS by documenting the presence of specific behavioural features not found in either of these conditions. The MCS has an upper border to posttraumatic amnesia or a fully conscious state, and patients in MCS do not consistently show for instance ability to functional communication or functional use of objects. The concept of MCS has been widely adopted in the field of neurorehabilitation.

1.4.3 Posttraumatic amnesia

Posttraumatic amnesia (PTA) is commonly explained as the time period from the injury until the patient has regained day-to-day memory; however there is a now a trend towards emphasizing the component of disturbed consciousness and similarity with other delirious syndromes [148].

Before the GCS was available, PTA was used to indicate severity of injury. Russell et al., in the sixties, studied a large TBI population and classified injuries as "severe concussion" if PTA duration was between one and seven days and as "very severe concussion" when PTA lasted more than one week, and they did not distinguish PTA above that length [123]. More recent studies, however, have recognized that many patients with severe TBI have longer PTA and still experience a favourable outcome, and that further differentiation of PTA duration is useful [158].

PTA is a strong predictor of outcome, but it is challenging to measure PTA accurately. There are several assessment scales, constructed to cover different aspects of the PTA syndrome. Generally, scales measuring primarily the disorientation [68, 82], tend to produce shorter estimates of PTA duration than those measuring memory for items presented the previous day [151]. For practical reasons, it is generally accepted that the PTA *duration* should be estimated from the day of the injury, thus the given time also comprise the duration of coma, VS and MCS. In several studies, cut off levels of PTA into weeks have been used, and this approach may be clinically useful. Taken together, PTA of less than one week has been

associated with high rate of good recovery [157] and better recovery of memory [17] and PTA duration of less than two weeks with less disability [157]. Presence of severe confusion at three weeks post-injury was associated with lower chances of return to productivity [137]. In a very recent study, the authors found four weeks post-injury to be a useful cut-off point, above which future moderate or severe disability is likely. Eight weeks of PTA was a clear cut-off above which good outcome was very unlikely and risk of severe disability increased [158].

1.5 Neuropathology and neurobiology of TBI

Traumatic brain injury (TBI) is characterized by a complex pathology. The primary lesions comprise focal / multifocal injury; haematomas and contusions and diffuse brain injury; axonal as well as neuronal and vascular [15]. At the microscopic level, a cascade of cellular processes take place within the brain parenchyma [114], and our understanding of these is constantly reviewed. Advances within the field of pathobiology of TBI include increased understanding of exitotoxicity, mitochondrial dysfunction and inflammation following TBI [73, 95], the complex functions of the glial cells [143], biomarkers [69], the microstructure and function of injured axons and patterns of cell death after diffuse brain injury [20, 44].

1.5.1 TBI and localization in the brain

Surface contusions are most severe in the frontal and temporal lobes due to the irregular bony surfaces of the anterior and the middle cranial fossa [15]. Diffuse axonal injury is typically seen in the gray-white matter junction of lobar white matter; most commonly in the frontal and temporal lobes, in the corpus callosum; typically in the splenium due to the close relation to the falx, and in the brainstem; the dorsolateral part of the midbrain and upper pons [48, 51, 109].

1.5.2 Diffuse axonal injury – neuropathology and experimental studies

Diffuse axonal injury (DAI) is an important constituent of the white matter pathology in TBI, and has been related to high energy traumas, as motor vehicle accidents. DAI is more extensive and more severe following severe TBI, but occurs across a larger spectrum of injury, and has also been detected in mild TBI [16]. The

22

concept of DAI has its origin from the field of neuropathology and experimental research with mechanical models and animal models. And also today, a direct observation of damaged axons is only possible through the microscope, although imaging methods for depicting the integrity of the nervous tissue are continuously improved. In experimental research, the term traumatic axonal injury (TAI) is preferred, but in general DAI and TAI seems to be used synonymously in the medical literature.

As early as 1943, Holbourn showed by use of a gelatine model of the brain, that structural deformations could induce injury to the brain and he also postulated major types of forces that could produce this deformation [62]. The importance of these observations were later recognized by Strich, who published the first pathologic descriptions of the shear injuries of the white matter in humans [147]. Later, Gennarelli et al. subjected primates to angular acceleration of the head. They found that three grades of DAI could be produced, with severity of DAI depending on the magnitude and duration of the acceleration and the direction of head motion [47]. In this model the DAI was similar to findings in man. Concurrently, comprehensive neuropathological research was undertaken, by Adams and Gennarelli et al. who performed autopsy of 635 TBI cases from 1968-1982 [3], and they proposed the following grading of DAI:

Grade 1: evidence of diffuse axonal damage in the white matter of the hemispheres including the corpus callosum, in the brain stem and occasionally in the cerebellum: this damage can only be identified microscopically.

Grade 2: A focal lesion was identified in the corpus callosum in addition to the diffuse damage described above, and in some cases this was also only identified microscopically.

Grade 3: A focal lesion was found in the dorso-lateral quadrant of the rostral brain stem in addition to the diffuse damage, and in many cases one of the focal lesions could only be identified microscopically.

(Grades 2 and 3 were said to be severe if they were apparent macroscopically.)

Since this work of Adams and Gennarelli, a lot of research has been conducted to investigate the effects of axonal injury at the microscopic level. The experimental

research conducted by Povlishock's group has demonstrated that the suggestion by Strich and Adams of a mechanical transsection of the axon resulting in axonal retraction and formation of axonal bulbs (primary axotomy) for a large part was not correct. Rather, the forces of injury diffusely alter segments of the axons regarding membrane permeability and axonal transport, but not uniformly. Thus, different populations of axons may respond in different fashions to injury. Especially in axons sustaining long duration of altered axolemmal permeability, a delayed process occurs, eventually leading to axonal failure and disconnection (secondary axotomy) [44]. Moreover, and contrary to earlier belief, axonal injury has also been demonstrated in unmyelinated fibres [118]. Even though the diffuse axonal injury is often followed by degeneration, it has also been demonstrated that not all axonal injury progress to cell death [43]. Furthermore, the mechanisms of diffuse cell death are complex, and not restricted to axotomy-related changes [44]. Taken together, following TBI, there are concurrent detrimental processes, scattered in the brain, targeting axons, neuronal cell bodies and also microvasculature. Thus, the concept "diffuse traumatic brain injury" probably covers this complexity better.

1.5.3 Brain stem injury

Brain stem injury associated with head injury can be characterized as primary; directly caused by the forces of the trauma, or secondary; resulting from the ischemia associated with herniation of the brain. The latter has been the most common type in autopsy studies, but also primary injuries have been demonstrated [98, 139]. Primary brain stem lesions comprise DAI, haemorrhage, contusions and lacerations [15]. The primary brain stem haemorrhages may be seen in the context of a lethal form of diffuse brain injury. Brain stem contusions may be associated with basal skull fractures or result from the impact against the free edge of the tentorium [125].

1.6 Computed Tomography in TBI

1.6.1 Classifications for research

The Marshall classification from 1991 was based on experiences from the Trauma Coma Data Bank and has been extensively used for prediction of outcome

[92] (Appendix 1). The Rotterdam classification was later developed as it could be shown that not only the radiological features covered by the Marshall Classification, but also other characteristics of the computed tomography (CT) scan were independently predictive of outcome [102] (Appendix 2). The most important components of the scales are mass lesions exceeding a certain volume, signs of raised intracranial pressure, such as size of the basal cisterns and presence of midline shift, and (in the Rotterdam classification) traumatic subarachnoid haemorrhage. For both scales, adequate inter-observer reliability was recently demonstrated, for neuroradiologists as well as for neurosurgeons [27]. It has recently been recommended that the worst CT scan should be subjected to classification [133].

1.6.2 The prognostic value of CT

The prognostic value of CT has been shown in many studies. Studies of CT and outcome have the advantage of being large [103] as CT is performed in the diagnostic setting in all cases. CT is probably most predictive in patients with severe injury, when life threatening hematomas or severe signs of increasing ICP are depicted [105].

1.7 Magnetic resonance imaging in TBI

The use of magnetic resonance imaging (MRI) was reported in head trauma patients early in the eighties, but especially after 1986, several important studies were conducted. It has consistently been demonstrated that MRI is more sensitive than CT in detection of parenchymal lesions; DAI, brain stem lesions and cortical contusions [50, 74, 169]. Gentry et al. studied the characteristics and distribution of traumatic lesions in a series of patients with TBI, and also compared these with autopsy findings [49]. They demonstrated that the patterns of lesions depicted in the white matter with MRI were identical to what was found in the pathologic and animal studies [49] and this has been the rationale for use of a modification of the grading of DAI of Adams et al. in MRI studies.

1.7.1 The clinical scan protocol for head injury

The first studies of MRI in TBI were performed with low field strength and few sequences. Today, a typical MRI scan protocol in head trauma is performed at a system with field strength of 1.5 or 3 Tesla, and in addition to T1 and T2, consists of a T2*-weighted gradient echo sequence, a fluid-attenuated inversion recovery (FLAIR) sequence and diffusion-weighted imaging (DWI).

T2*-weighted gradient echo MRI was introduced as early as in 1986 [40]. The technique utilizes the paramagnetic properties of the degradation products of haemoglobin which induce a focal signal loss. Thus, this technique is sensitive for the detection of cerebral micro-haemorrhages which appear dark on the scan (Fig 1.7.1). T2* is a sensitive method in diagnosing the micro-haemorrhages believed to be associated with DAI [128] . Even higher sensitivity is found for examinations performed at 3 Tesla since the focal signal loss from haemoglobin degradation products increases with higher magnetic field strength. [127]. Studies have found increased load of microbleeds in patients with more severe injury [155], but the clinical significance of the load of traumatic microbleeds or the spatial distribution is not yet clear [111].

Fig 1.7.1.

Transversal T2*-weighted gradient echo image. Arrow shows micro-haemorrhages in the frontal lobe white matter indicating DAI.

FLAIR is an MR imaging sequence that was introduced in 1992 [34], and reported used in head injury in 1997 [10, 34] It is a T2-weighted sequence where the high T2-signal from the cerebral spinal fluid is suppressed, while the signal from traumatic brain oedema or gliosis remains bright, thus increasing the depictability of tissue injury. The lesions typically appear as white matter hyper-intensities (Fig 1.7.2). In the acute stage, FLAIR sequences are used for the detection of oedema in the white matter, thought to reflect DAI [10, 109], whereas in the chronic stage, the hyper-intensities probably represent gliotic scarring secondary to the traumatic brain injury [110]. The volume and number of FLAIR lesions have been related to outcome [22, 91]. The oedema, and thus the hyper-intensities depicted acutely, however, gradually vanishes with time, and thus quantification of lesion volume will depend on the time passed since injury.

Fig 1.7.2

Sagittal FLAIR image. Arrow shows lesion in the corpus callosum, indicating DAI.

Diffusion-weighted imaging was developed in 1986 and was first reported in human TBI in 1999 [85]. The method is based on adding strong and rapid magnetic field diffusion sensitizing gradients to a fast T2-weighted imaging sequence. This technique provides image contrast, which results from the molecular diffusion of water molecules in the brain tissue [126]. Since the DWI contains both diffusion and T2- information, these images are compared to the apparent diffusion coefficient

(ADC) map which is a parametric image where the T2-effects have been eliminated while the diffusion effects remain. DWI can reliably distinguish between vasogenic oedema (elevated diffusion) and cytotoxic oedema (restricted diffusion). ADC values in certain regions of interest can also be quantified, which is a common design in research. Using ADC maps, it was demonstrated that ADC values were lower in normal appearing areas of the brain in individuals with TBI compared with controls. Furthermore a correlation with outcome was found [63].

1.7.2 Advanced methods

Several methods require post-processing of MRI data. Examples are MR spectroscopy, different methods for measurement of brain volumes, functional magnetic imaging (fMRI) and diffusion tensor imaging (DTI). Since DTI is increasingly used in MRI research, and is proposed to be a sensitive biomarker of DAI, this method will be briefly described.

In nerve fibres, diffusivity is greater in the direction of the axon, than perpendicular to the fibres (diffusion anisotropy). Diffusion tensor imaging (DTI) is based on sampling of diffusion weighted images for many directions, and computation of eigen-values for the three dimensions [80]. Then, within a voxel, diffusion anisotropy indices may be computed, like FA (fractional anisotropy) values. Processes that damage the microstructure of the axon (like TBI) may result in decreased axial diffusivity and lower FA value.

From the DTI data it is also possible to distract parameters for so-called fibre tracking, thus gaining information of in-vivo orientation of the tissue in space.

DTI is increasingly used in TBI research, and may depict axonal damage beyond that of conventional MRI [168]. It has been used in mild TBI [106, 124] where reduced FA values have been demonstrated in several areas compared with controls and also a correlation between abnormal regions and cognitive performance was found [106]. DTI has been used in patients with very severe injury, where DTI parameters were studied longitudinally and a higher tendency towards normalization was found in the patients who recovered function [140].

1.7.3 Brain stem injury

The earliest reports based on MRI of the occurence of brain stem lesions, are from Gentry et al. in the late eighties [51]. They compared CT and MRI in the detection and characterization of brain stem lesions and also investigated the frequency, location, distribution and the differentiating features of primary and secondary brain stem lesions. Later, Firsching et al. performed very early MRI in a large series of patients with severe injuries. They found a very high incidence of brain stem injury, 64%. Patients with bilateral pontine lesions had a 100 % mortality rate as opposed to patients without brain stem lesion; with 9% mortality [45]. In general lesions in pons and mesencephalon have been associated with poor prognosis, most notably when they are bilateral and symmetrical [45, 161].

Also with MRI, two patterns of brain stem lesions have been found. Patients with superficial, focal brain stem injury caused by the impact against the free tentorial edge, had a better prognosis than those with a deeper axonal injury in the dorsal brain stem [138].

1.7.4 Remaining questions

Much of the recent research regarding MRI in patients with TBI, has been performed in selected patients, and has focused on the development of more sensitive techniques as well as on investigation of mechanisms. Also correlations between findings and outcome have been studied. Some important contributions were described above in the section 1.7.1.

Still, studies of high external validity that are informative to clinicians regarding the clinical usefulness of MRI in TBI are few. Since the studies of Gentry et al, MRI characteristics have not been much studied in series of consecutive head injury patients. Particularly, more MRI studies of patients with moderate head injuries are needed. Firsching et al. studied a cohort of patients with very severe injuries, as did Kampfl et al. [72]. Lagares et al. studied consecutive patients with moderate to severe TBI, yet they did not report how patients were selected to MRI [76]. Some studies, like those of Gentry and Kampfl, were also performed before the introduction of the most sensitive MRI sequences that are now common in clinical protocols.

For example it is argued that DAI may be a common cause of poor outcome [104, 160] and that this type of injury is likely to be responsible for many of the cognitive deficits resulting from moderate to severe TBI [129]. However, we have not found any MRI studies that actually compared outcome in patients with and without DAI. And with the current understanding that DAI may be a component of all TBI from the mild injuries to the fatal cases, apparently the presence of DAI, as such, can not be regarded a general marker of poor prognosis. Thus, the sensitivity and relevance of the MRI based diagnosis of DAI still needs to be investigated.

Furthermore, the prognostic value of MRI for the clinicians is not well established [160], and few have studied the value of MRI *in addition to* established prognostic factors, such as age, injury severity, pupillary reactivity and CT characteristics in multivariable analyses [99].

1.8 Outcome and prognostic factors in TBI

Moderate and severe TBI have adverse effect on cognitive [36] and social [154] functioning, and is also associated with psychiatric [59] and neurological disorders [12]. The wide array of studies makes it an impossible task to summarize current knowledge of outcome after TBI within the context of this thesis. Still, it is a fact that it is difficult to compare findings across studies, since few have similar datasets when it comes to patient selections, outcome measures and time to follow-up. Moreover, there are large differences between countries regarding social conditions; access to health care and social benefits and general employment rate, and these further complicate comparisons. Finally, reviews have identified a high frequency of studies with significant methodological weaknesses [54, 135, 136]. After a consensus conference in USA in 1998, it was stated, that "mild, moderate and severe traumatic brain injury (TBI) differ greatly in symptoms, signs, recovery and outcomes, and that each category needed to be studied specifically" [115]. Nevertheless, when research since this conference was reviewed in a paper in 2006, one of the conclusions was that "the natural history of mild, moderate and severe TBI has still not been adequately investigated" [116].

Thus, there is still a need for updated studies of outcome, from different countries and different settings, to inform clinicians about what clinical course and outcomes to expect. In the following, some types of studies and research questions are briefly described.

1.8.1 The large databases of neurosurgical patients

There are some very large meta studies of patients recruited from a neurosurgical setting. These studies have typically investigated global outcome, measured with the Glasgow Outcome Scale (GOS), which is described in section 3.5.1. Follow-up has mostly been limited to the first 6 or 12 months post-injury [25, 65, 93, 99, 100, 120, 122]. One of the largest and most recent is the IMPACT database (International Mission for Prognosis and Clinical Trial design database), which utilized data from 8686 patients drawn from eight randomized controlled trials and three observational studies. The majority of the patients included had severe TBI, but some studies included up to a 28 % moderate cases [90]. The most powerful independent prognostic variables were age, GCS motor score, pupil response, CT characteristics, hypotension, hypoxia and abnormalities of glucose [99]. Given the excellent power of these studies, the major prognostic factors are now well established regarding death and disability, at least for severe disability, at 6 months post-injury.

1.8.2 Long-term outcome in neurosurgical cohorts

Surprisingly few studies have described long-term outcome in neurosurgical samples of survivors of severe head injuries. It may be too early to assess the true consequences of head injury after six months, especially in samples with severe injuries, where recovery tend to be slower and functional gains have been shown to occur even after the first year [32, 108]. In these studies, outcomes assessed are more varied; disability [61], return to work [33], cognitive functioning [37], psychological distress [35] and quality of life [37]. Unfortunately, these are often flawed by loss to follow-up of 30-50 %. As there are differences between participants and non-participants [30], this may have biased the results. Long term outcome after head injury was explored in a cohort from Glasgow; they found

disability in 76 % of the survivors of severe TBI; 36 % experienced severe disability [162].

1.8.3 Long-term outcome in cohorts of rehabilitation patients

In the US, the TBI Model System is a large dataset of more than 8000 TBI patients who have been admitted to a trauma center and subsequently received in-patient rehabilitation in one of the connected rehabilitation centres (http://www.tbindsc.org). The centres are of high quality, and professionals are obliged to carry out comprehensive data collection according to the study protocol. Each center also focuses specifically on selected research topics. This database contains longitudinal data up to 15 years post-injury, and has resulted in numerous well designed studies. However, as the included patients needed inpatient rehabilitation, this cohort consists of a more severely injured sample [31].

Many other cohorts and studies could be mentioned specifically. However, a systematic review on prognostic factors for long-term disability and productivity was published a few years ago [163]. Taken together, predictive of disability were older age, pre-injury substance abuse and more severe disability in the subacute phase. Wood reviewed really long-term outcome in 2008 [167], and found that functional abilities may improve over years, and the importance of initial injury severity as prognostic factor weakens over years. For late outcome, it was summarized that neuropsychological impairment, low pre-morbid education, lack of insight and coping style were negative predictors of outcomes.

1.8.4 Returning to work or school

Returning to work or school (productivity) is an important goal for individuals following head injury and is associated with higher quality of life, mental and physical health and social integration [6, 107]. Yet, participation in competitive work is low after severe TBI, also among those who were previously employed [18, 29, 113, 122]. Non-productivity has been associated with pre-injury unemployment, longer PTA duration, substance abuse and higher disability by admittance to rehabilitation [163]. There is also strong evidence that restrictions in working life are directly related to cognitive impairments in the early stage [11, 135]. It has been

shown that part-time work after TBI was related to higher social integration and engagement in home activities than full time work [107], which is not surprising given the reduced cognitive capacity and fatigue that is common after TBI [141]. Supported employment was cost-effective for individuals with TBI if carried out over time, and with structured support [159].

1.8.5 Outcome in patients with very severe injuries

In recent years, more attention has been paid to rehabilitation interventions and outcomes in the group of patients with the very severe head injuries. These patients show heterogeneity of outcome, with some individuals eventually experiencing a favourable outcome [53, 57, 77]. Consequently, the field of brain injury rehabilitation in Norway has developed more structured rehabilitation services for this group during the last years. This has, among other factors, been inspired by the Danish approach with centralization of early, intensive rehabilitation after very severe brain injury [41].

1.8.6 Posttraumatic epilepsy

Posttraumatic epilepsy (PTE) may be divided into early and late. Early seizures; that occur during the acute phase (often defined as within 1 week), are often interpreted as symptomatic. Late seizures imply high risk of new seizures, and antiepileptic drugs are usually initiated after just one seizure.

Findings from previous studies have shown that individuals suffering penetrating injury, injuries with certain radiological characteristics and severe head injury are at higher risk [9, 42, 46, 96]. There are, however, no studies exploring the risk and risk factors *within* samples of severe TBI.

1.9   Cognitive deficits and neuropsychological assessment

Cognitive dysfunction is very common after moderate and severe TBI [36]. Particularly vulnerable are information processing speed and attention [94, 164], memory [156] and executive functioning [38]. This is in line with the pathobiology of TBI described in section 1.5.1., as the frontal and temporal lobes are predilection sites of the diffuse axonal injury as well as contusions, and as the diffuse axonal

injury would reduce the efficacy of the networks within the brain. There is a dose-response relationship between injury severity and cognitive dysfunction [130, 141], and deficits are more pronounced early after the injury. Several studies have reported time course of recovery, and steepest recovery curves are seen for the first few months. Furthermore, recovery curves were not identical for the different cognitive domains [26]. It has been shown that cognitive impairments mediate the reduction in function commonly seen after TBI [117], and assessment of cognitive functioning with neuropsychological tests is an important part of the diagnostic of individuals with TBI. However, the traditional neuropsychological tests have been criticized for having low ecological validity [24], and the interpretation of the test results is also challenged by the fact that healthy individuals perform below the normal range in some percentage of administered tests [67, 131].

It is common to perform the first neuropsychological assessment during the first months after the injury, but after resolution of PTA [135].

1.9.1 Normative data and definition of impairment

Neuropsychological test results are typically given as raw scores, and also converted to standardized scores. A standardized score is a measure of the raw score compared with the mean of a reference sample, usually one that has been published by the manufacturer of the test. The reference sample usually comprises healthy individuals in the same age group, or a group matched on age and education. Standardized scores may be given as different units: Standard scores (S-scores) with mean of 10 and a standard deviation (SD) of 3, T-scores with a mean of 50 and a SD of 10, Z-scores with a mean of 0 and a SD of 1.0 or percentiles, given as the percentage of the reference sample performing as low or lower on the test, the mean being 50, and 1 SD corresponds to the 16th percentile.

An individual's standardized test score is often classified as impaired if it is below 1.5 SD according to the reference norms for the test (T-score $\leq$ 34, S-score $\leq$ 5; Z-score $\leq$ -1.5 or percentile $\leq$ 5). This is rather common practice in neuropsychology, but other cut-off points may also be applied. In the clinical context, before concluding that a low test score reflects impairment, it is also evaluated in the

light of general abilities and performance on other tests [146], but the empirical basis for this subjective evaluation is currently debated [67].

1.9.2 Effect sizes

During the last years, there has been a shift towards requesting researchers to present a measure of the magnitude of effects (effect size), not just the p-value indicating statistical significance. One frequently used measure in neuropsychology is a standardized difference of means, often computed as the Cohen's d:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s},$$

Cohen assumed equal variance and normal distribution, and did not give details of how s (= SD) should be applied in unequal samples. Many uses pooled SD if groups are unequal (s_{pooled}), and this is computed by the following formula:

$$s_{pooled} = \sqrt{\frac{s_1^2(n_1 - 1) + s_2^2(n_2 - 1)}{n_1 + n_2 - 2}}$$

Cohen denoted d = 0.8 as large, d=0.5 as medium and d=0.2 as small [28].

Other similar measures exist, like the Glass' Δ or d, using only the SD of one group, typically the control group:

$$\Delta = \frac{\bar{x}_1 - \bar{x}_2}{s_2}$$

When data are not normally distributed, an estimate of effect size may be computed by dividing the difference between the median scores by the Inter quartile range (IQR) x 0.75 [56].

The effect size is directly related to power and sample size; if the standardized difference between two groups is small, the sample needs to be very large to have sufficient power to detect a true effect. This was studied by Cohen in 1962, where he demonstrated that the majority of studies had low chances to prove true effects due to low power. A later review has shown that this concern is still relevant in neuropsychology [14].

The size of d may also be thought about in terms of overlap between two distributions (Fig 1.9.1).
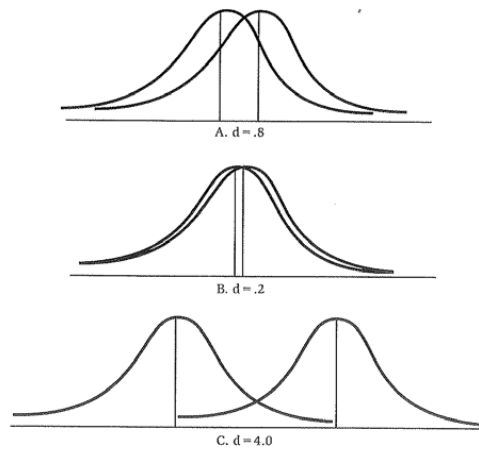
Figure 1.9.1. Overlap of populations as a function of effect size.

A: d=0.8 (large); 21 % of the lower population exceeds the mean of the higher. B: d=0.2 (small), C: d=4.0

(From "Introductory Statistics for the Behavioral Sciences"; Welkowitz, Cohen and Ewen; 2006; reprinted with permission from Wileys and Sons).

CHAPTER 2 AIMS OF THE THESIS

2.1 Paper I:

To describe long-term outcomes in a consecutive sample of patients admitted with severe head injury to our hospital in the five-year period from 1998 to 2002. The hospital is the only trauma centre serving a defined Norwegian health region, and thus, the study had the potential to provide some population-based estimates. Furthermore, we wanted to relate the outcomes to injury severity.

2.2 Paper II:

To describe the frequency and staging of DAI depicted with early MRI in consecutive patients with moderate and severe head injury admitted to a neurosurgical department from October 2004 to august 2008. Furthermore, we wanted to relate the findings to the Glasgow Coma Scale score and to global patient outcome.

2.3 Paper III:

In the same cohort of patients with moderate and severe head injury as described in paper II, we further sought to describe the depth distribution of primary traumatic lesions, describe the prevalence and outcome of different types of brainstem injury (BSI) and explore the possible prognostic value of early MRI scans.

2.4 Paper IV:

To explore the magnitude and frequency cognitive impairments three months after moderate and severe traumatic brain injury (TBI) and study the relation to presence of complaints or disability at one year follow-up.

CHAPTER 3   MATERIALS AND METHODS

3.1 Setting

3.1.1 The Health region of Central Norway and St. Olavs Hospital

Norway is divided into four health regional authorities, and patients who were included in the studies described in this thesis, mostly live in Central Norway. The region has three counties (Møre og Romsdal, Sør-Trøndelag and Nord-Trøndelag) and serves around 666 000 inhabitants.

St. Olavs Hospital is the regional university hospital and is situated in the city Trondheim, Sør-Trøndelag County. The studies in this thesis comprise only patients treated in this hospital. The hospital is the local hospital of the county; with 287 000 inhabitants, and the only level I trauma centre in the region. Furthermore, it is the only hospital in the region with neurosurgical service. Thus, the patients admitted with severe head injury came from the whole region. Regarding moderate head injuries in patients younger than 65 years, 50 % of the patients were inhabitants of Sør-Trøndelag County. The remaining 50 % lived outside the county, and thus belonged to other local hospitals, but were admitted to St. Olavs Hospital due to either location of the accident, or because observation in a neurosurgical unit was indicated.

3.2 Study design and study populations

3.2.1 Study population 1998-2002

The study in Paper I is an observational study that can be described as a prospective follow-up study, but where the participants and the injury-related variables were collected retrospectively. In this study we aimed at tracking all patients who had been treated with severe head injury at St. Olavs University Hospital during 1998-2002 for evaluation of long-term outcome. Figure 3.2.1 describes the study sample.

Figure 3.2.1. Study population 1998-2002


```
┌──────────────────────────┐         ┌──────────────────────────────┐
│ All patients admitted     │────────▶│ Death of other injuries      │
│ alive with severe head    │         │ first 24 hours               │
│ injury during 1998-2002   │         │ n= 2                         │
│                           │         └──────────────────────────────┘
│        n= 146             │────────▶┌──────────────────────────────┐
└──────────────────────────┘         │ No treatment initiated due   │
            │                         │ to irreversible intracranial │
            ▼                         │ hypertension                 │
┌──────────────────────────┐         │ n= 9                         │
│ All patients treated with │         └──────────────────────────────┘
│ severe head injury during │
│ 1998-2002                 │         ┌──────────────────────────────┐
│                           │────────▶│ Death due to the head injury │
│        n= 135             │         │ first 6 months               │
└──────────────────────────┘         │ n= 32                        │
            │                         └──────────────────────────────┘
            │                         ┌──────────────────────────────┐
            │────────────────────────▶│ Death due to other cause     │
            │                         │ first 6 months  n= 1         │
            │                         └──────────────────────────────┘
            │                         ┌──────────────────────────────┐
            │────────────────────────▶│ Death 6 – 36 months          │
            │                         │ post-injury; all causes n= 8 │
            ▼                         └──────────────────────────────┘
┌──────────────────────────┐
│ Patients invited for      │
│ outcome assessment        │         ┌──────────────────────────────┐
│                           │────────▶│ Did not consent; n= 1        │
│        n= 94              │         └──────────────────────────────┘
└──────────────────────────┘         ┌──────────────────────────────┐
            │────────────────────────▶│ Lost to Follow-up  n= 0      │
            ▼                         └──────────────────────────────┘
┌───────────────────────────────────────────────┐
│ PATIENTS EVALUATED FOR LONG-TERM OUTCOME       │
│ n= 93                                          │
└───────────────────────────────────────────────┘
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3.2.2 The Head Injury Project– running since 2004

The Head Injury Project is an on-going cohort study where all patients admitted with moderate and severe head injuries at St. Olavs University Hospital, are consecutively registered. The cohort study was started in October 2004. By the time the last participant in the studies (Paper IV) was included, in July 2009, 290 patients had been registered. There are no exclusion criteria. The cohort study is run in collaboration between several departments at the hospital: Department of Anaesthesia and Acute Medicine, Department of Neurosurgery, Department of Diagnostic Imaging and Department of Physical Medicine and Rehabilitation. The data collection is comprehensive and research topics are numerous within pre-hospital management, intensive care medicine, neurosurgery, neuroimaging, rehabilitation and outcome.

Up until July 2009, only 8 persons had not consented for follow-up, Thus, the participation rate is 97 %. Of those who have consented, only 3 (1 %) have been lost to follow-up.

The groups of individuals with TBI studied in Paper II-IV are all participants in this main cohort.

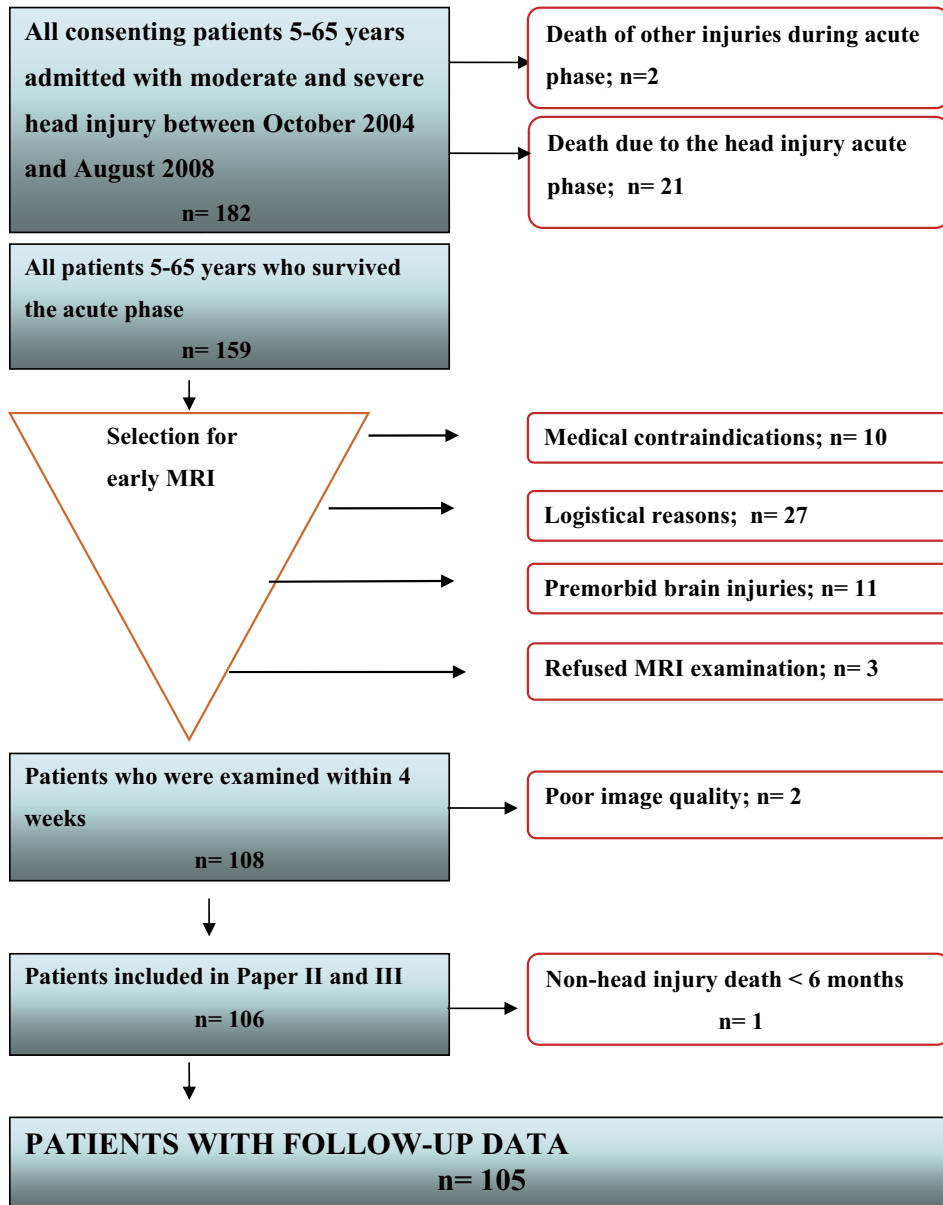### 3.2.3 The study sample in the MRI studies

The sample of patients in Paper II and III, encompass patients aged 5-65, where MRI was performed within 4 weeks post-injury. The selection of patients is described in Figure 3.2.2.

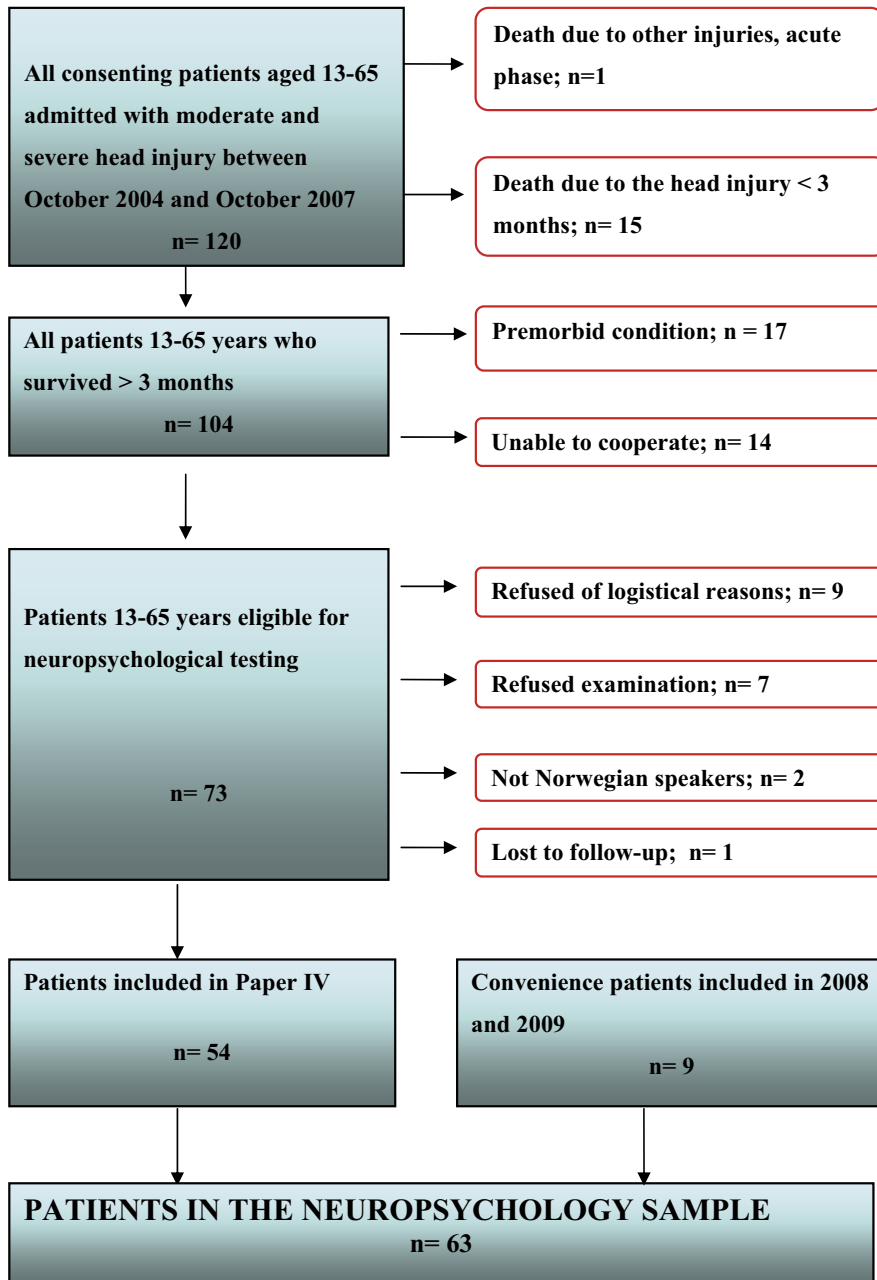### 3.2.4 The study sample in the neuropsychology study

The sample of patients in Paper IV, were patients aged 13-65, who had been assessed with a standardized neuropsychological test battery three months post-injury. The selection of patients is described in Figure 3.2.3.

Figure 3.2.2. Selection of patients for the MRI studies

All consenting patients 5-65 years admitted with moderate and severe head injury between October 2004 and August 2008
n= 182

Death of other injuries during acute phase; n=2

Death due to the head injury acute phase; n= 21

All patients 5-65 years who survived the acute phase
n= 159

Selection for early MRI

Medical contraindications; n= 10

Logistical reasons; n= 27

Premorbid brain injuries; n= 11

Refused MRI examination; n= 3

Patients who were examined within 4 weeks
n= 108

Poor image quality; n= 2

Patients included in Paper II and III
n= 106

Non-head injury death < 6 months
n= 1

PATIENTS WITH FOLLOW-UP DATA
n= 105

Figure 3.2.3. Selection of patients for the neuropsychology study

```
┌──────────────────────────────┐        ┌──────────────────────────────┐
│ All consenting patients aged  │───────▶│ Death due to other injuries,  │
│ 13-65 admitted with moderate  │        │ acute phase; n=1              │
│ and severe head injury        │        └──────────────────────────────┘
│ between October 2004 and      │        ┌──────────────────────────────┐
│ October 2007                  │───────▶│ Death due to the head injury  │
│              n= 120           │        │ < 3 months; n= 15             │
└──────────────────────────────┘        └──────────────────────────────┘
                │
                ▼
┌──────────────────────────────┐        ┌──────────────────────────────┐
│ All patients 13-65 years who  │───────▶│ Premorbid condition; n = 17   │
│ survived > 3 months           │        └──────────────────────────────┘
│              n= 104           │        ┌──────────────────────────────┐
│                               │───────▶│ Unable to cooperate; n= 14    │
└──────────────────────────────┘        └──────────────────────────────┘
                │
                ▼
┌──────────────────────────────┐        ┌──────────────────────────────┐
│ Patients 13-65 years eligible │───────▶│ Refused of logistical         │
│ for neuropsychological testing│        │ reasons; n= 9                 │
│                               │        └──────────────────────────────┘
│                               │        ┌──────────────────────────────┐
│                               │───────▶│ Refused examination; n= 7     │
│                               │        └──────────────────────────────┘
│              n= 73            │        ┌──────────────────────────────┐
│                               │───────▶│ Not Norwegian speakers; n= 2  │
│                               │        └──────────────────────────────┘
│                               │        ┌──────────────────────────────┐
│                               │───────▶│ Lost to follow-up;  n= 1      │
└──────────────────────────────┘        └──────────────────────────────┘
                │
                ▼
┌──────────────────────────────┐        ┌──────────────────────────────┐
│ Patients included in Paper IV │        │ Convenience patients included │
│                               │        │ in 2008 and 2009              │
│              n= 54            │        │              n= 9             │
└──────────────────────────────┘        └──────────────────────────────┘
                │                                        │
                └──────────────────┬─────────────────────┘
                                   ▼
┌──────────────────────────────────────────────────────────────────────┐
│         PATIENTS IN THE NEUROPSYCHOLOGY SAMPLE                         │
│                         n= 63                                         │
└──────────────────────────────────────────────────────────────────────┘
```

3.2.5 The control group

The control group was established from 2008 to 2009. It consisted of 48 persons and was matched with the patient group on the factors age, sex and years of education. One test technician and two master level students (psychology and neuroscience) performed the testing of control participants.

3.3 Procedures for inclusion and data collection

3.3.1 In the study of the patients from 1998-2002

The last author of the papers identified patients who had been consecutively admitted with severe head injury during the specified time period. Lists of hospitalized patients, with relevant diagnostic codes were checked for eligible patients and followed by review of the medical records to select patients with severe head injury. Medical records and CT scans were reviewed to collect the injury related variables of interest. Prior to the follow-up interviews, written information about the study was sent by mail. Next, they or their relatives were contacted by telephone, and then oral consent was obtained. Four patients had died more than three years post injury. In these cases we wrote to their relatives and asked for their consent to provide the information necessary to assign the patient to an outcome category based on their function prior to the disease that caused death.

3.3.2 In the Head Injury Project

Residents and research assistants at the neurosurgical department identified patients admitted with moderate or severe head injury, and patients or relatives were provided written information about the study. Demographic variables were obtained through contact with the families. Injury related variables were collected by the resident who first examined the patient at admittance, by completing a form designed to record the specified variables of interest. The residents had access to discuss inclusion criteria and case variables with experienced physicians in charge of the database. The data collection form is comprehensive and encompasses variables documenting demographic data, mechanism of injury, pre-hospital management and transportation times, variables describing physiological and cerebral state at several

time points as well as treatment and procedures applied in the different stages of the hospital stay. The variables relevant for this thesis are displayed in tables in the separate papers. Procedures regarding neuroimaging, outcome assessment and neuropsychological assessment are described in separate sections.

3.3.3 Duration of PTA

Duration of PTA, which was used in Paper IV, as well as the clinical condition at 4 weeks post-injury, used in Paper I, were estimates made by the author of this thesis. This was performed as a clinical judgement of the whether the observed or described behaviour was best described as (a) an oriented state; the patient being cooperative and oriented to place and situation, (b) posttraumatic confusion (PTA), (c) the minimally conscious state or (d) the vegetative state. For definitions, see section 1.4.3.

3.4 Neuroimaging

3.4.1 Computed Tomography

The CT variables in the study were derived from the CT examinations which were routinely performed as part of the clinical management. In the study described in Paper I, the CT scans were reviewed and classified according to the Marshall CT Classification [92] by a trained neurosurgeon.

In the study described in Paper II and III, the scans were all reviewed by a radiologist who participated in this study in order to classify findings according to the Marshall CT Classification and the more recently proposed Rotterdam CT Classification. See also section 1.6.1.

3.4.2 Magnetic Resonance Imaging

MRI was performed at 1.5 Tesla, by use of a protocol which included T1- and T2- weighted imaging, T2-weighted FLAIR imaging, T2*-weighted gradient echo imaging and diffusion weighted imaging, for description see also 1.7.1. A detailed description of the parameters of the scan protocol is given in Paper II.

MRI examinations were reported by two neuroradiologists. Later they, as well as the author of this thesis, reviewed the scans to obtain the following variables: DAI was graded 1-3 as described in Paper II, contusions were classified as uni- or bilateral and as 1 versus ≥ 2, brain stem lesions were classified as contusions or DAI; uni- or bilateral and depth of deepest lesion depicted as shown in the table below.

MRI derived depth of lesion

Level	Definition
Hemispheres	Traumatic lesions[1] confined to the cerebral cortex or lobar white matter
Central	Traumatic lesions[1] in the corpus callosum, thalami or basal ganglia[2]
Brainstem, Unilateral	Traumatic lesions[1] in the brain stem unilaterally[2]
Brainstem, Bilateral	Traumatic lesions[1] in the brain stem, bilaterally[2]
[1]Signal loss compatible with micro-bleeds (in the GRE sequence) or increased signal intensity compatible with tissue edema (in the FLAIR sequences). [2] Traumatic lesions at a higher level may also be present.	

We further made a distinction between two types of primary lesions in the brain stem. The primary were (a) brain stem contusions; these were superficial lesions, typically situated anteriorly, and hypothesized to result from the brain hitting the free tentorial edge and (b) DAI lesions; involving deeper parts of the brain stem, and these could be unilateral or bilateral. MR images of the two types of brain stem lesions are presented in paper III.

3.4.3 Inter-rater reliability

For evaluation of reliability of the classification of MRI lesions used in Paper II and III, 31 cases were drawn evenly and blindedly from the ascending list of patients. Their scans were scored by a third neuroradiologist who was blinded to clinical information and previous classification. Lesions were classified according to presence and staging of DAI, presence and type of brain stem lesions, and presence of lesions in deep gray matter.

3.5 Outcome measures

3.5.1 Glasgow Outcome Scale Extended

For global outcome, the Glasgow Outcome Scale Extended (GOSE) was used, which is an extended version of the widely used Glasgow Outcome Scale (GOS) [70, 71, 165]. The scales have been shown to have good discriminating abilities and low ceiling effect [64] and may also be used by telephone [112]. In the papers I-III, the term disability was used to cover severe and moderate disability defined as categories in the GOSE, and disability encompasses the outcome categories GOSE 2-6 (In GOS the corresponding categories would be GOS 2-4) (Appendix 3). In GOSE 7 and 8, symptoms caused by the injury may be present, and if to a degree that affects daily life, this may be denoted as "minor disability" (GOSE 7) [165]. In Paper IV, we dichotomized the GOSE score between 7 and 8, to study the occurrence of what we described as "complaints or disability", that is a GOSE score ≤ 7.

Outcome was assessed using the structured interview for GOSE [70, 71, 165] by telephone (Paper I), personal contact (Paper IV) or either of the two (Paper II and III). In order to reduce the potential error associated with the telephone setting [81], relatives or caregivers also provided information, and the best source of information was used. Relatives were interviewed in two thirds of the cases in Papers I-III. The author of this thesis conducted all the interviews in Paper I and IV and the majority of those in Paper II and III. The remaining were conducted by two research assistants, both experienced clinicians, who also had access to discuss scoring with the first author at any time.

We used a revised Norwegian translation of the GOSE in Paper II-IV. This was developed in 2007, by a national collaboration where the author of this thesis participated.

3.5.2 Employment and productivity

Employment was defined as paid work; full time or part time, even in combination with other governmental benefit. Housekeeping was rated as employment only if there were children in the family.

Productivity defines either paid work or participation in education without special adjustments.

3.6 Neuropsychological assessment

Neuropsychological assessment was performed at three months post-injury using a comprehensive battery of neuropsychological tests designed to cover the domains typically affected by TBI; attention, information processing speed, executive functions and memory. The test battery is shown in Table 3 in Paper IV. The assessment was part of a clinical follow-up, and test results, as well as the psychologist's clinical evaluation, were also used to guide subsequent rehabilitation interventions. Testing was performed by trained psychologists, one test technician and two master-level students at the Brain Injury Unit at the Department of Physical Medicine and Rehabilitation, St. Olavs University Hospital.

Raw scores were used, and they were also converted to standard scores by use of the material provided by the manufacturers of the tests, except for the SDMT; where a normative sample quoted by Lezak [83] was used. For a more detailed explanation, see section 1.9.1

3.7 Statistical methods

Statistical analyses have been described in detail in the individual papers, and some statistical considerations are also included in the Discussion section 5.1.6.

CHAPTER 4   SUMMARY OF RESULTS

4.1 Paper I

Objective: To assess long-term outcome in survivors after severe head injury and relate outcome to injury severity.

Design: Follow-up 3-8 years post-injury in a retrospectively collected sample.

Setting: A neurosurgical department in a regional trauma centre.

Subjects: Of 146 individuals admitted, 135 were actively treated. Twenty-four percent of these died within six months. Ninety-three of the 94 (age 1-88) who survived more than three years, were included in the follow-up. They were separated into groups based on their level of consciousness at four weeks post-injury: oriented (n =39), confused (n = 22) or in a minimally conscious/vegetative state (MCS/VS) (n=26) and not possible to assess (n = 6).

Outcome measures: Glasgow Outcome Scale Extended (GOSE), participation in work/education (productivity) and post-traumatic epilepsy (PTE).

Results: GOSE scores were: vegetative state: 3%, severe disability: 28% (22% lower level, 6% upper level), moderate disability: 39% (22% lower level, 17% upper level), and good recovery: 27% (10% lower level, 17% upper level). Productivity was 34% (age 7- 64). The three severity groups had different GOSE scores (p< 0.001) and different proportion of productive individuals (p< 0.001). Twenty-three percent experienced PTE, and PTE was significantly associated with the highest injury severity (p<0.001) and intracranial surgery (p=0.01).

Conclusions: Being independent in daily life, but unable to work, was the typical long-term outcome. Stratifying the patients based on consciousness at four weeks, we found different outcomes. Among oriented patients, almost all regained independency, whereas in the most severe group, poor outcomes and PTE were common.

4.2 Paper II

Objective: In this prospective cohort study we examined patients with moderate to severe head injuries with magnetic resonance imaging (MRI) in the early phase. The objective was to explore the occurrence of diffuse axonal injury (DAI) and if DAI was related to level of consciousness and patient outcome.

Methods: One hundred and fifty-nine patients with Glasgow Coma Scale (GCS) score 3-13, were admitted from Oct 2004 to Aug 2008 (age 5-65 years and surviving the acute phase). Out of these, 106 patients were examined with MRI within four weeks post-injury. Three stages of DAI were used; stage 1: lesions confined to the lobar white matter, stage 2: callosal lesions and stage 3: lesions in dorsolateral brain stem. Outcome measure was Glasgow Outcome Scale Extended (GOSE) 12 months post-injury.

Results: DAI was detected in 72% of the patients and a combination of DAI and contusions or hematomas was found in 50%. GCS score was significantly lower in patients with "pure DAI" (median 9) than in patients without DAI (median12; p=0.001). GCS score was related to outcome only in patients with DAI (r=0.47; p=0.001). Patients with DAI had GOSE score 7, and patients without DAI had GOSE score 8 (p=0.10). Outcome was better in patients with DAI stage 1 (median GOSE score 8) and DAI stage 2 (median 7.5) than in patients with DAI stage 3 (median 4; p=0.001). Thus, in patients without any brain stem injury, there was no difference in good recovery between patients with DAI (67 %) and patients without DAI (66 %).

Conclusion: Diffuse axonal injury was found in almost three-quarters of patients with moderate and severe head injury who survived the acute phase. DAI influenced the level of consciousness, and only in DAI patients was GCS score related to outcome. Finally, DAI was a negative prognostic sign only when located in the brain stem.

4.3   Paper III

Object: To describe the prevalence and impact of traumatic brainstem lesions in patients with moderate and severe head injury surviving the acute phase. Furthermore, we sought to explore the prognostic value of depth of lesions depicted with early magnetic resonance imaging (MRI).

Methods: In a cohort of 159 consecutive patients with moderate to severe head injury (age 5-65 years and surviving the acute phase) admitted to a regional level 1 trauma centre, 106 (67%) were examined with MRI within four weeks post-injury. Depth of lesions in MRI was categorized as: hemispheric level, central level, and brainstem injury (BSI). Outcome measure was Glasgow Outcome Scale Extended (GOSE) 12 months post-injury.

Results: Forty-six percent of patients with severe injuries and 14 % of patients with moderate injuries had BSI. In severe head injury, central or brainstem lesions in MRI together with higher Rotterdam CT score, pupillary dilatation and secondary adverse events were significantly associated with a worse outcome in age adjusted analyses. Bilateral BSI was strongly associated with a poor outcome in severe injury with positive and negative predictive values of 0.86 and 0.88, respectively. In moderate injury, only age was significantly associated with outcome in multivariable analyses.

Conclusion: Almost half of patients with severe head injury, but also some with moderate injury, had BSI depicted with MRI. In patients with severe head injury, surviving the acute phase, depth of lesion in the MRI was associated with outcome, and in particular, bilateral brainstem injury was strongly associated with poor outcome. In moderate head injury, surprisingly, there was no association between MRI findings and outcome when using the GOSE as outcome measure.

4.4 Paper IV

Objective: To explore the magnitude and frequency cognitive impairments three months after moderate and severe traumatic brain injury (TBI) and study their relation to presence of complaints or disability at one year follow-up.

Design: Follow-up study

Setting: Patients prospectively included from a regional level I trauma center.

Participants: Patients (aged 13-65 years) with definite TBI; i.e. Glasgow Coma Scale score 3-13 and injury documented by magnetic resonance imaging (n = 61) or computer tomography (n = 2) and 48 healthy volunteers.

Interventions: Not applicable

Main Outcome Measures: Neuropsychological assessment covering motor function, information processing speed, attention, visual and verbal memory, working memory and executive functions and Glasgow Outcome Scale Extended (GOSE).

Results: Subjects with TBI performed worse than controls; most consistently regarding information processing speed and verbal memory. However, only 2- 44 % of subjects with TBI had clinically impaired test scores defined as < 1.5 standard deviations below mean of normative data. Based on a selection of nine tests, 0-1 impaired score was seen in 47 of 48 (98 %) of controls and in 21 of 37 (57 %) after moderate and 9 of 24 (34 %) after severe TBI. At one year post-injury, disability or complaints affecting daily life, reflected by GOSE score $\leq$ 7, were seen in 74 % of those with ≥ 2 impaired test scores and in 43 % of those with 0-1 impaired score (p=0.017).

Conclusions: In this sample of patients with recent, definite TBI and healthy volunteers, presence of cognitive impairment was specific to TBI and associated with future complaints or disability. However, the tests demonstrated low sensitivity to TBI, and many experienced complaints affecting daily life at 12 months post-injury despite a seemingly normal test performance.

CHAPTER 5   GENERAL DISCUSSION

5.1 Methodological issues

5.1.1 The study population 1998-2002

This sample, studied in paper I, was characterized by injury-related variables that were collected retrospectively by review of medical records. Since this information was not recorded for the purpose of research, the injury related variables are probably less accurate than those collected in a prospective study. Strength of the study of this sample was that it comprised only individuals with severe TBI, and hence was more homogeneous than the prospective sample. The study was hospital-based; that is, we included foreigners and inhabitants of other parts of the country if admitted to the hospital, and we did not collect similar data of inhabitants of our region who had been treated for severe TBI in other regions. Still, the hospital is the only level I trauma center in the region, and almost all participants lived in the region, and thus we believe the data provide estimates of a complete sample of severe TBI, as is also discussed below in section 5.1.4.

5.1.2 The study population 2004-2009

This sample consisted of patients with moderate as well as severe injuries, and thus the sample was more heterogeneous. As will be discussed below, one interesting finding from this study was that, actually, these groups might not be confidently analyzed together in studies of prognosis. This study population is a cohort of individuals with TBI where data are collected prospectively, thus yielding stronger evidence. The participation rate for follow-up in the cohort is 97 %, and for the data collection at 3 (Paper IV), 6 and 12 months (Paper II and III), loss to follow-up was only around 1 %.

We included patients with GCS score 13, a score defining mild TBI in some previous studies. However, most of the patients with GCS 13 described in Papers II-IV had PTA duration >24 hours, and thus should have been classified as moderate

TBI according to several recommendations [21, 121]. Furthermore, there is an increasing trend to classify patients with GCS score 13 as moderate TBI [104, 144].

5.1.3 The control group

In Paper IV, the test scores of the individuals with TBI are compared with those of a reference group. The purpose of the comparison was to make inferences of how the brain injury had affected cognition, and thus, the reference group should be representative for the patients with TBI before they sustained their injury. All reference samples are usually selected to be representative regarding age and sex, but in addition, we also matched the samples for years of education. This is common practice in neuropsychological research as education is associated with performance for some tests. Some researchers argue, however, that this is not sufficient to obtain groups that represent the same underlying population [36].

In paper I, we observed some differences regarding the IQ scores that probably in part reflected premorbid functioning, and thus, we agree that the choice of control group is a relevant concern. Next, however, it is not simple to address this accurately. First, it is not well known which characteristics or traits that indicate susceptibility to the diverse mechanisms causing head trauma, and by no means would it be easy to measure these validly. This issue is also discussed in the context of confounding in section 5.1.6.

In a quantitative review of the effects of TBI, the choice of control group was studied. Studies using control participants with orthopaedic injuries, seemingly demonstrated somewhat smaller effect sizes, but this was not significant, and they concluded that control groups should not necessarily be selected on the base of such a priori concern [130]. Others have used non-head trauma controls treated in intensive care units [78]. This approach admittedly adjusts for many trauma-related, potentially harmful effects that can add up to the brain injury in TBI, but when the trauma is this severe, later disability is frequent [86], and methodological concerns may still be present. Furthermore, unrecognized diffuse brain injury, either primary or secondary must be carefully ruled out.

5.1.4 Reliability and validity of the measures

For some of the measures and variables used in this thesis, reliability and validity should be discussed.

The GCS scoring is the standard procedure for evaluation of coma or impaired consciousness in head trauma, and an important advantage is that it is simple and quick to administer. Furthermore, it is a common measure, used in all head injury research across the world, and thus may not easily be replaced. The GCS has lost some of its power as prognostic factor, probably due to the increased use of pre-hospital intubation [145]. The GCS score at the scene of accident may be influenced also by alcohol or other substances or by other factors often present in major trauma (hypothermia, hypoxia or hypotension) [97]. Actually, it has been reported that a GCS motor score of 2 (extension of limbs to pain; a positively observed, severe neurological sign) was associated with a worse prognosis than the more common score of 1 (no reaction observed), which may have several causes [8].

In our studies, the GCS score was corrected if initial GCS score clearly was affected by non-trauma factors, and the clinical course demonstrated a rapid rise to near normal values, a course not usually seen in moderate or severe injuries. This was a clinical judgment, performed by a few experienced clinicians in the project, and not a standardized procedure (as no such exists). In some of these cases, we were not able to assign the patient to an exact GCS score. Thus, we also use broader categories. With the experience from assigning GCS scores in this cohort, we believe that this is a problem in all trauma series; still this problem is not always accounted for.

PTA was not consistently assessed with rating scales developed for this purpose. Ideally, this should have been done. However, this was a clinical series of patients who were often transferred to local hospitals while still in PTA. It would have been practically impossible to track all patients with for instance the Galveston orientation and amnesia test (GOAT) [82], as the scale is most familiar in rehabilitation hospitals, and many of the patients in our studies did not receive in-patient rehabilitation. Rather than omitting information of PTA from the study protocol, we chose to use

the same kind of estimation that we apply in the clinical setting; gather information about confusion from records and staff in addition to own observations.

Furthermore, we chose to describe PTA according to fixed time points rather than as duration exactly in days. This makes sense, as it is difficult to obtain really valid and trustworthy exact PTA duration in many cases. The time period of sedation is sometimes lengthened by other factors than the state of the brain, for instance chest trauma or repeated orthopaedic surgery. If the patient is out of PTA at the end of sedation, its duration in days is unknown. Patients who have been sedated for a lengthy period of time may suffer from withdrawal symptoms, and the assessment of PTA will be difficult. Thus, in the end, assessing PTA, inevitably involves an element of clinical judgement. Just as with the GCS scores, we believe that this must be a matter in all TBI studies, but it is seldom explained.

The MRI and CT variables that were used in paper II and III, were based on visual inspection of scans, and thus also possibly biased by subjectivity of the raters. Regarding the MRI evaluation; this was addressed in our study of inter-rater agreement, as little is known from the literature. The kappa values indicated good inter-rater agreement. Ideally, the MRI examinations should have been standardized regarding time from injury to scanning. This was not possible as MRI was carried out without specific resources, and we had to fall into line with activities in other respects at the intensive care unit and the MRI lab. Neither would the clinical condition of all patients with severe TBI, and other traumas too, be stable enough for MRI at a given time.

The GOSE is an outcome measure developed to meet some weaknesses of the original GOS. Its reliability has been demonstrated (see also section 3.5.1) but recent studies have shown lower inter-rater reliability in the telephone setting [81] and in multicenter studies [166]. These papers also offered some solutions to reduce these concerns, which were followed in our work. One may also criticize that assessors of outcome in our studies had access to clinical information. According to the American Academy of Neurology's criteria for classes of evidence, this weakens the conclusions to be drawn. Still, we will argue that in a telephone setting, clinical experience and insight into the severity of the injury makes it less likely that falsely high scores were assigned in patients with poor self-awareness. Actually, there may

be a trade off in the outcome assessment between minimizing bias and reducing mistakes.

Reliability and validity of neuropsychological tests is a major issue, and a detailed description is beyond the scope of this thesis. Typically, data regarding reliability and validity are given for the different tests by the manufacturer, and are also listed in compendiums of tests [146]. One issue relevant for the study in Paper IV is inter-rater reliability. The neuropsychological testing was carried out by several psychologists and test technicians. In a research project, it would have been optimal if just one or two had been involved. To compensate for errors associated with several examiners, the protocol was carefully described for the research project, and all were supplied with oral and written instructions regarding for instance the order of the tests and scoring procedures.

Neuropsychological tests have been criticized for low ecological validity; that is their ability to measure the real difficulties of the patients [23]. This was probably one explanation to the findings described in Paper IV; that many of the individuals with TBI performed in the normal range on traditional neuropsychological tests, but still reported injury-related complaints. For researchers, and especially Non-English, this problem is not easy to address. There have been developed tests specifically for measuring everyday problems, especially for the executive domain, but not all of these have been translated into Norwegian or been validated in Norwegian samples.

We did not include any tasks measuring effort, or symptom validity. Albeit regarded more essential in the assessment of mild TBI, a majority of the patients had been injured in traffic accidents and will eventually be involved in litigation. We did not, however, experience that patients were concerned about compensation this early after the injury. Furthermore, other issues, like fitness to drive, were often addressed concurrently with the first assessment, and our impression was that the patients were motivated and performed with effort.

5.1.5 Internal and external validity of results

Internal validity describes the degree to which the results are representative for the population that was studied. The studies in this thesis describe rather complete (Paper I), or fairly representative (Paper II and III) TBI samples treated in our

hospital. Thanks to the high participation rate and the loss to follow-up near zero, we have reduced the sources of bias and sampling error to an acceptable level, and we believe that the internal validity of the studies was acceptable.

External validity is the degree to which the findings generalize to other settings, and is evaluated by comparing findings between similar studies from different places or by applying the same models or analyses on other datasets. One example of higher internal than external validity of results is that, internally, we found similar rates of severe disability after severe TBI in Paper I and Paper II, whereas in another Norwegian follow-up study, the authors found lower frequency of long-term severe disability [4]. Certainly, there were some differences in sample size, patient selections and loss to follow-up, but this may also illustrate the issue of generalization.

One potential source of error is the reliability of the measures for use at several places. It has been shown for the Functional Independence Measure (FIM) that inter-rater reliability was only fair for scorings at different facilities [75], and also for two of our key measures, the GCS and the GOSE [166], reliability has been questioned. An example of this was possibly demonstrated by two concurrent Norwegian publications of the incidence of hospital treated head injury; both reported figures of mild, moderate and severe head injury separately. In the study from the Stavanger region, the authors reported to have admitted 77 patients with severe head injury during one year in a hospital serving 385 000 inhabitants [60], and this is four times the incidence reported by the authors of a study from Ullevål University Hospital, for the municipal of Oslo, with 534 000 inhabitants, reporting 27 cases during one year [5].

In the study in Paper I, we found an incidence of severe head injury that was just below what was found from Oslo (4 versus 5 per 100.000 inhabitants per year), furthermore in the study in Paper I, we may have missed some cases of elderly, severely injured patients dying at their local hospital. Thus, we consider that our result strongly support the findings from Oslo.

5.1.6 Confounding, effect modification and the concern of low power

Confounding and effect modification are potential sources of error associated with observational studies [58]. These are complex issues, and for a satisfactory description, textbooks should be consulted [119]. A confounding factor is one that is associated with both the dependent variable and the explanatory variable, but is not a part of the causal chain. The presence of confounding factors may lead to an under- or overestimation of the effect of the explanatory variable. In observational studies, confounding factors are controlled for by stratification, subgroup analyses or by applying multivariable statistical methods.

Effect modification, or interaction, is present if the *strength* of the effect of an exploratory variable differs within strata of the sample. This is best dealt with by stratifying the sample.

In the field of TBI, these are very relevant issues as there is substantial heterogeneity within TBI samples. But even if some strategies to address the problems are recommended, there are challenges to overcome.

First, the sample needs to be large in order to run stratified analyses, subgroup analyses or analyses with many covariates. Certainly, very large studies exist as described in section 1.8.1. In these large scale studies, however, resource-demanding data as MRI or neuropsychological test scores have not been collected. Our MRI studies (Paper II and III) were not small compared with other studies, but in a much larger study, it would have been possible to include more covariates in the models and the odds ratios presented would have been more accurate.

Second, the confounder must be acknowledged by the researchers, and variables must exist that can describe or quantify the confounding factor, in order to adjust for it. One example of this challenge was demonstrated in Paper IV, where we found that patients who sustain TBI probably deviate somewhat from the general population. We found evidence of this by assessing general intellectual abilities. But this is probably just a surrogate marker of a personality trait associated both with higher risk of accidents and lower compliance at school. It is possible that this "factor" is related also to performance on other neuropsychological tests, and thus may confound the effect of TBI on cognition. Ideally, this should be controlled for, but

this is not straight forward, as there are no questionnaires or scales with demonstrated psychometric properties, assessing *premorbid* personality for use *after* a brain injury.

In paper II, we demonstrated that GCS score was lowest in patients with DAI, and also that it correlated with outcome only in this group. Thus, the variable that is uniformly used to adjust for injury severity may indeed be differentially related to outcome variables in subgroups of patients. Consequently, for conclusions to be valid also for patients with more focal injuries, other variables should be used to control for injury severity, but which would that be?

In paper III, we had to perform analyses separately for moderate and severe injuries, as we could demonstrate that having a deep lesion in the MRI was associated with a worse outcome in patients with severe injuries, but not in those with moderate. This indicates that moderate and severe injuries might not be included in the same model.

Another example of possible confounding appeared in Paper IV, as we demonstrated that there was a difference in the intellectual abilities of male and female patients with TBI. As discussed above, individuals at risk for accidents may differ from the normal population in some respects, but we have not seen any studies reporting sex differences regarding this issue. In TBI samples, 70-80 % of the patients are male, and this illustrates how large samples would need to be in order to generate sound evidence of the effect of TBI in women. The possible difference regarding personality traits or socio-economic background for men and women with TBI, might be of interest for the research focusing on possible differences in outcome of TBI in men and women; some of them also exploring effects of the female sex hormones on the brain [142].

5.1.7 Was it just an observational study?

The study design was best characterized as an observational study, as we did not intend to analyze effects of a specific intervention. Regarding the TBI population studied in Paper I, their outcomes could not be influenced by the mere fact of being studied, due to the partly retrospective design. In the prospective cohort study, however, this was different. Here, the procedures necessary for identification of

patients, for obtaining the informed consent and for collection of the follow-up data actually represented improvements in the clinical management and patient education as well. The phone calls were mostly made by the author of this thesis, who is experienced in brain injury rehabilitation and who was also familiar to the relatives due to the inclusion procedure. Furthermore, we believe that before the Head Injury Project, delay of rehabilitation or discharge without any scheduled follow-up was more common. Thus, when outcomes are to be evaluated against other settings, it is also necessary to compare what kind of rehabilitation and follow-up that has been offered to the patients.

5.2 Importance and clinical implications of the main findings

5.2.1 The frequency and impact of diffuse axonal injury

Diffuse axonal injury, visible in MRI scans, was found in almost three-quarters of patients with moderate and severe head injury who survived the acute phase. It is commonly believed that the conventional MRI examination is rather insensitive to DAI, and thus we consider that Paper II convey important new evidence of the prevalence of DAI detected by MRI. However, in almost half of the patients with moderate injury, no lesions compatible with DAI was found. If one assumes that all TBI essentially result in a component of DAI, then this MRI protocol was not sensitive enough, and hopefully in the future, clinical scan protocols will also include DTI. Yet, given the difference regarding GCS discussed below, possibly the cases without DAI actually *were* more focal or multifocal of nature in a way that makes sense, clinically.

We demonstrated that the presence of DAI stage 2; a callosal lesion, was not a negative prognostic sign in the absence of DAI lesions in the brain stem. Thus the proposed staging of DAI did *not* represent a successive increase in clinical severity.

5.2.2 The dissociation of GCS scores in DAI and contusions

In Paper II, we found that DAI influenced the level of consciousness, and only in DAI patients was GCS score related to outcome. Thus, in patients with contusions, but no evidence of DAI, one has to consider other factors than GCS score in

evaluation of severity and prediction of outcome. Also in the medico-legal context, this may be informative to experts; a high initial GCS should not be used as evidence against significant brain injury in cases of cortical contusions.

5.2.3 The characteristics of brain stem injury

We reproduced the previous finding of two types of primary brain stem lesions. When a brain stem lesion was found in a patient with moderate TBI, this was always unilateral, and these patients had a similar outcome as those without such lesions. Neither were unilateral DAI lesions in the brain stem associated with a poor outcome. Thus, it is important that clinicians hold a differentiated view of the implications of brain stem injury.

5.2.4 The clinical value of MRI

In Paper III important findings were (a) the high predictive value; positive *and* negative, of demonstrating a bilateral brain stem injury in surviving patients, and (b) the almost universal demonstration of parenchymal lesions.

Even with the inclusion of patients with GCS score of 13, we found evidence of traumatic parenchymal brain lesions in virtually all patients. Some patients had also sustained multi-trauma, and if the initial cerebral CT scan was negative, the surgeons naturally focused on the management of other traumas rather than the GCS score at the scene of accident. We repeatedly experienced that neither the patients nor the professionals were aware of the possible cerebral injury, and thus MRI became the only objective documentation of a brain injury.

5.2.5 The difference between moderate and severe injury

In Paper III the separate analyses of moderate and severe TBI resulted in some important findings. In individuals with moderate TBI, first of all, we found that global outcome was generally better than in severe TBI and that practically all achieved a favourable outcome and thus could live independently. Second, some of the traditional prognostic factors, like GCS score, pupillary dilatation and findings from neuroimaging [99] were not predictors of outcome. Age, however, was a strong

prognostic factor, and the proportion experiencing a good outcome was much higher in the young patients than in those older than 35 years.

In severe TBI the well known prognostic factors were more predictive, but also in this group, prediction of death and severe disability was more accurate than prediction of level of disability in the upper range of outcome.

It is important that researchers become aware of this. Effects may be accounted for solely by subgroups within the sample, and there is a risk that effect modifications are present in multivariable analyses.

5.2.6 The high rate of normal test performance

Patients were cognitively impaired compared with healthy controls, and effect sizes of severe TBI were large, and thus in line with previous reports [130]. However, even when effect sizes are large, there is 50 % overlap between the two groups. In Paper IV, we studied deviations from normative data in individual cases of TBI. With this approach, we demonstrated that more than half of the individuals with moderate TBI, and even one third of those with severe TBI, performed almost indistinguishably to healthy controls. Possibly, these individuals have normalized their cognitive functioning, but since 43 % of those with normal assessment experienced some injury-related disability or complaints reflected in GOSE score ≤ 7 at one year follow-up, low sensitivity or poor ecological validity of the tests may also explain this.

Our findings might contribute to a differentiation of the discussion of how to interpret the neuropsychological assessment, especially in the medico-legal context. Lately, there has been a strong emphasis on the high rate of abnormal findings in healthy persons, on methods for detecting malingering and on the effect sizes of other conditions, like depression. Yet, we must not forget that individuals with TBI may suffer from relevant, cognitive decline that the neuropsychological tests do not convincingly verify. Hopefully, in the future, use of more sophisticated imaging and neurophysiologic methods will supply the tests as diagnostic tools and improve our understanding and diagnosing of the true impact of TBI.

5.2.7 The risk of severe disability after head injury

One important finding in Paper I, which was confirmed in Paper III, was that also samples of only severe TBI comprise patients with very different outcome. We found that one third of those surviving a severe TBI (31 % in paper I and 33 % in Paper III) eventually experienced long-lasting, *severe* disability, in line with the study from Glasgow [162]. In Paper I we showed that patients who were still in a minimally conscious state or even worse, at four weeks post-injury were those at risk of severe disability. In Paper III, we further extended the knowledge of risk factors for severe disability by demonstrating the strong association with bilateral brain stem injury. This is important information to clinicians and researchers. This group of patients benefits from early intensive rehabilitation and should be given high priority for in-patient rehabilitation in specialized clinics [55, 132]. Knowledge of the future risks and needs of these patients can improve our ability to focus rehabilitation interventions and design research projects aiming at minimizing their disability.

5.2.8 The risk of falling outside working life

In paper I, a disappointing finding was that individuals who had suffered severe TBI, had just as high risk of falling outside working life as was shown decades ago [18]. We found that the clinical condition four weeks post injury was predictive of future work status. In the group of patients who were in the minimally conscious or vegetative four weeks post-injury, employment rate was zero. Even if ordinary, competitive work position may be unrealistic in this subgroup, many of these are individuals who may well participate in working life; provided qualified and lengthy support and suitable workplaces.

In the subgroup of individuals who had been oriented by four weeks, two thirds were able to work or study without special adjustment. Future studies should explore with more scrutiny which were the factors responsible for successful employment in this subgroup.

In summary, rehabilitation professionals should acknowledge the real chances of employment; set up realistic goals and tailor the intervention to the needs of the individual from the first day on.

5.2.9 The difficulty of predicting a good recovery

No wonder, a full recovery is the initial goal for everyone sustaining a head injury. In our studies, we experienced that predicting outcome in the upper range is more difficult than predicting severe disability. In individuals with moderate TBI, among the traditional prognostic factors, only age was predictive of outcome. Furthermore, having measurable cognitive impairments at three months post-injury was associated with later complaints, but this was not studied in multivariable analyses, and neither was the association strong enough to be really useful.

When the damage of brain tissue is less extensive, probably a wider spectrum of factors influences the biological recovery of the brain as well as the coping and adaptation of the individual as illustrated in the WHO's International Classification of Functioning, Disability and Health, ICF (Fig 5.2.1) [2]. This illustrates the methodological challenges associated with outcome research in patients with less severe brain injuries. A broad selection of explanatory variables should be applied; they must be valid and reliable, and collected in a really large sample of patients. The development of core sets according to the ICF is a promising step to progress in this field [13].
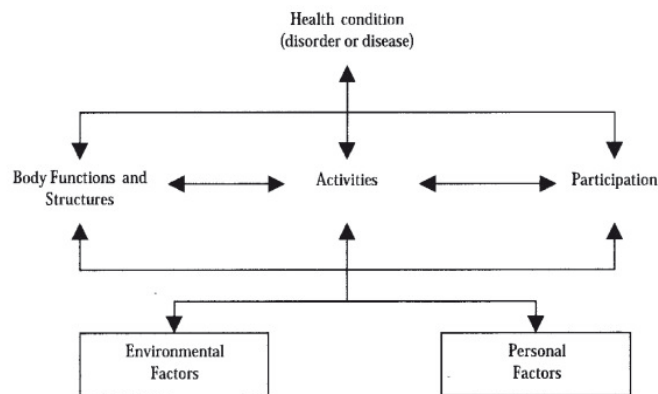
Fig. 5.2.1. The ICF model.

CHAPTER 6   FUTURE PERSPECTIVES

A vision and source of motivation has been that these studies should be just the beginning of multidisciplinary TBI research in our hospital. During this work, a foundation for future studies has been created, and the perspectives are exciting.

In another few years, the sample size of moderate as well as severe head injuries will be large enough to separately analyze outcome in relation to a wider range of prospectively collected variables. Another interesting future project will be that of the 5 years outcome assessment. This includes quality of life, using the new measure; QOLIBRI (Quality of Life after Brain Injury) and questionnaires on reported psychological health and TBI related complaints. We plan to collect more detailed information of vocational status and also of which services and interventions that have been offered to the individuals regarding vocational rehabilitation.

The individuals subjected to neuropsychological testing, were tested at 12 months too, and for the time being, we also perform testing of more individuals 12 months after TBI. Thus we increase the sample size and eventually will be able to compare patients with different patterns of MRI findings, which we originally planned for this thesis, not realizing how few patients there would be without DAI.

We may also explore the relationship between cognitive functioning at 3 months as well as 12 months with the outcomes recorded at 1 and 5 year follow-up.

Furthermore, MRI was performed again at 3 and 12 months post-injury in the same subset of the patients, including a 3D sequence for volume computation. The longitudinal evolution of MRI characteristics will be included in future studies of the project.

Finally, during the last year, many of the patients in the cohort and also the majority of the controls have consented to participate in a study where DTI, different functional MR imaging paradigms as well as ERP and quantitative EEG are used to characterize brain structure and function. These will be related to outcomes on the level of activities and participation as described above as the 5 year outcome measures.

CHAPTER 7   CONCLUSIONS

Paper I

Being independent in daily life, but unable to work, was the typical long-term outcome. Stratifying the patients based on consciousness at four weeks, we found different outcomes. Among oriented patients, almost all regained independency, whereas in the most severe group, poor outcomes and PTE was common.

Paper II and III

Diffuse axonal injury was found in almost three-quarters of patients with moderate and severe head injury who survived the acute phase. DAI influenced the level of consciousness, and only in DAI patients was GCS score related to outcome. DAI was a negative prognostic sign only when located in the brain stem.

Depth of lesion in the MRI was associated with outcome, and in particular, bilateral brainstem injury was strongly associated with poor outcome. In moderate head injury, surprisingly, there was no association between MRI findings and outcome when using the GOSE as outcome measure.

Paper IV

In a sample of patients with recent, definite TBI and healthy volunteers, presence of cognitive impairment was specific to TBI and associated with future complaints or disability. However, the tests demonstrated low sensitivity to TBI, and many experienced complaints affecting daily life at 12 months post-injury despite a seemingly normal test performance.

CHAPTER 8   REFERENCES

1.   Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med 1994;330:1499-508.
2.   International Classification of Functioning, Disability and Health. http://wwwwhoint/classifications/icf/en/. World Health Organization. WHO; Accessed February 15. 2010.
3.   Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology 1989;15:49-59.
4.   Andelic N, Hammergren N, Bautz-Holter E, Sveen U, Brunborg C, Roe C. Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. Acta Neurol Scand 2009;120:16-23.
5.   Andelic N, Sigurdardottir S, Brunborg C, Roe C. Incidence of hospital-treated traumatic brain injury in the Oslo population. Neuroepidemiology 2008;30:120-8.
6.   Andelic N, Sigurdardottir S, Schanke AK, Sandvik L, Sveen U, Roe C. Disability, physical health and mental health 1 year after traumatic brain injury. Disabil Rehabil 2010.
7.   Andrews K. The vegetative state--clinical diagnosis. Postgrad Med J 1999;75:321-4.
8.   Andrews PJ, Sleeman DH, Statham PF, McQuatt A, Corruble V, Jones PA, Howells TP, Macmillan CS. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: a comparison between decision tree analysis and logistic regression. J Neurosurg 2002;97:326-36.
9.   Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20-4.
10.   Ashikaga R, Araki Y, Ishida O. MRI of head injury using FLAIR. Neuroradiology 1997;39:239-42.
11.   Atchison TB, Sander AM, Struchen MA, High WM, Jr., Roebuck TM, Contant CF, Wefel JS, Novack TA, Sherer M. Relationship between neuropsychological test performance and productivity at 1-year following traumatic brain injury Clin Neuropsychol 2004;18:249-65.
12.   Bazarian JJ, Cernak I, Noble-Haeusslein L, Potolicchio S, Temkin N. Long-term neurologic outcomes after traumatic brain injury. J Head Trauma Rehabil 2009;24:439-51.
13.   Bernabeu M, Laxe S, Lopez R, Stucki G, Ward A, Barnes M, Kostanjsek N, Reed G, Tate R, Whyte J, Zasler N, Cieza A. Developing core sets for persons with traumatic brain injury based on the international classification of functioning, disability, and health. Neurorehabil Neural Repair 2009;23:464-7.
14.   Bezeau S, Graves R. Statistical power and effect sizes of clinical neuropsychology research. J Clin Exp Neuropsychol 2001;23:399-406.

15. Blumbergs P, Reilly P, Vink R. Trauma. Greenfield's Neuropathology. 8th ed.: Edward Arnold Ltd; 2008. p 733-832.
16. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury J Neurotrauma 1995;12:565-72.
17. Brooks DN. Wechsler Memory Scale performance and its relationship to brain damage after severe closed head injury. J Neurol Neurosurg Psychiatry 1976;39:593-601.
18. Brooks N, McKinlay W, Symington C, Beattie A, Campsie L. Return to work within the first seven years of severe head injury. Brain Inj 1987;1:5-19.
19. Bruns J, Jr., Hauser WA. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44 Suppl 10:2-10.
20. Buki A, Povlishock JT. All roads lead to disconnection?--Traumatic axonal injury revisited. Acta Neurochir 2006;148:181-93.
21. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004:113-25.
22. Chastain CA, Oyoyo U, Zipperman M, Joo E, Ashwal S, Shutter L, Tong K. Predicting Outcomes of Traumatic Brain Injury by Imaging Modality and Injury Distribution. J Neurotrauma 2009.
23. Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychol Rev 2003;13:181-97.
24. Chaytor N, Schmitter-Edgecombe M, Burr R. Improving the ecological validity of executive functioning assessment. Arch Clin Neuropsychol 2006;21:217-27.
25. Choi SC, Barnes TY, Bullock R, Germanson TA, Marmarou A, Young HF. Temporal profile of outcomes in severe head injury. J Neurosurg 1994;81:169-73.
26. Christensen BK, Colella B, Inness E, Hebert D, Monette G, Bayley M, Green RE. Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. Arch Phys Med Rehabil 2008;89:S3-15.
27. Chun KA, Manley GT, Stiver SI, Aiken AH, Phan N, Wang V, Meeker M, Cheng SC, Gean AD, Wintermark M. Interobserver Variability in the Assessment of CT Imaging Features of Traumatic Brain Injury. J Neurotrauma 2009.
28. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed.: Hillsdale, NJ: Erlbaum; 1988.
29. Colantonio A, Ratcliff G, Chase S, Kelsey S, Escobar M, Vernich L. Long-term outcomes after moderate to severe traumatic brain injury. Disabil Rehabil 2004;26:253-61.
30. Corrigan JD, Harrison-Felix C, Bogner J, Dijkers M, Terrill MS, Whiteneck G. Systematic bias in traumatic brain injury outcome studies because of loss to follow-up. Arch Phys Med Rehabil 2003;84:153-60.

31. Corrigan JD, Selassie AW, Lineberry LA, Millis SR, Wood KD, Pickelsimer EE, Rosenthal M. Comparison of the Traumatic Brain Injury (TBI) Model Systems national dataset to a population-based cohort of TBI hospitalizations. Arch Phys Med Rehabil 2007;88:418-26.

32. Corrigan JD, Smith-Knapp K, Granger CV. Outcomes in the first 5 years after traumatic brain injury. Arch Phys Med Rehabil 1998;79:298-305.

33. Dawson DR, Schwartz ML, Winocur G, Stuss DT. Return to productivity following traumatic brain injury: cognitive, psychological, physical, spiritual, and environmental correlates. Disabil Rehabil 2007;29:301-13.

34. De Coene B, Hajnal JV, Gatehouse P, Longmore DB, White SJ, Oatridge A, Pennock JM, Young IR, Bydder GM. MR of the brain using fluid-attenuated inversion recovery (FLAIR) pulse sequences. AJNR Am J Neuroradiol 1992;13:1555-64.

35. Dikmen SS, Bombardier CH, Machamer JE, Fann JR, Temkin NR. Natural history of depression in traumatic brain injury Arch Phys Med Rehabil 2004;85:1457-64.

36. Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. J Head Trauma Rehabil 2009;24:430-8.

37. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to severe traumatic brain injury. Arch Phys Med Rehabil 2003;84:1449-57.

38. Dikmen SS, Machamer JE, Winn HR, Temkin NR. Neuropsychological Outcome at 1-Year Post Head-Injury. Neuropsychology 1995;9:80-90.

39. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma Mortality in Mature Trauma Systems: Are We Doing Better? An Analysis of Trauma Mortality Patterns, 1997-2008. J Trauma 2010.

40. Edelman RR, Johnson K, Buxton R, Shoukimas G, Rosen BR, Davis KR, Brady TJ. MR of hemorrhage: a new approach. AJNR Am J Neuroradiol 1986;7:751-6.

41. Engberg AW. A Danish national strategy for treatment and rehabilitation after acquired brain injury. J Head Trauma Rehabil 2007;22:221-8.

42. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, Hughes R, Bergman W. Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. Arch Phys Med Rehabil 2003;84:365-73.

43. Farkas O, Lifshitz J, Povlishock JT. Mechanoporation induced by diffuse traumatic brain injury: an irreversible or reversible response to injury? J Neurosci 2006;26:3130-40.

44. Farkas O, Povlishock JT. Cellular and subcellular change evoked by diffuse traumatic brain injury: a complex web of change extending far beyond focal damage. Prog Brain Res 2007;161:43-59.

45. Firsching R, Woischneck D, Diedrich M, Klein S, Ruckert A, Wittig H, Dohring W. Early magnetic resonance imaging of brainstem lesions after severe head injury. J Neurosurg 1998;89:707-12.

46. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia 2003;44 Suppl 10:11-7.

47. Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. Ann Neurol 1982;12:564-74.
48. Gentry LR. Imaging of closed head injury. Radiology 1994;191:1-17.
49. Gentry LR, Godersky JC, Thompson B. MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. AJNR Am J Neuroradiol 1988:101-10.
50. Gentry LR, Godersky JC, Thompson B, Dunn VD. Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. AJR Am J Roentgenol 1988;150:673-82.
51. Gentry LR, Godersky JC, Thompson BH. Traumatic brain stem injury: MR imaging. Radiology 1989;171:177-87.
52. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349-53.
53. Giacino JT, Kalmar K. The Vegetative and Minimally Coscious States: A Comparison of Clinical Features and Functional Outcome. J Head Trauma Rehabil 1997;12:36-51.
54. Gordon WA, Zafonte R, Cicerone K, Cantor J, Brown M, Lombard L, Goldsmith R, Chandna T. Traumatic brain injury rehabilitation: state of the science. Am J Phys Med Rehabil 2006;85:343-82.
55. Gray DS. Slow-to-recover severe traumatic brain injury: a review of outcomes and rehabilitation effectiveness. Brain Inj 2000;14:1003-14.
56. Grissom RJ, Kim JJ. Effect Sizes for Research. A Broad Practical Approach.: Lawrence Erlbaum Associates, Inc; 2005.
57. Groswasser Z, Sazbon L. Outcome in 134 patients with prolonged posttraumatic unawareness. Part 2: Functional outcome of 72 patients recovering consciousness. J Neurosurg 1990;72:81-4.
58. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37.
59. Hesdorffer DC, Rauch SL, Tamminga CA. Long-term psychiatric outcomes following traumatic brain injury: a review of the literature. J Head Trauma Rehabil 2009;24:452-9.
60. Heskestad B, Baardsen R, Helseth E, Romner B, Waterloo K, Ingebrigtsen T. Incidence of hospital referred head injuries in Norway: a population based survey from the Stavanger region. Scand J Trauma Resusc Emerg Med 2009;17:6.
61. Hoffmann B, Duwecke C, von Wild KR. Neurological and social long-term outcome after early rehabilitation following traumatic brain injury. 5-year report on 240 TBI patients. Acta Neurochirurgica Suppl 2002;79:33-5.
62. Holbourne AHS. Mechanics of head injuries. The Lancet 1943;2:4.
63. Hou DJ, Tong KA, Ashwal S, Oyoyo U, Joo E, Shutter L, Obenaus A. Diffusion-weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. J Neurotrauma 2007;24:1558-69.
64. Hudak AM, Caesar RR, Frol AB, Krueger K, Harper CR, Temkin NR, Dikmen SS, Carlile M, Madden C, az-Arrastia R. Functional outcome scales in traumatic brain injury: a comparison of the Glasgow Outcome Scale

(Extended) and the Functional Status Examination. J Neurotrauma 2005;22:1319-26.

65. Hukkelhoven CW, Steyerberg EW, Rampen AJ, Farace E, Habbema JD, Marshall LF, Murray GD, Maas AI. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. J Neurosurg 2003;99:666-73.

66. Ingebrigtsen T, Romner B, Kock-Jensen C. Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries.The Scandinavian Neurotrauma Committee. J Trauma 2000;48:760-6.

67. Iverson GL, Brooks BL, Holdnack JA. Misdiagnosis of Cognitive Impairment in Forensic Neuropsychology. In: Heilbronner RL, editor. Neuropsychology in the Courtroom: Expert Analysis of Reports and Testimony 1st ed.: The Guilford Press 2008. p 243-66.

68. Jackson WT, Novack TA, Dowler RN. Effective serial measurement of cognitive orientation in rehabilitation: the Orientation Log. Arch Phys Med Rehabil 1998;79:718-20.

69. Jain KK. Neuroprotection in traumatic brain injury. Drug Discov Today 2008;13:1082-9.

70. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.

71. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 1981;44:285-93.

72. Kampfl A, Schmutzhard E, Franz G, Pfausler B, Haring HP, Ulmer H, Felber S, Golaszewski S, Aichner F. Prediction of recovery from post-traumatic vegetative state with cerebral magnetic-resonance imaging. Lancet 1998;351:1763-7.

73. Kelley BJ, Lifshitz J, Povlishock JT. Neuroinflammatory responses after experimental diffuse traumatic brain injury. J Neuropathol Exp Neurol 2007;66:989-1001.

74. Kelly AB, Zimmerman RD, Snow RB, Gandy SE, Heier LA, Deck MD. Head trauma: comparison of MR and CT--experience in 100 patients. AJNR Am J Neuroradiol 1988;9:699-708.

75. Kohler F, Dickson H, Redmond H, Estell J, Connolly C. Agreement of functional independence measure item scores in patients transferred from one rehabilitation setting to another. Eur J Phys Rehabil Med 2009;45:479-85.

76. Lagares A, Ramos A, Perez-Nunez A, Ballenilla F, Alday R, Gomez PA, Kaen A, Lobato RD. The role of MR imaging in assessing prognosis after severe and moderate head injury. Acta Neurochir 2009;151:341-56.

77. Lammi MH, Smith VH, Tate RL, Taylor CM. The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. Arch Phys Med Rehabil 2005;86:746-54.

78. Lannoo E, Colardyn F, Vandekerckhove T, De Deyne C, De Soete G, Jannes C. Subjective complaints versus neuropsychological test performance after moderate to severe head injury. Acta Neurochir (Wien) 1998;140:245-53.

79. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 2004;3:537-46.

80. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications J Magn Reson Imaging 2001;13:534-46.

81. LeGrand SA, Hindman BJ, Dexter F, Moss LG, Todd MM. Reliability of a telephone-based Glasgow Outcome Scale assessment using a structured interview in a heterogenous population of patients and examiners. J Neurotrauma 2007;24:1437-46.

82. Levin HS, O'Donnell VM, Grossman RG. The Galveston Orientation and Amnesia Test. A practical scale to assess cognition after head injury. J Nerv Ment Dis 1979;167:675-84.

83. Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed.: Oxford University Press; 2004.

84. Ling G, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. J Neurotrauma 2009;26:815-25.

85. Liu AY, Maldjian JA, Bagley LJ, Sinson GP, Grossman RI. Traumatic brain injury: diffusion-weighted MR imaging findings. AJNR Am J Neuroradiol 1999;20:1636-41.

86. Livingston DH, Tripp T, Biggs C, Lavery RF. A fate worse than death? Long-term outcome of trauma patients admitted to the surgical intensive care unit. J Trauma 2009;67:341-8; discussion 8-9.

87. Lu J, Marmarou A, Choi S, Maas A, Murray G, Steyerberg EW. Mortality from traumatic brain injury. Acta Neurochir Suppl 2005;95:281-5.

88. Malec JF, Brown AW, Leibson CL, Flaada JT, Mandrekar JN, Diehl NN, Perkins PK. The Mayo classification system for traumatic brain injury severity. J Neurotrauma 2007;24:1417-24.

89. Marmarou A, Lu J, Butcher I, McHugh GS, Murray GD, Steyerberg EW, Mushkudiani NA, Choi S, Maas AI. Prognostic value of the Glasgow Coma Scale and pupil reactivity in traumatic brain injury assessed pre-hospital and on enrollment: an IMPACT analysis. J Neurotrauma 2007;24:270-80.

90. Marmarou A, Lu J, Butcher I, McHugh GS, Mushkudiani NA, Murray GD, Steyerberg EW, Maas AI. IMPACT database of traumatic brain injury: design and description. J Neurotrauma 2007;24:239-50.

91. Marquez de la Plata C, Ardelean A, Koovakkattu D, Srinivasan P, Miller A, Phuong V, Harper C, Moore C, Whittemore A, Madden C, Diaz-Arrastia R, Devous M, Sr. Magnetic resonance imaging of diffuse axonal injury: quantitative assessment of white matter lesion volume. J Neurotrauma 2007;24:591-8.

92. Marshall LF, Marshall SB, Klauber MR, Clark MB, Eisenberg HM, Jane JA, Luerssen TG, Marmarou A, Foulkes MA. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:S14-S20.

93. Masson F, Thicoipe M, Mokni T, Aye P, Erny P, Dabadie P. Epidemiology of traumatic comas: a prospective population-based study Brain Inj 2003;17:279-93.

94. Mathias JL, Wheaton P. Changes in attention and information-processing speed following severe traumatic brain injury: a meta-analytic review. Neuropsychology 2007;21:212-23.

95. Mazzeo AT, Beat A, Singh A, Bullock MR. The role of mitochondrial transition pore, and its modulation, in traumatic brain injury and delayed neurodegeneration after TBI. Exp Neurol 2009;218:363-70.

96. Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia 2003;44:569-74.

97. McNett M. A review of the predictive ability of Glasgow Coma Scale scores in head-injured patients. J Neurosci Nurs 2007;39:68-75.

98. Mitchell DE, Adams JH. Primary focal impact damage to the brainstem in blunt head injuries. Does it exist? Lancet 1973;2:215-8.

99. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, Marmarou A, Steyerberg EW. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24:329-37.

100. Murray GD, Teasdale GM, Braakman R, Cohadon F, Dearden M, Iannotti F, Karimi A, Lapierre F, Maas A, Ohman J, Persson L, Servadei F, Stocchetti N, Trojanowski T, Unterberg A. The European Brain Injury Consortium survey of head injuries. Acta Neurochir 1999;141:223-36.

101. Mushkudiani NA, Engel DC, Steyerberg EW, Butcher I, Lu J, Marmarou A, Slieker F, McHugh GS, Murray GD, Maas AI. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24:259-69.

102. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery 2005;57:1173-82; discussion -82.

103. Maas AI, Steyerberg EW, Butcher I, Dammers R, Lu J, Marmarou A, Mushkudiani NA, McHugh GS, Murray GD. Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24:303-14.

104. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol 2008;7:728-41.

105. Nelson DW, Nystrom H, Maccallum RM, Thornquist B, Lilja A, Bellander BM, Rudehill A, Wanecek M, Weitzberg E. Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. J Neurotrauma 2009.

106. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT, McCandliss BD. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol 2008;29:967-73.

107. O'Neill J, Hibbard MR, Brown M, Jaffe M, Sliwinski M, Vandergoot D, Weiss MJ. The effect of employment on quality of life and community integration after traumatic brain injury. J Head Trauma Rehabil 1998;13:68-79.

108. Olver JH, Ponsford JL, Curran CA. Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury. Brain Inj 1996;10:841-8.

109. Parizel PM, Ozsarlak, Van Goethem JW, van den HL, Dillen C, Verlooy J, Cosyns P, De Schepper AM. Imaging findings in diffuse axonal injury after closed head trauma. Eur Radiol 1998;8:960-5.

110. Parizel PM, Van Goethem JW, Ozsarlak O, Maes M, Phillips CD. New developments in the neuroradiological diagnosis of craniocerebral trauma Eur Radiol 2005;15:569-81.

111. Paterakis K, Karantanas AH, Komnos A, Volikas Z. Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase. J Trauma 2000;49:1071-5.

112. Pettigrew LE, Wilson JT, Teasdale GM. Reliability of ratings on the Glasgow Outcome Scales from in-person and telephone structured interviews J Head Trauma Rehabil 2003;18:252-8.

113. Ponsford JL, Olver JH, Curran C, Ng K. Prediction of employment status 2 years after traumatic brain injury. Brain Inj 1995;9:11-20.

114. Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. J Head Trauma Rehabil 2005;20:76-94.

115. Ragnarsson KT. Results of the NIH consensus conference on "rehabilitation of persons with traumatic brain injury". Restor Neurol Neurosci 2002;20:103-8.

116. Ragnarsson KT. Traumatic brain injury research since the 1998 NIH Consensus Conference: accomplishments and unmet goals. J Head Trauma Rehabil 2006;21:379-87.

117. Rassovsky Y, Satz P, Alfano MS, Light RK, Zaucha K, McArthur DL, Hovda D. Functional outcome in TBI I: neuropsychological, emotional, and behavioral mediators. J Clin Exp Neuropsychol 2006;28:567-80.

118. Reeves TM, Phillips LL, Povlishock JT. Myelinated and unmyelinated axons of the corpus callosum differ in vulnerability and functional recovery following traumatic brain injury. Exp Neurol 2005;196:126-37.

119. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed.: Lippincott Williams &Wilkins; 2008.

120. Rudehill A, Bellander BM, Weitzberg E, Bredbacka S, Backheden M, Gordon E. Outcome of traumatic brain injuries in 1,508 patients: impact of prehospital care. J Neurotrauma 2002;19:855-68.

121. Ruff RM, Iverson GL, Barth JT, Bush SS, Broshek DK. Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. Arch Clin Neuropsychol 2009;24:3-10.

122. Ruff RM, Marshall LF, Crouch J, Klauber MR, Levin HS, Barth J, Kreutzer J, Blunt BA, Foulkes MA, Eisenberg HM. Predictors of outcome following severe head trauma: follow-up data from the Traumatic Coma Data Bank. Brain Inj 1993;7:101-11.

123. Russell WR, Smith A. Post-Traumatic Amnesia in Closed Head Injury. Arch Neurol 1961;5:4-17.

124. Rutgers DR, Toulgoat F, Cazejust J, Fillard P, Lasjaunias P, Ducreux D. White Matter Abnormalities in Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study. AJNR Am J Neuroradiol 2007.

125. Saeki N, Yamaura A, Sunami K. Brain stem contusion due to tentorial coup injury: case report and pathomechanical analysis from normal cadavers. Br J Neurosurg 1998;12:151-5.

126. Schaefer PW. Applications of DWI in clinical neurology. J Neurol Sci 2001;186 Suppl 1:S25-S35.

127. Scheid R, Ott DV, Roth H, Schroeter ML, von Cramon DY. Comparative magnetic resonance imaging at 1.5 and 3 Tesla for the evaluation of traumatic microbleeds. J Neurotrauma 2007;24:1811-6.

128. Scheid R, Preul C, Gruber O, Wiggins C, von Cramon DY. Diffuse axonal injury associated with chronic traumatic brain injury: evidence from T2*-weighted gradient-echo imaging at 3 T. AJNR Am J Neuroradiol 2003;24:1049-56.

129. Scheid R, Walther K, Guthke T, Preul C, von Cramon DY. Cognitive sequelae of diffuse axonal injury. Arch Neurol 2006;63:418-24.

130. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning Int Rev Psychiatry 2003;15:341-9.

131. Schretlen DJ, Testa SM, Winicki JM, Pearlson GD, Gordon B. Frequency and bases of abnormal performance by healthy adults on neuropsychological testing. J Int Neuropsychol Soc 2008;14:436-45.

132. Semlyen JK, Summers SJ, Barnes MP. Traumatic brain injury: Efficacy of multidisciplinary rehabilitation. Arch Phys Med Rehabil 1998;79:678-83.

133. Servadei F, Nasi MT, Giuliani G, Cremonini AM, Cenni P, Zappi D, Taylor GS. CT prognostic factors in acute subdural haematomas: the value of the 'worst' CT scan. Br J Neurosurg 2000;14:110-6.

134. Servadei F, Teasdale G, Merry G. Defining acute mild head injury in adults: a proposal based on prognostic factors, diagnosis, and management. J Neurotrauma 2001;18:657-64.

135. Sherer M, Novack TA, Sander AM, Struchen MA, Alderson A, Thompson RN. Neuropsychological assessment and employment outcome after traumatic brain injury: a review. Clin Neuropsychol 2002;16:157-78.

136. Sherer M, Roebuck-Spencer T, Davis LC. Outcome Assessment in Traumatic Brain Injury Clinical Trials and Prognostic Studies. J Head Trauma Rehabil 2009.

137. Sherer M, Yablon SA, Nakase-Richardson R, Nick TG. Effect of severity of post-traumatic confusion and its constituent symptoms on outcome after traumatic brain injury. Arch Phys Med Rehabil 2008;89:42-7.

138. Shibata Y, Matsumura A, Meguro K, Narushima K. Differentiation of mechanism and prognosis of traumatic brain stem lesions detected by magnetic resonance imaging in the acute stage. Clin Neurol Neurosurg 2000;102:124-8.

139. Shukla D, Mahadevan A, Sastry KV, Shankar SK. Pathology of post traumatic brainstem and hypothalamic injuries. Clin Neuropathol 2007;26:197-209.

140. Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P, Paulson OB, Jernigan TL, Rostrup E. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. Brain 2008;131:559-72.

141. Sigurdardottir S, Andelic N, Roe C, Schanke AK. Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. J Int Neuropsychol Soc 2009;15:740-50.

142. Slewa-Younan S, van den Berg S, Baguley IJ, Nott M, Cameron ID. Towards an understanding of sex differences in functional outcome following moderate to severe traumatic brain injury: a systematic review. J Neurol Neurosurg Psychiatry 2008;79:1197-201.

143. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol 2010;119:7-35.

144. Stein SC, Spettell C. The Head Injury Severity Scale (HISS): a practical classification of closed-head injury. Brain Inj 1995;9:437-44.

145. Stocchetti N, Pagan F, Calappi E, Canavesi K, Beretta L, Citerio G, Cormio M, Colombo A. Inaccurate early assessment of neurological severity in head injury. J Neurotrauma 2004;21:1131-40.

146. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary. Third ed.: Oxford University Press; 2006

147. Strich SJ. Shearing of nerve fibres as a cuase of brain damage due to head injury. A pathological study of twenty cases. The Lancet 1961;2:5.

148. Stuss DT, Binns MA, Carruth FG, Levine B, Brandys CE, Moulton RJ, Snow WG, Schwartz ML. The acute period of recovery from traumatic brain injury: posttraumatic amnesia or posttraumatic confusional state? J Neurosurg 1999;90:635-43.

149. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J Neurotrauma 2008;25:719-38.

150. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochir(Wien) 2006;148:255-68.

151. Tate RL, Pfaff A, Jurjevic L. Resolution of disorientation and amnesia during post-traumatic amnesia. J Neurol Neurosurg Psychiatry 2000;68:178-85.

152. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81-4.

153. Teasdale GM, Murray L. Revisiting the Glasgow Coma Scale and Coma Score. Intensive Care Med 2000;26:153-4.

154. Temkin NR, Corrigan JD, Dikmen SS, Machamer J. Social functioning after traumatic brain injury. J Head Trauma Rehabil 2009;24:460-7.

155. Tong KA, Ashwal S, Holshouser BA, Nickerson JP, Wall CJ, Shutter LA, Osterdock RJ, Haacke EM, Kido D. Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Ann Neurol 2004;56:36-50.

156. Vakil E. The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: a selective review. J Clin Exp Neuropsychol 2005;27:977-1021.

157. van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. J Neurol Neurosurg Psychiatry 1999;66:207-13.

158. Walker WC, Ketchum JM, Marwitz JH, Chen T, Hammond F, Sherer M, Meythaler J. A multicentre study on the clinical utility of post-traumatic amnesia duration in predicting global outcome after moderate-severe traumatic brain injury. J Neurol Neurosurg Psychiatry 2010;81:87-9.

159. Wehman P, Kregel J, Keyser-Marcus L, Sherron-Targett P, Campbell L, West M, Cifu DX. Supported employment for persons with traumatic brain injury: a preliminary investigation of long-term follow-up costs and program efficiency. Arch Phys Med Rehabil 2003;84:192-6.

160. Weiss N, Galanaud D, Carpentier A, Naccache L, Puybasset L. Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. Crit Care 2007;11:230.

161. Weiss N, Galanaud D, Carpentier A, Tezenas de Montcel S, Naccache L, Coriat P, Puybasset L. A combined clinical and MRI approach for outcome assessment of traumatic head injured comatose patients. J Neurol 2008;255:217-23.

162. Whitnall L, McMillan TM, Murray GD, Teasdale GM. Disability in young people and adults after head injury: 5-7 year follow up of a prospective cohort study. J Neurol Neurosurg Psychiatry 2006;77:640-5.

163. Willemse-van Son AH, Ribbers GM, Verhagen AP, Stam HJ. Prognostic factors of long-term functioning and productivity after traumatic brain injury: a systematic review of prospective cohort studies. Clin Rehabil 2007;21:1024-37.

164. Willmott C, Ponsford J, Hocking C, Schonberger M. Factors contributing to attentional impairments after traumatic brain injury. Neuropsychology 2009;23:424-32.

165. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15:573-85.

166. Wilson JT, Slieker FJ, Legrand V, Murray G, Stocchetti N, Maas AI. Observer variation in the assessment of outcome in traumatic brain injury: experience from a multicenter, international randomized clinical trial. Neurosurgery 2007;61:123-8; discussion 8-9.

167. Wood RL. Long-term outcome of serious traumatic brain injury. Eur J Anaesthesiol Suppl 2008;42:115-22.

168. Xu J, Rasmussen IA, Lagopoulos J, Haberg A. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. J Neurotrauma 2007;24:753-65.

169. Zimmerman RA, Bilaniuk LT, Hackney DB, Goldberg HI, Grossman RI. Head injury: early results of comparing CT and high-field MR. AJR Am J Roentgenol 1986;147:1215-22.

Paper I

Paper II

Paper III

Is not included due to copyright

Paper IV

Cognitive Impairment Three Months After Moderate and Severe Traumatic Brain Injury. A prospective follow-up study.

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Objective: To explore the magnitude and frequency cognitive impairments three months after moderate and severe traumatic brain injury (TBI) and study their relation to presence of complaints or disability at one year follow-up.

Design: Follow-up study

Setting: Patients prospectively included from a regional level I trauma center.

Participants: Patients (aged 13-65 years) with definite TBI; i.e. Glasgow Coma Scale score 3-13 and injury documented by magnetic resonance imaging (n = 61) or computer tomography (n = 2) and 48 healthy volunteers.

Interventions: Not applicable

Main Outcome Measures: Neuropsychological assessment covering motor function, information processing speed, attention, visual and verbal memory, working memory and executive functions and Glasgow Outcome Scale Extended (GOSE).

Results: Subjects with TBI performed worse than controls; most consistently regarding information processing speed and verbal memory. However, only 2- 44 % of subjects with TBI had clinically impaired test scores defined as < 1.5 standard deviations below mean of normative data. Based on a selection of nine tests, 0-1 impaired score was seen in 47 of 48 (98 %) of controls and in 21 of 37 (57 %) after moderate and 9 of 24 (34 %) after severe TBI. At one year post-injury, disability or complaints affecting daily life, reflected by GOSE score ≤ 7, were seen in 74 % of those with ≥2 impaired test scores and in 43 % of those with 0-1 impaired score (p=0.017).

Conclusions: In this sample of patients with recent, definite TBI and healthy volunteers, presence of cognitive impairment was specific to TBI and associated with future complaints or disability. However, the tests demonstrated low sensitivity to TBI, and any experienced complaints affecting daily life at 12 months post-injury despite a seemingly normal test performance.

Key words: Craniocerebral Trauma; Neuropsychology; Prognosis; Neuropsychological Tests; Longitudinal Studies

Cognitive impairment is a common consequence of moderate and severe traumatic brain injury (TBI),[1] particularly affecting information processing speed and attention,[2, 3] memory [4] and executive functioning.[5] The first assessment is typically performed during the first months; when deficits are most evident. A common research design has been comparisons of mean test performances between subjects with TBI and a control group, and tests have typically been described as sensitive if highly significant differences have been found. The magnitude of the effect of TBI on cognition, effect size, may be expressed as Cohen's d; the standardized difference of means in two groups. In a meta-analysis, a large mean effect size ($d_{pooled} = 0.97$) of TBI across studies was found for moderate to severe TBI within the first six months.

In the individual clinical assessment, however, interpretation of neuropsychological test scores must be based on comparison with normative data. When evaluating whether a low test score reflects injury-related impairment, it should also be interpreted in relation to general intellectual capacity and performance on other cognitive tests [6], but the empirical basis for this subjective evaluation is currently debated[7]. In some settings, such as legal expert examinations and research, objective criteria of impairment should be sought, but there is no such general definition.[7] The issue is further complicated by the fact that also healthy subjects perform below the normal range in some percentage of administered tests.[7, 8]

In the meta-analysis by Schretlen & Shapiro, it was pointed out that while cases of moderate and severe TBI typically are analyzed together in neuropsychological research, they constitute a heterogeneous group. Thus, the reported effects might be overestimated for moderate TBI and/or underestimated regarding severe TBI.[9]

For the present study we performed neuropsychological testing three months post-injury as part of a large follow-up study in patients who were admitted with moderate and severe head injury to a regional level I Trauma center. We have previously, in a larger subgroup of the main cohort, demonstrated that virtually all the patients had parenchymal lesions detected with early magnetic resonance imaging (MRI). Diffuse axonal injury was frequently found as well as contusions; often in concert.[10]

The aim of the present study was to explore the magnitude and frequency of cognitive impairments three months after moderate and severe TBI in comparison with healthy controls. Furthermore, we sought to relate cognitive functioning to concurrent and one year global functioning and to duration of post traumatic amnesia (PTA).

METHODS

The Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services (NSD) approved the study and written consent was obtained from the patients and from parents of patients younger than 16 years.

Participants

Sixty-three patients (age 13-65) admitted to the Neurosurgical department, St. Olavs Hospital, Trondheim University Hospital, Norway participated in the study. The hospital is a Level I Trauma Center, and has an ongoing database that includes patients treated with moderate and severe head injuries according to the Head Injury Severity Scale (HISS) criteria [11] with no exclusion criteria. The project has achieved 97 % participation and only around 1 % loss to follow-up of. For the present study, patients were invited to participate in neuropsychological testing at 3 and 12 months post injury with the following inclusion criteria: (a) resolution of PTA before the time of testing as well as ability to cooperate during testing and (b) no ongoing substance abuse, diagnosed neurological or psychiatric condition or previous moderate to severe head injury according to the same criteria. The main inclusion period was from October 2004 to October 2007. During this period, 172 patients were admitted, of whom 169 consented to follow-up. Thirty-six died, 31 were outside the relevant age-group, 12 could not cooperate at three months, 17 were excluded due to premorbid conditions, 7 refused all testing, 9 preferred testing locally, 2 were not fluent Norwegian speakers and 1 was lost to follow-up. Thus, fifty-four patients were included, and these constitute 86 % of the study sample. The remaining nine patients were recruited among patients who geographically belonged to our hospital and were seen for a three months follow-up evaluation during 2008 and 2009. The control group consisted of 48 healthy persons, matched for age, sex and education, recruited via advertisements, among family and friends of patients with head injury and among acquaintances of researchers and staff.

Injury-related variables

These were mechanism of injury, MRI findings, Glasgow coma scale (GCS) score (scoring procedures have been described in an

earlier publication[10]), injury being moderate (GCS score of 9-13) or severe head injury (GCS score of ≤8). Duration of PTA, defined as the period of posttraumatic confusion,[12] was evaluated by the first author as a clinical judgment during the first few weeks based on medical notes or clinical assessments. It was classified as lasting < 1 week or ≥ 1 week, a cut-off point previously associated with high rates of good recovery.[13]

MR imaging

MR imaging (1.5 Tesla) was performed at median 10 days post injury (range 1-120). The scan protocol included T1 and T2- weighted sequences, a T2*-weighted gradient echo sequence, fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted imaging. MRI parameters and procedure of evaluation have been reported previously.[10]

Procedures for neuropsychological testing and scoring

Neuropsychological assessment was performed at mean 98 (± 10) days post-injury. Testing was performed by psychologists, master level students and test technicians at St. Olav University Hospital. Raw scores were converted to standard scores by use of normative data provided by the manufacturers of the tests, except for the Symbol Digit Modality Test; where a normative sample quoted by Lezak was used.[14] Standard scores were given as T-scores, Scaled scores (S-scores), Z-scores or percentiles. An individual's standardized test score was classified as impaired if it was below 1.5 standard deviation (SD) according to the reference norms for the test (T-score ≤ 34, S-score ≤ 5; Z-score ≤ -1.5 or percentile ≤ 5).

Neuropsychological measures

The four subtests of the Wechsler Abbreviated Scale of Intelligence (WASI),[15] were administered to estimate general intellectual capacity. In order to avoid future retest effects in a planned reassessment, we used a split-half procedure, and a raw score was estimated. The control participants were tested once, with all items, and raw scores were calculated after the same procedure. The following neuropsychological methods were used to assess different domains of cognitive function:

I. Motor function: Grooved Pegboard, dominant [16]; Trail Making Test (TMT), condition 5 (motor speed) from the Delis Kaplan Executive Function System (D-KEFS).[17]

II. Information processing: Trail Making Test, condition 1 (visual scanning), 2 (number sequencing), and 3 (letter sequencing) ; Color-Word Interference Test (CWIT), condition 1 (color naming) and 2 (word reading) from D-KEFS and Symbol Digit modality Test (SDMT), oral and written version.[18]

III. Attention and vigilance: Conners' Continuous Performance Test II (CCPT-II).[19]

IV. Visual learning and memory: Continuous Visual Memory Test (CVMT)[20]; Taylor Complex Figure (TCF).[21] The TCF was not administered to controls. Raw scores for the TCF were converted to standard scores based on normative data for the Rey-Osterrieth Complex Figure.[22]

V. Verbal learning and memory: California Verbal Learning Test II (CVLT-II).[23]

VI. Working memory: Digit Span Backwards from the Wechsler Adult Intelligence Scale - Third edition (WAIS-III) [24]; Letter-Number Sequencing from WAIS III.

VII. Executive functions: Wisconsin Card Sorting Test (WCST), computer version[25]; Verbal Fluency Test from D-KEFS; TMT, condition 4 -Number-Letter Sequencing, from D-KEFS; CWIT, condition 3 and 4 - Inhibition and Inhibition/Switching, from D-KEFS; Tower Test from D-KEFS.

The different sub-scores obtained from each test are shown in Table 3 and 4.

Global outcome

Global functioning was assessed by the first author with GOSE at 3 and 12 months using the structured interview.[26] GOSE score ≤ 7 denotes presence of head injury-related disability or complaints to a degree that they affect daily life.

Statistical analysis

Dependent variables were checked for normality in subjects with TBI and control participants by inspection of Q-Q plots. Raw scores for each test are presented as mean and SD for normally distributed data and otherwise as median with inter quartile range (IQR; the 25th and 75th percentile). Likewise, comparisons between subjects with TBI and control participants were performed by use of Student's t-test and Mann-Whitney U test respectively. A Student's t-test with unequal variance was used when Levene's test gave evidence of variance heterogeneity. Effect sizes were calculated both as Cohen's d based on pooled variance (d_{pooled}) and as Glass' d, where the denominator is the SD of the control group ($ES_{control}$).[27] For the tests where data were non-normally distributed, standardized effect size was estimated by

dividing the difference between the median scores by the IQR of controls x 0.75 (ES[control]).[27] Cohen defined d of 0.8, 0.5 and 0.2 as large, medium and small respectively,[28] and we applied these such as large being d ≥ 0.8 and so forth.

Proportions were compared using the exact z pooled test as recommended for small counts when expected value was less than 5 for any cell.[29] Available case analysis was used in the presence of missing data. The reported p-values are two-sided; to adjust for multiple tests, a p-value of ≤ 0.01 was regarded significant when analyzing of the total battery of the neuropsychological tests, and otherwise α-level of 0.05 was applied. Statistical analyses were performed using the statistical software SPSS for Windows, version 16.0 (Copyright SPSS.Inc, 1995-2009), except exact unconditional tests performed by http://www.stat.ncsu.edu/exact/

RESULTS

Demographic and injury-related characteristics of the patients and the control participants are presented in Table 1 and 2. In one case of severe TBI, duration of PTA could not be assessed due to long lasting sedation not related to the TBI.

Neuroimaging

All patients were examined with MRI except one, who had cortical contusions depicted with computed tomography (CT). One of the 62 patients had no lesions in the brain parenchyma when examined with MRI 21 days post-injury. This patient had a moderate injury with four days of PTA, and multiple contusions and subarachnoid hemorrhage on the initial CT scan. Thus, all patients had definite TBI, and 71 % had diffuse axonal injury detected with MRI.

Intellectual abilities

Subjects with TBI had significantly lower verbal, performance and total IQ than control participants (p < 0.001). Women with TBI had significantly higher total IQ scores than men with TBI (p=0.02), and performed in the similar range as the controls. Among controls there was no difference between genders (p=0.34). Severity of injury did not significantly affect IQ (Table 2).

Test performance and effect sizes

Raw scores were impaired in subjects with TBI compared to control participants across all cognitive domains (Table 3). All measures of information processing speed and verbal memory were significantly impaired in patients compared with controls. Within the remaining domains, significant differences in mean performance were shown only for some of the measures, except for working memory, where no significant differences were found.

Effect sizes for significant differences were medium to large and typically larger when the variance in the control group was used for standardization.

Frequency of impairments according to normative data

Table 4 displays the proportions of patients scoring in the impaired range according to normative data for each test; with cut-off criterion of 1.5 SD. Across all tests, 2 % - 44 % of the subjects with TBI had clinically impaired scores in contrast to 2 %-6% among controls. The tests of information processing speed, Grooved Pegboard and the delayed recall tasks of the CVLT had the highest proportion of impaired scores while they also yielded very few impaired scores in the control group. On several executive tasks, as well as on the working memory task and the CCPT measures, no significant difference in frequency of impairment was found between the groups.

Cognitive functioning in subgroups of patients according to severity of injury

To study subgroups of patients, we chose nine tests, across all the domains, that are frequently used in clinical practice, and that in the preceding analyses were associated with large effect sizes or good ability to discriminate patients and controls: Grooved Pegboard; dominant hand, CWIT; color naming and inhibition/switching, VF; letters, TMT; number sequencing and number-letter switching, SDMT; written, CVMT; hits and CVLT; delayed recall. Table 6 shows number of impaired scores (standardized test score below 1.5 SD) out of the nine tests. In the healthy volunteers, 98 % had 0-1 impaired score, which was subsequently evaluated as normal performance in this sample, whereas having ≥ 2 impaired scores was evaluated as cognitive impairment.

Severe and moderate TBI

Test performance of moderate and severe TBI is shown in Table 5. Mean d[pooled] for the normally distributed tests (Grooved Pegboard; dominant hand, VF; letters, CWIT; color naming and SDMT; written) was 0.64 for moderate and 0.95 for severe TBI.

Of those with moderate injury, 43 % demonstrated cognitive impairment, as did 65 % of subjects with severe TBI (p=0.09).

Test performance in relation to PTA duration

4

The subjects with PTA < 1 week performed significantly worse than control participants on the TMT; numbers and TMT switching, and CWIT; inhibition/switching (p-values < 0.001, 0.007 and 0.013 respectively), with $ES_{control}$ of 1.4, 1.0 and 1.0. For the remaining six tests, no significant difference was found.

In subjects with PTA of $\geq$ 1 week, differences were all highly significant (p≤0.001), and effect sizes were large for all tests ranging from 0.9-2.1, except for the CVMT; hits with medium effect size of 0.67.

Eleven of the 30 subjects (37 %) with PTA < 1 week and 22 of 32 (69 %) with PTA $\geq$ 1 week had $\geq$2 impaired test score among the nine tests shown in Table 5 (p=0.015). (Data regarding PTA are not shown.)

Concurrent functional outcome

GOSE score was $\leq$ 7 in 20 (69 %) of subjects with 0-1 impaired test scores, in 17 (85 %) of those with 2-3 impaired scores and in 7 (85 %) of subjects with 4-9 impaired scores.

Functional outcome at 12 months post-injury

Follow-up GOSE scores at 12 months were available for 61 subjects with TBI. GOSE score was $\leq$ 7 in 43 % in the group with 0-1 impaired score, in 75 % of subjects with 2-3 impaired scores and in 73 % of subjects with 4-9 impaired scores. The difference in proportion of GOSE score $\leq$ 7 between those with 0-1 impaired score and those with $\geq$ 2 impaired scores was significant (p=0.017).

The proportion of subjects with GOSE score $\leq$ 7 was higher when TBI was severe (75 %) than moderate (49 %) (p=0.044) and also higher in subjects with PTA of $\geq$ 1 week (83 %) than in those with PTA < 1 week (47 %) (p=0.040).

DISCUSSION

We studied neuropsychological test performance in a neurosurgical cohort of patients three months after moderate and severe TBI; with parenchymal lesions demonstrated with MRI in virtually all cases. Subjects with TBI performed worse than control participants in almost all domains, with largest effect sizes for speed dependent tests. When the injury was moderate, however, the majority of the subjects had 0-1 impaired score out of nine of the most sensitive tests, and even after severe injury, this was found in one third. Having $\geq$ 2 impaired scores was associated with later GOSE score $\leq$ 7, but this outcome was also experienced by almost half of the subjects with 0-1 impaired score.

Effect sizes of TBI and sensitivity of tests

We found that the effect sizes were medium to large and varied with the method of computation; $ES_{control}$ being larger than d_{pooled}, and thus confirmed the findings of Schretlen and Shapiro. However, even when effect sizes are large, overlap between groups is considerable. For example d_{pooled} of 0.8 and 1.5 yields overlap between groups of 53 % and 29 % respectively,[30] which is incompatible with high sensitivity as well as specificity.

We used 1.5 SD as cut-off level for evaluation of the standardized scores, which corresponds to 5 % rate of impairment in healthy subjects (false positives). The control group performed fairly well in line with that, and thus the tests demonstrated high specificity to TBI with this definition of impairment. But the sensitivity to TBI was low, as no test indicated impairment for more than 44 % of the patients. Hence, there is a need for new test paradigms or other methods of examinations with higher discriminative abilities. Reitan et al. argued that typical neuropsychological tests with continuous score distribution should be supplemented by tests identifying specific deficits as present or absent; yielding a dichotomous distribution.[31] They presented promising results with rather few false negative tests in a sample of subjects with mixed brain injuries by use of an alternative set of tests. Yet, the applicability in patients with TBI is unknown.

Seemingly, a substantial proportion of the subjects with TBI had recovered their cognitive capacity at this early stage, a course of recovery previously demonstrated for mild TBI.[9, 32] Still, 69 % of the subjects with 0-1 impaired score had concurrent GOSE score $\leq$ 7, indicating that injury-related problems were present. If cognitive dysfunction mediates the functional problems, which has previously been demonstrated,[33, 34] this supports the raised concern about low ecological validity of common neuropsychological tests.[35] On the other hand, injury-related factors other than impaired cognition, like pain or affective symptoms might also contribute to their functional decline.

Test performance in relation to injury severity

Subjects with moderate TBI had significantly lower test scores than controls. Dikmen et al. reviewed cognitive outcome more than 6 months post injury, and concluded that the evidence of cognitive dysfunction after moderate TBI was "limited and suggestive".[1] In the present study we have demonstrated that moderate TBI clearly affects cognition three months post-injury, and

future studies are needed to explore the cognitive outcome in moderate TBI later in recovery. We included patients with GCS score 13, a score defining mild TBI in some previous studies. However, all but one of these had PTA duration >24 hours, and thus would have been classified as moderate TBI according to several recommendations.[36, 37] Furthermore, there is an increasing trend to classify patients with GCS score 13 as moderate TBI.[38]

An important finding was that more than half of the subjects with moderate TBI performed comparable to healthy controls using normative data. Consequently, these are persons with definite and recent TBI, but whose neuropsychological assessment might be described as normal as early as three months post-injury.

PTA duration may serve as an alternative indicator of injury severity in patients with missing GCS score. In this sample, a cut off level of PTA at 1 week, divided the subjects with TBI into equally large groups with different cognitive functioning and different outcome.

Test performance in relation to MRI findings

Diffuse axonal injury was found in 71 % of TBI cases. DAI has previously been related to impairments of information processing speed,[39] executive functions and verbal memory.[40, 41] However, in some of these studies the diagnosis of DAI was based on CT characteristics, which is not optimal,[39, 40] or cases of DAI were not compared to cases without DAI.[41] The findings in our study support that DAI may be an important explanation to the large effects on measures of speed that was found in this study. Few patients had no evidence of DAI in our study, and variances in test performance were large. Thus, power was not sufficient to compare cases with and without DAI, but hopefully, this will be explored in a future, larger study.

Test performance in relation to cognitive domains and evaluation of measures

The speed dependent tests, like the TMT, SDMT and CWIT, showed the largest effect sizes. Impairments demonstrated by these tests were specific to TBI as 20-30 percent of the subjects with TBI, but very few control participants performed in the impaired range. The most sensitive test was SDMT, but even for this test, reported to be "extremely sensitive" to brain insults,[6] the percentage of the subjects with TBI with test performance below 1.5 SD was only 30 % for the oral version, and 44 % for the written version.

The measures of working memory; digit span backwards and letter-number sequencing, were surprisingly insensitive to TBI. Possible, these tests measure working memory constructs that are only mildly affected by TBI, and that tests requiring more simultaneous processing, like the n-back paradigms,[42] might be more useful in future studies of working memory deficits following TBI.

In visual memory, measured as CVMT total score, we found very similar results in both groups. This was due to a higher rate of false alarms among the control participants than reported in the normative sample.[20] Given the generally strong abilities of our control group, this is difficult to explain. In a study of criterion validity of the CVMT in moderate to severe TBI, the authors concluded that the CVMT was clinically useful, but they did not make any comparisons to the normative data.[43]

The Conners' CPT also failed to discriminate well between subjects with TBI and control participants. Other CPT measures have been found to be sensitive to dysfunction of the attention system[44]. Thus, possibly the Conners' CPT-II is less useful than other CPT's in TBI patients. However, our finding may also support previous research demonstrating relatively preserved vigilance after TBI.[45]

Cognitive functioning in relation to one year functional outcome

We found a high frequency of complaints or disability one year post-injury in subjects with cognitive impairment three months post-injury, which was expected as it has been demonstrated in previous studies.[46] Thus, we confirmed that cognitive impairments in the early phase may be regarded a risk factor for future complaints. On the other hand, a significant proportion, 43 %, of those with a normal early assessment experienced later complaints.

Study limitations

We might have included measures of symptom validity since many subjects with TBI were injured in traffic accidents and eventually will be involved in litigation. However, if poor effort was present, we would presumably have found a falsely *high* rather than low sensitivity of the tests.

PTA duration should preferably have been evaluated with a validated measure. In our neurosurgical cohort, however, with several discharge destinations, this would have been impractical and associated with inaccurate or missing data.

Subjects with TBI had significantly lower intellectual abilities than the control participants. First, this may demonstrate an adverse effect of TBI to these functions, which has also previously been found.[47] The high scores among the women with TBI argue against this as the sole explanation. Most of our controls and patients were manual workers or had work positions outside the academic field, but still, there seems to be some underlying differences. Recruitment of control group has been challenged in TBI research,[1, 9] but there is no general agreement on the method of choice.

CONCLUSIONS

Persons with TBI were cognitively impaired compared to a healthy control group, and cognitive impairments at three months were associated with later complaints or disability. We demonstrated a fair specificity of impairments below 1.5 SD, as this was seldom found in the control group. On the other hand, the sensitivity to TBI of a conventional assessment was low, and from a clinical perspective, we consider this an important finding. A seemingly normal assessment was common in patients with recent TBI, confirmed by MRI findings, yet their risk of future problems was considerable.

REFERENCES

1   Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. J Head Trauma Rehabil 2009;24:430-8.

2   Mathias JL, Wheaton P. Changes in attention and information-processing speed following severe traumatic brain injury: a meta-analytic review. Neuropsychology 2007;21:212-23.

3   Willmott C, Ponsford J, Hocking C, Schonberger M. Factors contributing to attentional impairments after traumatic brain injury. Neuropsychology 2009;23:424-32.

4   Vakil E. The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: a selective review. J Clin Exp Neuropsychol 2005;27:977-1021.

5   Dikmen SS, Machamer JE, Winn HR, Temkin NR. Neuropsychological Outcome at 1-Year Post Head-Injury. Neuropsychology 1995;9:80-90.

6   Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary. Third ed.: Oxford University Press; 2006

7   Iverson GL, Brooks BL, Holdnack JA. Misdiagnosis of Cognitive Impairment in Forensic Neuropsychology. In: Heilbronner RL, editor. Neuropsychology in the Courtroom: Expert Analysis of Reports and Testimony 1st ed.: The Guilford Press 2008. p 243-66.

8   Schretlen DJ, Testa SM, Winicki JM, Pearlson GD, Gordon B. Frequency and bases of abnormal performance by healthy adults on neuropsychological testing. J Int Neuropsychol Soc 2008;14:436-45.

9   Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning Int Rev Psychiatry 2003;15:341-9.

10 Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. J Neurosurg 2009.

11 Stein SC, Spettell C. The Head Injury Severity Scale (HISS): a practical classification of closed-head injury. Brain Inj 1995;9:437-44.

12 Stuss DT, Binns MA, Carruth FG, Levine B, Brandys CE, Moulton RJ, Snow WG, Schwartz ML. The acute period of recovery from traumatic brain injury: posttraumatic amnesia or posttraumatic confusional state? J Neurosurg 1999;90:635-43.

13 van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. J Neurol Neurosurg Psychiatry 1999;66:207-13.

14 Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed.: Oxford University Press; 2004.

15 Wechsler D. Wechsler Abbreviated Scale of Intelligence Scale. San Antonio, TX: The Psychological Corporation; 1999.

16 Matthews CG, Klove K. Instruction manual for the Adult Neuropsychology Test Battery. Madison, Wisc.: University of Wisconsin Medical School; 1964.

17 Delis DC, Kaplan E, Kramer J. Delis Kaplan Executive Function System. San Antonio, TX: The Psychological Corporation.; 2001.

18 Smith A. Symbol Digit Modality Test, Ninth printing 2002, (SDMT) Manual. Los Angeles: Western Psyhological Services; 1982.

19 Conners CK, Staff M. Conners' Continuous Performance Test II (CPT II) Computer Program for Windows, Technical Guide and Software Manual. Toronto, ON: Multi-Health Systems Inc; 2000.

20 Trahan DE, Larrabee GJ. Continous Visual Memory Test. Odessa, FL: Psychological Assessment Resources; 1988.

21 Taylor LB. Localisation of cerebral lesions by psychological testing. Clin Neurosurg 1969;16:269-87.

22 Meyers JE, Meyers KR. Rey Complex Figure test and Recognition Trial: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1995.

23 Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test, Second edition (CVLT-II). Adult Version, Manual. San Antonio, TX: The Psychological Corporation.; 2000.

24 Wechsler D. Wechsler Adult Intelligence Scale - 3rd edition. San Antonio, TX: The Psychological Corporation; 1997.

25 Heaton RK. Wisconsin Card Sorting Test, Computer Version -2 Research Edition. Odessa, FL: Psychological Assessment Resources, Inc.; 1993.

26 Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15:573-85.

27 Grissom RJ, Kim JJ. Effect Sizes for Research. A Broad Practical Approach.: Lawrence Erlbaum Associates, Inc; 2005.

28 Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed.: Hillsdale, NJ: Erlbaum; 1988.

29 Lydersen S, Fagerland MW, Laake P. Recommended tests for association in 2 x 2 tables. Stat Med 2009;28:1159-75.

30 Zakzanis KK. Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effect size analyses for neuropsychological researchers. Arch Clin Neuropsychol 2001;16:653-67.

31 Reitan RM, Wolfson D. Can neuropsychological testing produce unequivocal evidence of brain damage? I. Testing for specific deficits. Appl Neuropsychol 2008;15:33-8.

32 Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. J Int Neuropsychol Soc 2005;11:215-27.

33 Novack TA, Bush BA, Meythaler JM, Canupp K. Outcome after traumatic brain injury: pathway analysis of contributions from premorbid, injury severity, and recovery variables ArchPhysMedRehabil 2001;82:300-5.

34 Rassovsky Y, Satz P, Alfano MS, Light RK, Zaucha K, McArthur DL, Hovda D. Functional outcome in TBI I: neuropsychological, emotional, and behavioral mediators. J Clin Exp Neuropsychol 2006;28:567-80.

35 Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychol Rev 2003;13:181-97.

36 Ruff RM, Iverson GL, Barth JT, Bush SS, Broshek DK. Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper. Arch Clin Neuropsychol 2009;24:3-10.

37 Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004:113-25.

38 Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol 2008;7:728-41.

39 Felmingham KL, Baguley IJ, Green AM. Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. Neuropsychology 2004;18:564-71.

40   Fork M, Bartels C, Ebert AD, Grubich C, Synowitz H, Wallesch CW. Neuropsychological sequelae of diffuse traumatic brain injury. Brain Inj 2005;19:101-8.

41   Scheid R, Walther K, Guthke T, Preul C, von Cramon DY. Cognitive sequelae of diffuse axonal injury. Arch Neurol 2006;63:418-24.

42   Hill BD, Elliott EM, Shelton JT, Pella RD, O'Jile JR, Gouvier WD. Can we improve the clinical assessment of working memory? An evaluation of the Wechsler Adult Intelligence Scale-Third Edition using a working memory criterion construct. J Clin Exp Neuropsychol 2009:1-9.

43   Strong CA, Donders J. Validity of the Continuous Visual Memory Test (CVMT) after traumatic brain injury. J Clin Exp Neuropsychol 2008;30:885-91.

44   Riccio CA, Reynolds CR, Lowe P, Moore JJ. The continuous performance test: a window on the neural substrates for attention? Arch Clin Neuropsychol 2002;17:235-72.

45   Zoccolotti P, Matano A, Deloche G, Cantagallo A, Passadori A, Leclercq M, Braga L, Cremel N, Pittau P, Renom M, Rousseaux M, Truche A, Fim B, Zimmermann P. Patterns of attentional impairment following closed head injury: a collaborative European study. Cortex 2000;36:93-107.

46   Sherer M, Sander AM, Nick TG, High WM, Jr., Malec JF, Rosenthal M. Early cognitive status and productivity outcome after traumatic brain injury: findings from the TBI model systems. Arch Phys Med Rehabil 2002;83:183-92.

47   Kersel DA, Marsh NV, Havill JH, Sleigh JW. Neuropsychological functioning during the year following severe traumatic brain injury. Brain Inj 2001;15:283-96.

Table 1: Demographic, injury-related and outcome variables in individuals with moderate and severe TBI.

Variable	n	No. of Cases (%)[*]
Age at testing; years (SD)	63	29.5 (14.3)
Male / female (%)	63	46 (73) / 17 (27)
Days post injury; mean (SD)	63	98.2 (10.6)
GCS score; mean (SD) [†]	63	9.3 (3.2)
Moderate / severe injury (%)	63	37 (59) / 26 (41)
PTA < 1 week / PTA ≥ 1 week[‡]	62	30 (48) / 32 (52)
Mechanism of injury	63	
Fall		21 (34)
Traffic accident		36 (57)
Other		6 (10)
MRI examination	62[§]	
No findings		1 (2)
Pure DAI		14 (23)
Cortical contusions		17 (27)
DAI and contusions		30 (48)
GOSE score at testing	62[‡]	
8		14 (22)
7		3 (5)
6		15 (24)
5		28 (45)
4		1 (2)
3		1 (2)
GOSE score at follow-up	61[§§]	
8		25 (41)
7		13 (21)
6		12 (19)
5		11 (18)

Abbreviations: TBI, Traumatic Brain Injury; SD, Standard Deviation; GCS, Glasgow Coma Scale; MRI, Magnetic Resonance Imaging; DAI, Diffuse Axonal Injury; GOSE, Glasgow Outcome Scale Extended
[*]unless otherwise stated; [†] Exact GCS score available in 59 cases; [‡] Data not available in one case; [§]one patient not examined with MRI; [§§]Data not available in two cases.

Table 2: Intellectual ability in relation to gender and injury severity

Variable Mean (SD)*	Controls (n=48)	TBI All patients (n=60)	Moderate TBI (n=35)	Severe TBI (n=25)	Men TBI (n=44)	Women TBI (n= 16)
VIQ	117 (12)	106 (17)	108 (13)	103 (21)	102 (16)	117 (14)
PIQ	115 (13)	106 (17)	107 (12)	104 (13)	104 (12)	111 (13)
Total IQ[†]	118 (12)	106 (16)[‡]	108 (12)	103 (20)	102 (15) [§]	116 (14)
PTA<1 week / ≥1 week, %[§§]	n.a	48 / 52	65 / 35	24 / 76	44 / 56	63 / 37
Age	29.9 (13.4)	29.5 (14.3)	32.0 (12.1)	25.9 (15.4)	28.6 (13.3)	31.9 (17.0)
Education	11.9 (1.9)	11.7 (2.3)	11.7 (2.3)	11.7 (2.3)	11.5 (1.7)	12.5 (2.9)

Abbreviations: SD, Standard Deviations; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; PTA, Posttraumatic Amnesia

*Unless otherwise stated; [†]3 patients had not IQ scores from Wechsler Abbreviated Scale of Intelligence; [‡]Significantly lower than in controls; [§]Significantly lower than in women with TBI; [§§]Available in 62 patients

Table 3: Neuropsychological test performance in patients and controls.

Test; mean (SD) or median (25%-75%)	n	Patients	n	Controls	p-value	ES$_{control}$*	d$_{pooled}$†
Motor function							
TMT; motor†‡	62	25 (19-34)	48	22 (18-28)	0.12		
Grooved Pegboard; dominant hand (sec)	63	72.7 (18.0)	48	64.0 (7.3)	0.001	1.19	0.60
Grooved Pegboard; non-dominant hand (sec)	62	80.6 (17.6)	48	70.3 (8.3)	0.000	1.24	0.72
Information processing speed							
TMT; visual scanning†‡ (sec)	63	26 (23-33)	48	29 (17.25-23)	0.000	1.39	
TMT; numbers‡ (sec)	63	34 (29-47)	48	24 (21-29)	0.000	1.67	
TMT; letters‡ (sec)	63	34 (29-49)	48	24 (20.25-30)	0.000	1.37	
CWIT; color naming (sec)	61	35.0 (9.3)	48	29.0 (4.7)	0.000	1.28	0.79
CWIT; word reading (sec)	61	25.4 (5.7)	48	22.4 (3.5)	0.001	0.86	0.61
SDMT; oral version	61	55.5 (17.4)	48	66.7 (11.7)	0.000	0.96	0.73
SMDT; written version	63	44.9 (13.2)	48	53.7 (8.1)	0.000	1.09	0.78
Sustained attention							
CPT; omissions†‡	59	3 (1-6)	48	1 (0-2)	0.011	1.33	
CPT; comissions†‡	59	12.5 (9-22)	48	9.5 (5.25-15)	0.005	0.40	
CPT; hit RT	59	378.7 (82.2)	48	391.7 (63.8)	0.37		
CPT; hit RT SE‡	59	5.8 (4.4-6.7)	48	4.9 (3.9-5.9)	0.035	0.30	
CPT; detectability	59	0.67 (0.39)	48	0.91 (0.43)	0.005	0.56	0.56
CPT; hit RT by block‡	59	0.0 (-0.01-0.01)	48	0.0 (-0.01-0.02)	0.63		
CPT; hit RT by block SE‡	59	0.000 (-0.033-0.033)	48	0.005 (-0.030-0.050)	0.53		
CPT; hit RT by ISI‡	59	0.040 (-0.000-0.070)	48	0.040 (-0.030-0.060)	0.26		
CPT; hit RT by ISI SE	59	-0.012 (0.09)	48	0.034 (0.11)	0.022	0.42	0.45
Visual memory							
CMVT ;hits‡	60	38 (34-39)	48	39 (37-41)	0.009	0.33	
CMVT; total correct	60	73.3 (9.5)	48	77.1 (6.2)	0.018	0.61	0.47
CMVT; false‡	60	16 (10-20)	48	15 (11-19.75)	0.86		
CVMT; delayed	60	4.3 (1.5)	48	4.8 (1.4)	0.080	0.36	0.34
Verbal memory							
CVLT; total recall trial 1-5	63	47.7 (12.8)	48	53.6 (8.9)	0.005	0.66	0.52
CVLT, short-delay free recall‡	63	10 (8-12)	48	12 (10-13.75)	0.009	0.71	

	N		N		p*	ES	ES
CVLT, long-delay free recall[‡]	63	11 (8-14)	48	12.5 (11-14)	0.005	0.67	
Working memory							
Digitspan backwards	62	6.7 (2.2)	48	6.9 (2.4)	0.68		
Letter-number sequencing	61	10.2 (3.1)	48	11.4 (2.8)	0.044	0.43	0.39
Executive function							
WCST; total errors[‡]	62	20 (14-38)	48	14 (10-20)	0.002	0.80	
WCST; perseverative responses[‡]	62	11 (7-19)	48	8 (6-10.75)	0.009	0.84	
WCST; categories achieved[‡]	62	6 (6-6)	48	6 (6-6)	0.62		
Verbal Fluency; letter	62	32.4 (10.8)	48	39.5 (11.3)	0.001	0.63	0.64
Verbal Fluency; category	62	39.5 (10.1)	48	52.6 (10.9)	0.000	1.20	1.25
Verbal Fluency; category switching; tot corr	62	12.7 (2.9)	48	13.8 (2.8)	0.052	0.39	0.38
Verbal Fluency; category switching; tot sw	62	11.4 (3.3)	48	11.9 (3.1)	0.40		
Tower; total achievement	63	17.4 (3.6)	48	18.1 (3.5)	0.28		
TMT; letter-number switching[‡] (sec)	63	82 (65-108)	48	60.5 (50.25-76)	0.000	1.11	
TMT; switching vs number (sec)	63	0.16 (3.1)	48	-0.60 (2.1)	0.15		
CWIT; inhibition (sec)	61	59.2 (18.5)	48	49.9 (8.0)	0.001	1.16	0.62
CWIT; inhibition/switching[‡] (sec)	61	70.0 (56.6-83.0)	48	54 (50.25-64.0)	0.000	1.55	

Abbreviations: SD, standard deviation; RT, reaction time; SE, standard error; ISI, inter stimulus interval; sec, seconds; ES, effect size

* Cohen's d; mean difference divided by the pooled SD

[†] For tests yielding normally distributed data; Glass' d; effect size is the standardized mean, using the SD in the control group. For the non-normally distributed data, $ES_{control}$ was calculated as difference between medians divided by 0.75 x Inter Quartile Range$_{control}$.

[‡] Data not normally distributed.

Table 4: Proportion of scores below 1.5 SD. All patients and controls.

Test		TBI < 1.5 SD		Controls < 1.5 SD	p-value
Motor function					
PEG dominant side	63	12 (19)	48	1 (2)	0.007
PEG non-dominant side	63	17 (27)	48	1 (2)	0.004
Trail Making Test 5	63	5 (8)	48	1 (2)	0.22
Information processing speed					
TMT; visual scanning	63	15 (24)	48	1 (2)	0.002
TMT; numbers	63	14 (22)	48	0	0.002
TMT; letters	63	14 (22)	48	2 (4)	0.008
CWIT; color naming	61	18 (30)	48	2 (4)	0.002
CWIT; word reading	61	12 (20)	48	2 (4)	0.016
SDMT; oral version	60	18 (30)	48	0	0.001
SMDT; written version	63	28 (44)	48	1 (2)	0.001
Sustained attention/ vigilance					
CCPT; omissions	60	8 (13)	48	3 (6)	0.24
CCPT; comissions	60	5 (8)	48	2 (4)	0.41
CCPT; hit RT	60	6 (10)	48	4 (8)	0.79
CCPT; hit SE	60	6 (10)	48	5 (10)	0.93
CCPT detect	60	0 (0)	48	1 (2)	0.35
CCPT; hit RT by block	60	4 (7)	48	2 (4)	0.63
CCPT; hit SE by block	60	6 (10)	48	5 (10)	0.95
CCPT; hit RT SE by ISI	60	1 (2)	48	3 (6)	0.29
CCPT ;hit RT SE byISI	60	3 (5)	48	5 (10)	0.31
Visual memory					
CVMT; hits	60	13 (22)	48	4 (8)	0.062
CVMT; false	60	19 (32)	48	14 (29)	0.79
CVMT; total	60	21 (35)	48	13 (27)	0.40
CVMT; delayed	60	9 (15)	48	2 (4)	0.071
Taylor Complex Figure; delayed	61	8 (13)	0	n.a.	
Verbal memory					
CVLT; total recall trial 1-5	63	9 (14)	48	1 (2)	0.026
CVLT; short-delay free recall	63	16 (25)	48	2 (4)	0.002
CVLT; long-delay free recall	63	17 (27)	48	3 (6)	0.006
Working memory					

Letter-number sequencing	62	5 (8)	48	1 (2)	0.20
Executive function					
WCST; total errors	61	5 (8)	48	1 (2)	0.20
WCST; perseverative responses	61	5 (8)	48	2 (4)	0.43
WCST; categories achieved	61	1 (2)	48	1 (2)	1.00
Letter Fluency	62	10 (16)	48	1 (2)	0.015
Category Fluency	62	10 (16)	48	0	0.004
Category switching; total correct	62	7 (11)	48	3 (6)	0.37
Category switching; total switch	62	8 (13)	48	2 (4)	0.12
CWIT inhibition	61	11 (18)	48	1 (2)	0.008
CWIT inhibition/ switching	61	16 (25)	48	2 (4)	0.003
TMT; letter-number switching	63	11 (18)	48	0	0.003
Tower; total achievement	63	1 (2)	48	1 (2)	0.95

Abbreviations: RT, reaction time; SE, standard error; ISI, inter stimulus interval

Table 5: Test performance in relation to injury severity. Moderate and severe TBI compared to control subjects.

Test; mean (SD) or median (25%-75%)	Moderate TBI	p-value	ES_{control}[†]	d_{pooled}[*]	Severe TBI	p-value	ES_{control}[†]	d_{pooled}[*]
Motor function								
Grooved Pegboard; dominant hand (sec)	68.9 (11.5)	0.028			78.9 (23.7)	0.007	2.04	0.92
Information processing speed								
TMT; numbers[‡] (sec)	34 (29-47)	<0.001	1.67		35 (27.5-51)	<0.001	1.83	
CWIT; color naming (sec)	33.8 (8.7)	0.005	1.02	0.71	36.9 (10.0)	0.001	1.68	1.13
SMDT; written version	46.8 (11.7)	0.003	0.85	0.71	42.2 (15.0)	0.001	1.42	1.05
Visual memory								
CMVT; hits[‡]	39 (36-40)	0.23			36 (31-39)	0.001	1.0	
Verbal memory								
CVLT, long-delay free recall[‡]	11 (8.5-13.75)	0.029			11 (3.75-14.0)	0.011	0.67	
Executive function								
Verbal Fluency; letter	32.9 (10.5)	0.008	0.58	0.60	31.8 (11.3)	0.007	0.68	0.68
TMT; letter-number switching[‡] (sec)	82 (67-103.5)	<0.001	1.11		81.5 (63.25-127.5)	0.002	1.11	
CWIT; inhibition/switching[‡] (sec)	65 (55.25-79.5)	0.001	1.07		72 (55.25-79.5)	<0.001	1.75	

Abbreviations: SD, standard deviation; sec, seconds; ES, effect size
[*] Cohen's d; mean difference divided by the pooled SD
[†] For tests yielding normally distributed data; Glass' delta; effect size is the standardized mean, using the SD in the control group. For the non-normally distributed data, ES_{control} was calculated as difference between medians divided by 0.75 x Inter Quartile Range_{control}.
[‡] Data not normally distributed.

Table 6: Relative frequency of impaired test scores out of nine tests according to normative data. Number of patients and controls (%)

Number of low test scores[*]	Moderate TBI (n=37) n (%)	Severe TBI (n=26) n (%)	Controls (n=48) n (%)
0	13 (35)	5 (19)	36 (75)
1	8 (22)	4 (15)	11 (23)
2-3	10 (27)	10 (39)	1 (2)
4-5	6 (16)	3 (12)	0
6-7	0	1 (4)	0
8-9	0	3 (12)	0

Abbreviations: SD, standard deviation;
[*]standardized test scores < 1.5 SD

Appendices and erratas

APPENDICES

APPENDIX 1

MARSHALL CT CLASSIFICATION

(Marshall et al. 1991)

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift 0-5 mm and/or lesions densities present; no high or mixed density lesion > 25 cc. May include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm; no high or mixed density lesion > 25 cc.
Diffuse injury IV (shift)	Midline shift > 5 mm; no high or mixed density lesion > 25 cc.
Evacuated mass lesion	Any lesion surgically evacuated
Nonevacuated mass lesion	High or mixed density lesion > 25 cc, not surgically evacuated

APPENDIX 2

THE ROTTERDAM CT CLASSIFICATION

(Maas, Hukkelhoven, Marshall and Steyerberg. 2005)

PREDICTOR VALUE	SCORE
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift, or shift ≤ 5 mm	0
Shift > 5mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or tSAH[1]	
Absent	0
Present	1
Sum score[2]	+ 1

[1] tSAH; traumatic subarachnoid haemorrhage

[2] The authors chose to add plus 1 to make the grading numerically consistent with the grading of the motor score of the GCS and with the Marshall CT classification.

2

APPENDIX 3

GOS AND GOSE

	Glasgow Outcome Scale **GOS**		**Glasgow Outcome Scale Extended** **GOS-E**
1	**Death**	**1**	**Death**
2	**Vegetative state**	**2**	**Vegetative state**
		3	**Lower severe disability**
3	**Severe disability**	**4**	**Upper severe disability**

Poor outcome

Dependent in daily living

--   --

Favourable outcome

4	**Moderate disability** Independent in daily living, but unable to participate at previous level at work, socially or with family	**5**	**Lower moderate disability**
		6	**Upper moderate disability**
		7	**Lower good recovery**
5	**Good recovery** No restrictions in work, but small changes in social, leisure and familiy life or symptoms may exist	**8**	**Upper good recovery**

ERRATA

In Paper I; Author list:

The correct name of the second author is Tom Ivar Lund *Nilsen*. (Not Tom Ivar Lund; as was printed in the paper)

Chapter 7; page 62; under Paper II and III, second paragraph should be: depth of lesion in the MRI was associated with outcome **in severe head injury**, and….

Table 3, paper I: total n should be 83, not 84.

Table 4, paper IV: CCPT; hit RT SE by ISI was listed twice as variable name. The correct should be first CCPT; hit RT by ISI, and beneath that: CCPT; hit RT SE by ISI.

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1992

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1993

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1994

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1995

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1996

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1997

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1998

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1999

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151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
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2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
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2001
178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
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2002

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2003

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