DETECTION AND OUTCOME OF MILD TRAUMATIC BRAIN INJURY IN PATIENTS AND SPORTSMEN

Persisting symptoms, disabilities and life satisfaction in relation to S-100B, NSE and cortisol

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To Per,
Clara and Oscar
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ABSTRACT

Traumatic brain injuries are common (hospitalization incidence: 250-300 per 100,000 inhabitants/year) and a great majority of these injuries (80-85%) are classified as mild traumatic brain injury (MTBI/concussion). Many patients with MTBI (20-80%) suffer from subsequent persistent and often disabling symptoms. In previous studies serum levels of biochemical markers of brain tissue damage (S-100B and neuron-specific enolase, NSE) have been propounded to serve as predictors of persisting symptoms. In the present studies serum concentrations of S-100B, NSE and cortisol in acute phase and post-concussion symptoms, post-traumatic stress-related symptoms, disabilities and life satisfaction one year after the trauma, were investigated in 88 patients (53 men and 35 women) with MTBI. Serum concentrations of S-100B and NSE were also assessed in elite players (n=54) of typical contact sports (ice-hockey and soccer), which are known to be high risk activities with respect to head injury. Basketball players (n=18) were used as a control group.

A majority of patients with MTBI showed higher serum concentrations of S-100B, NSE and cortisol on admission compared with a second blood sample obtained about 7 hours later (p<0.001 for all analyses). Sequelae were common one year after the injury. Post-concussion symptoms were encountered in 45% of the patients, stress-related symptoms in 17% and disabilities in 48%, but only 3 patients (4%) were on sick-leave on follow-up due to the head trauma. There was a statistically significant negative correlation between the total score of life satisfaction and the total score of disability (r=-0.514, p<0.001). Symptoms on admission (dizziness, nausea) and S-100B were statistically significantly associated with disabilities (p<0.024, multiple logistic regression analysis). Nausea on admission was also statistically significantly associated with life satisfaction (p=0.004). A statistically significant association was found only for S-100B with early (0-1 week post-injury, p=0.008) and only for cortisol with late (more than 52 weeks post-injury, p=0.022) post-traumatic stress-related symptoms.

Concentrations of S-100B after game were statistically significantly increased in comparison with the levels before game (soccer, p<0.001; ice-hockey, p<0.001; basketball (p<0.001). Concentrations of NSE were only raised after soccer play (p<0.001). Increases in S-100-B (post-game minus pre-game values) were correlated to the number of jumps in basketball play (r=0.706, p=0.002). For soccer, increases in S-100B were correlated to the number of headers (r=0.428, p=0.02) and to the number of acceleration/deceleration events other than heading (r=0.453, p=0.02).

The findings provide support for the idea that injury of brain tissue is involved in the genesis of persisting disabilities and long-term changes of life satisfaction in MTBI. Since S-100B increases in serum were correlated to the number of headers and since soccer play also increased serum levels of NSE (in contrast to ice hockey and basketball), it seems that heading may have an impact on brain tissue. The studies have also shown that ordinary playing of the team sports in question (i.e. soccer, ice hockey and basketball) increases S-100B serum concentrations, which has to be taken into consideration when S-100B is used for the detection of injury of brain tissue in sportsmen with acute/overt head trauma during sport practice. An analysis of the biochemical markers of brain damage (in particular S-100B) may be an additional source of valuable information in the management of patients and sportsmen with MTBI. S-100B also seems to be promising for the prediction of impairments and disabilities after MTBI.
ABBREVIATIONS

MTBI  Mild traumatic brain injury
LOC   Loss of consciousness
PTA   Post-traumatic amnesia
PCS   Post concussion symptoms
GCS   Glasgow Coma Scale
GOS   Glasgow Outcome Scale
GOSE  Glasgow Outcome Scale Extended
RLS   Reaction Level Scale
RPQ   Rivermead Post Concussion Symptoms Questionnaire
RHFUQ Rivermead Head Injury Follow-Up Questionnaire
IES   Impact of Event Scale
LiSat-11 Life satisfaction 11 items
OR    Odds ratio
CI    Confidence interval
S100  Soluble in 100% ammonium sulphate saturated solution
NSE   Neuron-specific enolase
LDH   Lactate dehydrogenase
CK-BB Creatine kinase isoenzyme
MBP   Myelin basic protein
c-tau Cleaved tau-protein
H-FABP B-FAHB Fatty acid-binding proteins
GFAP  Glial fibrillary acidic protein
CSF   Cerebrospinal fluid
CT    Computer tomography
MRI   Magnetic resonance imaging
PET   Positron emission tomography
SPECT Single photon emission computed tomography
ICD-10 The International Classification of Disease 10th edition
DSM IV Diagnostic and Statistical Manual of Mental Disorders 4th edition
PCD   Post-concussion disorder
PTSD  Post traumatic stress disorder
DAI   Diffuse axonal injury
WHO   World Health Organization
ORIGINAL PAPERS

The present thesis is based on the following papers, which will be referred to by their Roman numerals:


The published articles are reprinted with kind permission of Lippincott Williams & Wilkins (Clinical Journal of Sport Medicine) and of Taylor and Francis (Brain Injury)
PREFACE

Working as a physician in Rehabilitation Medicine I have often met patients with long-lasting symptoms and disabilities after mild traumatic brain injuries. I remember some of those first meetings several years ago which rather confused me because the patients showed such a varying clinical picture. Some complained of headaches and neck pains while others displayed cognitive symptoms with concentration and memory difficulties. There were also patients with a combination of symptoms such as fatigue, irritability, dizziness, and light or noise sensitivity. All these symptoms did not seem to fit in with my conception of concussion as I thought that patients recovered soon after the injury. Most of the patients I met had been referred to the clinical department of Rehabilitation Medicine by their general practitioner, but there were also patients who had been referred from one specialist physician to another, a process that had gone on for some months. Finally the patients ended up at our department and by then a long period of time had passed since the head injury occurred.

Although many of the patients were extensively investigated with a number of radiological examinations, the results were normal and they were still looking for a diagnosis. This state of affairs made me ask myself two questions: Why did these patients, who had only been observed for 1-2 days, still suffer from symptoms several months and even one year after the injury? What was the actual cause? I looked for information in various ways, but the answers I found were incomplete. Finally I found out that there was a lack of diagnostic tools and there seemed to be insufficient knowledge on this subject. That was the beginning of my interest in mild traumatic brain injuries and this thesis is a result of my studies.
INTRODUCTION

Head injuries affecting brain function are very common. If post-traumatic amnesia is taken as a criterion for disrupted brain function, then the incidence of such injuries is 300-500 per 100 000 inhabitants/year (1-3) out of which 200-300 are hospitalized (1). A great majority of the injuries (80-85%) are classified as mild head injuries/mild traumatic brain injury (MTBI) (4, 5). These injuries have attracted increasing interest during recent years due to a growing awareness of their possible serious and long-term consequences. A significant number of patients with a single head injury (up to 80%) may suffer from rather persistent post-concussion symptoms (PCS) such as headache, fatigue, dizziness, irritability, sleep disturbance and cognitive sequelae such as reduced concentration and memory problems (2, 6, 7) PCS may regularly interfere with the patient’s return to work and resumption of social activities (5, 6, 8, 9). Also, children who are subjected to mild head injury may develop considerable psychosocial, psychological and educational difficulties (10, 11). Furthermore, previous head injury is also reported as a risk factor for Alzheimer’s disease (12).

Sport and recreation contribute substantially to the number of head injuries and account for 5-12 % of all MTBI/concussions (4). MTBI/concussions in sports and recreation are most frequent in younger adults (4, 5) and they are particularly prevalent in contact sports such as ice-hockey, soccer, boxing and rugby (13). During recent years, there has been an increasing awareness of the risk of serious negative consequences with long-term persisting symptoms and cumulative effects of several concussions with cognitive and neurological impairments e.g. in soccer players (14-17). In boxing, repetitive trauma to the head is known to cause late complications such as chronic traumatic encephalopathy, punch-drunk syndrome and dementia pugilistica (18).

This thesis has focused on MTBI, a common injury among people in general, occurring particularly frequently in young people and in sportsmen. A significant number of individuals with MTBI report persisting symptoms which interfere with their working capacity and leisure activities. There is a need for the early detection of subjects running a risk of developing long-lasting impairments and disabilities in order to find predictors of outcome which could then be used to select which patients are in need of rehabilitation and to determine when sportsmen can return to sport practice. Moreover, knowledge of the pathophysiological mechanisms and the injury’s neuro-biological background seems essential in order to understand the clinical condition of MTBI.
GENERAL BACKGROUND

Classification of head injuries

There are several instruments available for the rating of the severity of head injury and assessment of the level of consciousness. In Sweden the Reaction Level Scale (RLS85) (19) is used in most hospitals (20). RLS is a scale for the direct assessment of overall reaction in patients with acute brain disorders. The scale consists of 8 levels (from 1 to 8), a higher RLS level indicating a more severe head injury. However, the Glasgow Coma Scale (GCS) is generally the most used instrument for categorizing head injuries (21). The GCS provides a quantitative measure of depth of impaired consciousness after head injury by assessing reactions of eye opening, motor response, and verbal response (Table 1). According to this scale a brain injury is classified as mild when the GCS score is 13-15, moderate when 8-12 and severe when the CCS score is 3-8 (21). The scale was not intended to distinguish between different types of milder injury. An extended version of the GCS (GCS-E) has therefore been devised in which an amnesia score was added to the GCS in order to more finely classify patients with MTBI (22).

<table>
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<tr>
<th>Eye opening</th>
<th>Spontaneous</th>
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<tr>
<td>To Sound</td>
<td>3</td>
<td></td>
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<tr>
<td>To pain</td>
<td>2</td>
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<tr>
<td>None</td>
<td>1</td>
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<tr>
<td>Best motor response</td>
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<tr>
<td>Localize</td>
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<tr>
<td>Withdraws</td>
<td>4</td>
<td></td>
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<tr>
<td>Abnormal flexion</td>
<td>3</td>
<td></td>
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<tr>
<td>Extends</td>
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<tr>
<td>None</td>
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<td>Verbal response</td>
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<td>Confused</td>
<td>4</td>
<td></td>
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<tr>
<td>Inappropriate</td>
<td>3</td>
<td></td>
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<tr>
<td>Incomprehensible</td>
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<tr>
<td>None</td>
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<tr>
<td>Total</td>
<td>Eye + motor + verbal</td>
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(From Teasdale and Jennett ,1974) (21)

Despite a high frequency of concussions in sport, there is no generally accepted management routine (23). At present there are at least 25 different grading scales and guidelines published, which can be broken down into a number of groups such as neurosurgical scales and sporting injury scales etc. These instruments are based on clinical
symptoms, such as headache, dizziness or tinnitus, different durations of post traumatic amnesia and loss of consciousness and brief neurological examinations. Each scale has its own criteria for assessing the severity of concussion e.g. the lowest time limit of loss of consciousness for a severe concussion can vary between 60 seconds and 60 minutes between the different scales. Amnesia is another criterion which varies between different scales, from not being included at all to more than 12 hours for a severe concussion (23). None of the sport-related concussion severity scales has been prospectively validated (24). The WHO collaborating centre task force examined 18 sports-related guidelines and concluded that none was evidence-based (25).

Diagnostic nomenclature and definitions of MTBI

In the literature and in clinical practice several diagnoses are used synonymously with mild traumatic brain injury i.e. mild head injury (26), minor head injury, commotio cerebri and concussion (5, 27). A number of definitions of MTBI are available and vary regarding the length of amnesia and loss of consciousness (LOC) etc. (28-30). The definition of MTBI proposed 1991 by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (31) has been adopted in many studies and is presented in Table 2.

**Table 2. Definition of mild traumatic brain injury. Developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (31)**

A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function as manifested by at least one of the following:

1. any period of loss of consciousness
2. any loss of memory for events immediately before or after the accident
3. any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused)
4. focal neurological deficit(s) that may or may not be transient

But where the severity of the injury does not exceed the following:

- loss of consciousness of approximately 30 minutes or less
- after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13-15
- post-traumatic amnesia (PTA) not greater than 24 hours
Epidemiological aspects

MTBI is common in active people, especially affecting young adults in the second and third decades of life (5). Several studies have documented a higher injury rate in males, about twice as high as for females. The gender differences become less important with increasing age (4, 25, 32).

The causes of MTBI vary between countries partly because of geographical and socio-economic factors. In some recent epidemiological studies of head injuries in Sweden by Kleiven et al (2003) (32) and Peloso et al (2004) (25) falls was the most common injury cause reported. Compared with studies done in the USA and Scotland, traffic accidents and violence injuries in Sweden made up a smaller proportion of the total injury causes (32).

Aspects of MTBI specifically related to ice hockey and soccer

Concussion has been reported to account for 2 -14% of all injuries in ice hockey (33). The play in ice hockey is intense with many frequent forceful player contacts and contacts with numerous hard surfaces and objects such as the boards, ice, goal posts and other players (34). The situations where speed and rigid obstacles are combined may lead to acceleration and deceleration events of the player’s body and head (35).

In soccer, concussion accounts for 2-4.5 % of all injuries (33) and may be the result of collision with other players, the ground, goal post or ball (36, 37). As the head is purposefully used to direct the ball in ordinary soccer play, the head may meet the ball moving at a velocity of more than 70-80 km/h (37), and thus, it may be subjected to peak accelerations of more than 54g (38). Recently, it was estimated that in several cases of mild head injury/concussion, head accelerations lower than 54 g were involved (39). This raises the question whether or not ordinary heading of the ball in soccer may cause brain injury. The answers to this question which have been presented so far are conflicting. In a number of studies neurological abnormalities and cognitive dysfunction have been shown to occur in both retired and active soccer players (14-17). In contrast, other studies failed to demonstrate any signs of chronic brain damage in soccer players (36, 40, 41).

Morphological and functional changes at micro level in MTBI

Microscopic changes in patients with MTBI had not been described in detail until the 1950s and 1960s (42-44). Oppenheimer (44) demonstrated diffuse axonal injury (diffuse
axon retraction balls) and his findings were corroborated later on both in animal and in human studies (45, 46). In 1998 Genarelli et al. (1998) finally proposed the classification of axonal injury into 3 stages depending on the injury severity (47). The axonal damage may also trigger deafferentation and reorganisation in distant target sites within the CNS (46). Evidence for cellular injury and for abnormal membrane metabolism of white matter has also been presented in MTBI patients (48). To date, the prevailing hypothesis is that the neuropathology of mild head trauma is on the same continuum as that of moderately severe and severe diffuse injury (49).

**ACUTE PHASE (0-3 months after trauma)**

*Symptoms/impairments*

During the first month after MTBI, most patients suffer from symptoms such as headache, dizziness/vertigo, vomiting and fatigue (50). Cognitive impairments are also commonly reported with attention, memory and concentration difficulties (51). The natural course of recovery consists of a successive resolution of many symptoms within 3 months, but a number of patients continue to have persisting or even worsening symptoms (52-54). After a review of previous studies, the WHO collaborating centre task force on mild traumatic brain injury concluded that symptoms and cognitive deficits are common in patients after MTBI in the acute stage, that these symptoms and deficits are largely resolved within 3 months and that recovery occurs for most patients within 3-12 months (55).

*Diagnostic methods and management routines*

There is a risk of intracranial complications in acute phase after MTBI such as tissue-contusions, subdural, epidural and subarachnoidal hematomas (27, 56-58). The prevalence of these lesions is about 5% in patients with a GCS score of 15, around 20% in patients with a GCS score of 14 and around 30% or higher in patients with a GCS score of 13 (59, 60). The mortality rate for patients with MTBI is reported to be 0.2% or less (61-63). Early diagnosis is essential and the diagnostics in the acute phase is therefore focused on identifying patients with these injuries or at risk of these injuries.

Computer tomography (CT) is the primary diagnostic tool for evaluating acute head injury and detecting intracranial hematomas. However, the sensitivity of detecting diffuse axonal damage is low (64) and normal CT-findings do not exclude brain tissue damage or subsequent long term symptoms. During recent years, several studies have focused on CT-
scanning in patients with MTBI (27, 57, 63, 65-67), but policies for the use of CT-scans in Sweden have been shown to vary between hospitals as well as among physicians within the same hospital (20). A need for management guidelines has therefore been voiced. Recently several studies have demonstrated that clinical symptoms and signs are related to intracranial pathology in patients with MTBI (63, 67). Haydel et al (2000) (67) reported that one or more of the following factors: headache, vomiting, age over 60 years, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicle and seizure, were associated with a positive CT-scan (67). Based on these findings recommendations for acute management and decision rules for the use of CT have been formulated (67).

Magnetic Resonance Imaging (MRI) has been shown to be more sensitive to white matter abnormalities than CT (5, 68) and is more useful in evaluating injury lesions of MTBI both in the acute and post-acute phase after trauma (5, 68). Studies with functional imaging such as PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) have demonstrated reduced cerebral blood flow in the frontal and temporal areas in MTBI patients (69). These techniques appear to be more sensitive than either CT or MRI when it comes to detecting cerebral abnormalities after MTBI, especially in patients with post-concussion symptoms (70-72).

Neuropsychological investigations
Cognitive symptoms with impairments of attention, speed of information processing and memory are common during the first months after head injury (73-77). Neuropsychological investigations have been carried out to measure cognitive effects of MTBI on patients. Tests of attention, memory and speed of information processing have shown deficits (78-80). Neuropsychological assessment in acute phase after MTBI is foremost used in sports. There are several web-based computerized instruments available for monitoring cognitive symptoms due to sport-related concussions (81, 82). In sports, the conditions are unique because of the possibility of performing pre-injury cognitive baseline evaluations which can be compared with post-concussion test results. Furthermore, after the initial assessment subsequent follow-up tests can be used for detecting the presence or resolution of cognitive symptoms and for an injured athlete the tests can be helpful to avoid a premature return to competition (82, 83).
LATE PHASE (more than 3 months after trauma)

Post-concussion symptoms – syndrome/disorder

Most studies of patients with MTBI have focused on symptoms in the acute phase and outcome determined at 3 to 6 months, but a considerable number of patients (10-80%) continue to suffer from post-concussion symptoms more than one year after the injury (52, 54, 84, 85). These symptoms may be divided into three main categories 1. somatic: headache, dizziness, fatigue, blurred vision, neck-pain etc; 2. emotional: irritability, frustration, anxiety, depression and 3. cognitive: memory problems, poor concentration, slower thinking, sensitivity to light or noise, sleep disturbance (6). However, post-concussion symptoms are not exclusively encountered in patients after mild head trauma but they are also frequently reported by apparently healthy people (86-89) and for instance by patients with chronic pain (90), whiplash-associated disorder (91) and depression (92, 93). The WHO collaborating centre task force on mild traumatic brain injury concluded that symptoms in patients with MTBI are common, especially headache in the acute stage. Because symptoms are also evident in other types of injuries and in healthy control persons they should be assessed in MTBI with attention to other possible contributing factors (55).

In the literature of this field the set of post-concussion symptoms are often used synonymously with the diagnosis post-concussion syndrome by The International Classification of Disease 10th edition (ICD-10) (94). The syndrome requires a history of head trauma with loss of consciousness preceding the onset of symptoms by a period of 4 weeks and symptoms which may include headache, dizziness, fatigue, irritability, depression, emotional lability, difficulty in concentration, and in performing mental tasks, memory problems, insomnia and reduced tolerance to alcohol and to stress (94). Moreover, the diagnosis post-concussion disorder (PCD), by the American Psychiatric Association (DSM IV) (95) demands specific criteria with 3 or more symptoms present for at least 3 months following the head injury and evidence from neuropsychological testing of difficulty in attention or memory (DSM IV) (95).

There are studies which have identified several general risk factors of persistent symptoms and slow recovery after MTBI. Some of these factors are female gender, age over 40 years, prior MTBI, malingering, alcohol abuse (73, 96-98). The WHO collaborating centre task force on mild traumatic brain injury reported that litigation/compensation was consistently
identified as a prognostic factor for delayed recovery, and little consistent evidence for other predictors was found (55).

Neuropsychological deficits
Long-term neuropsychological impairments have been documented after MTBI with for instance attention deficits after MTBI up to 6 months after trauma (51, 99) while other studies reported that cognitive symptoms were resolved within one to three months post-injury (77, 100, 101). The conflicting results reported in the literature may be due to design differences between the studies, especially regarding the choice of control group, small sample sizes and the variation in time between injury and neuropsychological examination (102). Multiple head injuries are described as having a cumulative effect on cognitive function, foremost on information processing capacity which is reduced to a greater degree and for a longer time (103). The WHO collaborating centre task force does not report of long-lasting neuropsychological impairments after MTBI as the authors of the report consider most cognitive deficits to be resolved within three months (55).

Disabilities
Most studies of patients with MTBI have focused on symptoms and only a few have documented the consequences of the injury on disability and quality of life level, which is in contrast to the studies done of patients with severe head injuries (5). In a study by Thornhill et al (2000) (104), the Glasgow Outcome Scale (GOS) was used as a measure of disability. They reported that one year after the injury 47% of patients with MTBI had moderate or severe disability according to the GOS. Disability one year after trauma was found to be as common in patients with MTBI as after moderate or severe head injuries (104). The GOS is an overall measure of outcome after head injury and was intended to describe outcome in groups of patients. An extended version of the GOS (GOSE) has therefore been developed for measures of health outcome incorporating the patient’s own perspective such as independence inside and outside the home, work, social and leisure activities (105). The WHO collaborating centre task force concluded that patients sustaining more serious MTBI (e.g patients with GCS 13 or 14, focal brain lesions or depressed skull fractures) appear to have increased rates of disability, as assessed by the GOS or by awarding of disability pensions. Moreover, the task force reported that in most studies MTBI-related disabilities are not distinguished from those associated with injuries to other parts of the body (55).
Most patients with MTBI return to work or school shortly after the trauma despite having symptoms related to the accident (9, 53). Decreased working capacity is commonly documented during the first months after MTBI (8, 9, 106) and occupational problems are also the most frequently reported disability 6 months after head trauma (107).

Impact on leisure and social activities are common in patients with MTBI several months after the injury (107). In a study by Johansson et al (1991) (108) using follow-up 1½ to 3 years after the injury, leisure was affected in 9% of patients with MTBI and it was also the most commonly reported disability among the subjects.

**Life Satisfaction**
As patient’s social and occupational activities are affected after MTBI, it can be assumed that quality of life might also be decreased after injury. Although quality of life has been identified as an important outcome measure (109), only a few studies have investigated quality of life in patients with MTBI (110-113). In a follow-up study one year after MTBI by Emanuelsson et al (2003) ratings of quality of life using the instrument SF-36 (a standardized health survey) (113) were reported lower by the patients than by a gender and age-matched control group (110).

**Treatment**
Post-concussion symptoms are most frequently treated with medications (114). However, few pharmacological studies exist and the most commonly recommended medications are non-steroidal anti-inflammatory analgesics or antidepressant and benzodiazepine (114, 115).

In studies from the USA about 40% of patients with persistent symptoms after MTBI are referred for psychological treatment (115). Controlled treatment outcome studies have shown that early brief psychological single session treatment including education, reassurance and reattribution is effective to prevent protracted symptoms (114). Specific cognitive rehabilitation is proposed if the neuropsychological assessment has demonstrated specific defects of memory or perception (116, 117).
Several studies have suggested early intervention with printed and verbal educational information of prognosis of symptoms and advice on return to regular activities (118-120). These interventions are shown to reduce the number of symptoms and to result in less disruption of social and occupational functioning compared with patients not receiving information. The WHO collaborating centre task force found some evidence that early educational information can reduce long-term complaints and that this early intervention needs not to be intensive (121).

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) may develop after a traumatic experience. It is an anxiety disorder that is defined by special criteria, the patient must have been exposed to or witnessed a threatening event and the patient must show intrusive symptoms which include the re-experiencing of images and perceptions flashbacks. Moreover, there must be marked avoidance which can include avoidance of stimuli such as thoughts, feelings or other reminders associated with trauma. The patient must also suffer marked arousal such as irritability, insomnia, and difficulty in concentrating. Finally, these symptoms must cause impairment (122-124).

It has been a long-standing debate on whether people who suffer MTBI can develop PTSD. In several studies it is argued that PTSD cannot develop after MTBI because of impaired consciousness. On the other hand, studies of patients with MTBI even those with loss of consciousness, have shown that such patients may meet the criteria for PTSD. It now seems clear that both disorders may occur simultaneously (122, 125).

ETIOLOGY – POST-CONCUSSION SYMPTOMS

During the last thirty years there has been an ongoing controversy concerning whether post-concussion symptoms are of organic or psychological origin. Although the debate has continued and the arguments are conflicting, the answer to the question may become clearer because of increasing interest and research in the field of MTBI (126).
Some arguments for the different origins of post-concussion symptoms are given here below.

**Arguments which have been proposed for the organic origins:**

- Cellular damage and metabolic abnormalities have been found in frontal white matter in patients with MTBI and normal MRI scan within the first few weeks after the injury (48).
- MRI abnormalities, the location of which is related to specific neurological dysfunction (64).
- Post-mortem studies have demonstrated diffuse axonal injury after MTBI both in humans and animals (44).

**Arguments for mainly psychological origin:**

- Persisting symptoms are found to be related to depression, anxiety and poor motivation (127).
- Psychological factors prevent the resolution of symptoms (85).
- There is worse outcome where there is pre-existing psychopathological disorder (128).
- Expectation is the major cause of symptom persistence (129).
- Desire for compensation is suggested to lead to a prolongation of symptoms. Clinical evaluation of patients after MTBI is proposed to include consideration of the effect of financial incentives on symptoms and disability (130, 131).

**Arguments for mixed organic and psychological origin:**

- Complex interactions between organic and psychological factors (7, 128).
- Different ‘windows of vulnerability’ emerge at different times after injury, which increases the role of psychological factors (126).
- Coping hypothesis: post-concussion symptoms result from the increased stress that head-injured patients experience when they are not able to cope with environmental demands (132). Stress levels and poor psychological adjustment may contribute to the persistence of symptoms (133).
BIOCHEMICAL MARKERS OF BRAIN TISSUE DAMAGE

During the last decade, there has been an increasing interest in neurobiochemical markers of brain tissue damage with respect to both diagnostic and prognostic purposes for patients with traumatic brain injuries (134). Several biochemical markers have been investigated: e.g. lactate dehydrogenase (LDH), adenylate kinase, creatine kinase isoenzyme (CK-BB), myelin basic protein (MBP), cleaved tau-protein (c-tau), fatty acid-binding proteins (H-FABP, B-FAHB), glial fibrillary acidic protein (GFAP), neurofilament, catecholamines, cortisol, neuron specific enolase (NSE) and S-100B (134-138).

Biochemistry and functional roles of S-100B

S-100B is a protein and a member of the S100 protein family which was originally isolated from bovine brain tissue by Moore, (1965). The protein was named S100 because the constituents are soluble in 100% saturated ammonium sulphate at neutral pH. The S-100 family consists of 21 small calcium and zinc binding proteins of low molecular weight (9-13kD), composed of two immunologically distinct subunits, S100A and S100B, with three dimeric isoforms: S-100A1A1 (S-100a0), S-100A1B (S-100a) S-100BB (S-100b) (139, 140) which have different distributions and different ways of acting. The isoforms A1B are mainly found in glial cells, BB isoforms in glial and Schwann cells. The S-100B monomer is mostly to be found in the brain (80-90% of the total S-100) (141). Lower concentrations of S-100B are found in adipose tissue, melanocytes and chondrocytes. Chromosomal localization is identified for several members of the S-100 family and S-100B is located on chromosome 21 (139). The different S-100 proteins share various degrees of amino acid homology and each subunit is characterised by two different Ca\(^{2+}\) - binding sites, described as EF hands (140, 141).

Intracellularly, S-100B is involved in several cellular functions including regulation of energy metabolism, cell growth, cell division, cell-cell communication and calcium homeostasis (139, 142). S-100 B also exerts extracellular functions and is therefore actively secreted (143). Depending on its concentration secreted S-100B exerts trophic or toxic effects. In concentrations in the nanomolar range the marker has shown neurotrophic qualities e.g. stimulating of neuronal outgrowth enhancing the survival of neurons during development (144) and after injury (145). In contrast, micromolar levels of S-100B may have deleterious effects by induction of apoptosis (142).
Animal studies have indicated that S-100B may modulate synaptic plasticity. One suggested possible mechanism is that S-100B secreted from astrocytes binds to a receptor on the neuronal membrane and drives subsequent signalling cascades involved in neuronal synaptic plasticity (146). Several studies have focused upon S-100B and its cognitive function. Homeostasis of S-100B seems to be important for cognitive functions (142) as over- respectively under-expression of S-100B in animals, have been shown to have an impact on memory function (147, 148).

Clinical studies of S-100B

In clinical studies, concentrations of S-100B have been analysed in cerebrospinal fluid and in blood. Increased concentrations in CSF with age (149, 150) and a difference between male and female subjects have been documented (149). In contrast, concentrations of S-100B in plasma have been found to be age and gender independent (151). In studies of controlled alcohol exposure, serum levels of S-100B were not influenced by alcohol (152, 153).

Several studies have revealed increased concentration of S-100B in CSF and in serum in patients with severe traumatic brain injury and in patients with MTBI (155-159). S-100B is one of the most studied biochemical markers in MTBI and it has even been proposed for use in clinical practice (160). Increased serum levels are found to reflect severity of brain tissue damage in acute head injuries (156, 158, 161) and they may have prognostic value after MTBI (157). Studies have shown high serum concentrations of S-100B to be associated with post-concussion symptoms (162) and impaired neuropsychological functioning in patients with MTBI (157, 163). In patients with visible lesions on CT-scans, concentrations of S-100B have been found to be increased in acute blood samples (161). Moreover, a significant association between detectable concentrations of S-100B and brain contusion visible on MRI has been shown in patients with normal CT-scans post trauma (161). However, the specificity of S-100B as a marker of brain tissue has been questioned by Anderson et al (2001) (164) as they found increased serum levels of S-100B in patients with multitrauma without head injury, especially in patients with bone fractures. A release of S-100B is proposed to take place via the blood-brain-barrier, exhibiting an increased or disturbed permeability (138, 165). Another way of possible release of S-100B into the blood is along with the CSF via absorption into the intracranial venous sinuses (166). In addition to brain injuries, some other areas of application for S-100B are within ischemic
stroke and subarachnoid haemorrhage fields (SAH) (167-169) in Alzheimer’s disease (142), as a tumour marker in malignant melanoma (170) and as an early marker of the blood-brain barrier openings (171).

**S-100B and prediction of post-concussion symptom**

In several studies focusing on the relationship between, on the one hand, persisting post-concussion symptoms in MTBI patients and, on the other hand, biochemical markers of brain injury, accidental data and early post-trauma symptoms and signs, the authors came to the conclusion that data on S-100B shortly after the trauma (162, 163), combination of S-100B data and specific symptoms, e.g. dizziness (162, 172), duration of post-traumatic amnesia alone (106) or duration of post-traumatic amnesia together with other measures (54, 98, 173-175), could possibly serve to predict long-term persisting symptoms i.e. predict which patients are at risk of developing post-concussion disorder.

**Biochemistry and clinical studies of neuron-specific enolase**

Neuron-specific enolase (NSE) was originally described by Moore and McGregor in 1965 (176). NSE is an isoenzyme of the glycolytic enzyme enolase, and is predominantly present in neurons (176). The molecular mass of NSE is 78 kDa (176) and the biological half-life is more than 20 hours (177). NSE is located in the cytoplasm of neurones and is suggested to be involved in increasing neuronal chloride levels during the onset of neuronal activity (176). The enzyme is not secreted into the extracellular liquid by intact neurons but set free by cell destruction. Therefore, increased levels of NSE can be detected in peripheral blood after neuronal damage (176). However, NSE is also present outside the central nervous system (CNS), in neuroendocrine cells, erythrocytes, and platelets (176). It is important to notice that NSE might be released in blood by hemolysis, which may influence the results of analysis (177). Concentrations of NSE are found to be age-independent (149, 150).

Thus, NSE is a marker which directly reflects traumatic damage of neurons. In several studies of MTBI, NSE has been investigated as an indicator of acute brain injury (154, 157, 158, 178, 179). Increased levels of NSE in acute phase have been reported to be associated with neuropsychological dysfunction (157) and the marker has been found valuable for prognostic purposes in patients with MTBI (157, 172). In clinical practice NSE is also used as a marker for tumours e.g. small-cell lung cancer and neuroblastoma (180).
**Cortisol**

Cortisol is a hormone secreted into the blood by the adrenal glands and is involved in stress reactions together with the catecholamines epinephrine and norepinephrine. Physical and psychological stress is found to activate the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) –axis resulting among other things in increased levels of cortisol in plasma (181). Cortisol in serum varies with the time of day, and exhibits a circadian variation in secretion. Thus, cortisol may be considered as being a measure of biological response to stress and the hormone has attracted interest in investigations of stress and trauma. The adrenocortical response to brain injury was studied by Woolf and co-workers (1990) (182) who found that similar rises in plasma cortisol levels were encountered in patients on admission irrespective of injury severity (182). Moreover, in studies by Cernak et al (1999) (183, 184) and Koiv et al (1997) (183, 184) increased cortisol concentrations were demonstrated in patients with MTBI as well as in patients with more severe head injuries. However, increases of serum cortisol concentrations are not head injury specific. Similar increases are observed in patients with severe trauma without head injury (185) and in healthy individuals under stressful conditions (186). The relationship between cortisol and post-traumatic stress related symptoms has been investigated in some studies. Delahanthy et al (2000) (187) found that the levels of urinary secretion of cortisol were lower in motor vehicle accident victims diagnosed with post-traumatic stress disorder one month post-trauma than in victims without PTSD. McFarlane et al (1997) (123) showed lower levels of blood cortisol in motor vehicle accident victims who subsequently developed PTSD in comparison with victims without PTSD.
AIMS

The general purpose of this thesis was to elucidate, by studying patients with MTBI in acute phase and healthy sportsmen during sport practice, if an analysis of the biochemical markers of brain tissue damage S-100B and NSE in blood may contribute to the management of MTBI. In patients with MTBI the occurrence of post-traumatic stress-related symptoms and concentrations of serum cortisol were also investigated.

The specific aims were to

- investigate serum concentrations of S-100B and NSE in patients with MTBI in acute phase in relation to post-concussion symptoms, disabilities and life satisfaction one year after the trauma.

- investigate acute phase serum cortisol levels (used as a biochemical marker of “stress”), together with serum levels of S-100B and NSE and study the relationship of these markers to the duration of post-traumatic stress-related symptoms.

- shed some light on whether S-100B and NSE may be useful for the detection of brain tissue damage in contact-sports associated with MTBI/concussion by studying the serum levels of these markers before and after competitive games in elite players of ice hockey and soccer.
METHODS

Patients and subjects
(Papers I and II)
Complete data were obtained for 88 patients (53 men and 35 women, age 40.9 ± 19.5 years) with mild traumatic brain injury (MTBI) (Glasgow Coma Scale 13-15, loss of consciousness less than 30 minutes) leading to hospitalization for observation. In most cases, MTBI was reported to be due to bicycle accidents (32%), outdoors falls (27%), indoors falls (14%) and sports (8%). Twenty-four patients (27%) had been under the influence of ethanol at the time for trauma. Previous concussions were reported by 29 patients (33%). Sixty-nine patients (78%, 39 men and 30 women) participated in a follow-up performed by mail 15 ± 4 months after trauma.

(Papers III and IV)
Members of 2 ice hockey teams (26 players), two basketball teams (18 players) and 4 elite soccer teams (28 players, 2 competitive games) participated in the studies which involved competitive games in the Swedish Elite Leagues of Ice Hockey, Basketball and Soccer. The characteristics of the participants (all were males) were as follows: ice hockey players, age 28 ± 4 years, body weight 87 ± 5 kg, height 182 ± 5 cm, number of previous concussions 1.4 ± 1.2 (range 0-4); basketball players, age 25 ± 4 years, body weight 96 ± 11 kg, height 198 ± 7 cm, number of previous concussions 0.9 ± 1.1 (range 0-4); soccer players, body length: 182±5 cm, body weight: 79±6 kg, age: 26±5 years, number of previous concussions: 1.8±2.1 (range: 0-7).

All studies were approved by the ethics committee of Umeå University.

Blood samples and analysis
Venous blood samples were taken from the patients (3.0±2.2 hours post trauma) and again about 7 hours later (10.3±3.3 hours post trauma) (Papers I and II). Venous blood samples were taken from all elite players 1-5 hours before and immediately after the game (Papers III and IV).

The blood was allowed to clot and was kept at 5º C until centrifugation. The sera were frozen and kept at −78º C until analysis. All samples from the patients were analyzed with respect to S-100B as one batch (Paper III) and the samples from the ice hockey and
basketball players were analyzed as an other batch (Paper IV). The samples from soccer players were similarly analyzed as one batch. Serum protein S-100B was analyzed using immunoluminometric assays (LIAISON Sangtec 100, Sangtec Medical, Bromma, Sweden), which measure A1B isoforms (present mainly in glial cells) and BB isoforms (occurring mostly in glial cells and Schwann cells) of the protein S-100 by assessing its B-subunit as defined by three monoclonal antibodies. The detection limit of the test is 0.02 µg/L. It has been demonstrated that 95% of healthy men and women have serum concentrations below 0.15 µg/L. The laboratory was blind to the aim of the study.

Since the biological half-life of S-100B is rather short (less than 2 hours) and since the time for sampling blood varied considerably between the patients (Papers I and II; range: 0.4 -12.5 hours), we tried to correct and adjust the concentration differences taking into consideration the various time delays between the trauma and blood sampling. Thus, adjusted S-100B was calculated according to the method by Savola et al (2003) (162), which assumes biological half-life of S-100B to be 120 minutes:

\ \[
\text{Adjusted S-100B} = 2 \exp\left(\frac{\text{time from trauma to blood sampling in minutes}}{120 \text{ min}}\right) \times \text{measured S-100B}.
\]

NSE was determined with an immunoluminometric assay based on monoclonal antibodies (LIAISON NSE, Sangtec Medical Bromma Sweden). The detection limit of the kit is less than 1.0 µg/L.

Serum cortisol (Paper II) was analyzed using solid-phase, chemiluminescent immunoassay (immunolite system, DPC, Los Angeles, USA) with a detection limit of 5.5 nmol/L and interassay variation of less than 10%.

**Assessment of accelerations/decelerations events in sports**

All games (one ice hockey game and one basketball game, Paper III, and two competitive soccer games, Paper IV) were videotaped for later analysis of acceleration/deceleration events. This analysis was performed by independent investigators (two for the ice hockey and soccer games and three for the basketball game) using criteria agreed on beforehand. The number of acceleration/deceleration events (for ice hockey: body checkings, falls, collisions and boardings; for basketball: jumps, collisions and falls, and for soccer: headers, jumps, falls and collisions) was assessed by each investigator. Mean values were calculated for each player and taken as estimates of the number of acceleration/deceleration events.
Follow-up measurements

The Rivermead Post-Concussion Symptoms Questionnaire (Papers I-IV)

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) presents 16 of the most commonly encountered post-concussion symptoms (headaches, feelings of dizziness, nausea and/or vomiting, noise sensitivity, sleep disturbance, fatigue) and asks the patient to rate the extent to which these symptoms have been any more of a problem over the previous 24 hours compared with pre-morbid levels, using a rating scale with values 0-4.

A total symptoms score can be calculated as a sum of all scores for which good reliability and validity has been demonstrated (188-190). Twenty four to 48 hours after the game, the sportsmen (Papers III and IV) were asked to fill in the RPQ (189) The duration of post-concussion symptoms for the patients (Papers I and II) was assessed one year after the head injury by using questions of the Rivermead Post-Concussion Symptom Questionnaire (RPQ) (189). The duration of each post-concussion symptom was rated by the patients using the following scale: a) no symptom at all after the accident/no difference before and after the accident, b) symptom less than 1 week, c) symptom less than 4 weeks, d) symptom less than 12 weeks, e) symptom less than 52 weeks, f) symptom is still present at follow-up.

The Impact of Event Scale questionnaire (Paper II)

The Impact of Event Scale (IES) is a self-report scale which was developed to assess anxiety and stress reactions as a result of a specific event (191). It comprises seven statements regarding intrusive symptoms and eight regarding avoidance symptoms. Though IES does not show particularly high content validity as a measure of post-traumatic stress disorder, it has been considered to be a standard measure of post-traumatic stress for a long time and its relationship to PTSD is clearcut (192). Accordingly, in order to rate the duration of post-traumatic stress-related symptoms (Paper II), questions from the Impact of Event Scale questionnaire (IES) (191) were employed. For each item of the IES the patient was asked to mark one of the following alternatives: a) no symptom at all after the trauma, b) symptom less than 1 week, c) symptom less than 4 weeks, d) symptom less than 12 weeks, e) symptom less than 52 weeks and f) symptom is still present.

The Rivermead Head Injury Follow-Up Questionnaire (Paper I)

The level of disability at follow-up was measured by the Rivermead Head Injury Follow-Up Questionnaire (RHFUQ). The RHFUQ is a short reliable and valid measure and consists of 10 items concerning everyday life, work, relationships and social, leisure and
domestic activities which are commonly influenced by brain injury. The questionnaire is particularly suitable for patients with mild or moderate brain injury of disability specially designed for patients with mild to moderate head injury (188).

The LiSat-11 (Paper I)

Life satisfaction at follow-up was assessed using the LiSat-11 questionnaire. LiSat-11 was used by Fugl-Meyer et al (2002) (193) and comprises 11 items, with one item concerning life as a whole and with 10 other items including vocation, economy, leisure, contacts, sexual life, ADL, family life, partner, somatic health, and psychological health. LiSat-11 is a further development of the LiSat-9 (194) which was widely used for measuring life satisfaction in a range of rehabilitation contexts including multiple trauma with brain affections (195). Levels of satisfaction are rated on a six-grade ordinal scale from 1 (very dissatisfied) to 6 (very satisfied) of life.

Statistics

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.5 (Papers I and II) and version 10.0 (Papers III and IV). Data are reported as means ± standard deviations unless not indicated otherwise. For the study of paired observations Wilcoxon’s signed-ranks-test was used, as the samples were rather small. Mann-Whitney test was used for the comparison of continuous variables (Papers I-IV). For the analysis of bivariate correlations Spearman’s correlation coefficients (Papers I and II) and Pearson’s correlation coefficient (Papers III and IV) was used. For the study of complex relationship between a dependent variable and several independent variables multiple regression and logistic regression techniques were used. Continuous dependent variables were studied with multiple regression analysis. For categorial variables (i.e. presence or absence of IES-symptoms, differentiation of patients with 5 or more post-concussion symptoms and patients with 4 or less symptoms) the dependent variables were dichotomized and coded as a binary variable (1 and 0 respectively) and logistic regression analysis was applied. The data file used for multiple linear and logistic regression analysis was obtained from all available data on the acute phase by deleting variables with many missing values (>20%). The number of independent variables was thus reduced and the final data matrix comprised 9 continuous independent variables (age, serum concentrations of NSE, cortisol, S-100B, including adjusted S-100B (see above) and length of anterograde amnesia) and 24 categorical independent variables (presence/absence of different
symptoms during acute phase, ethanol ingestion, fracture etc). Stepwise forward logistic regression analysis was performed using $p<0.05$ for entry limit and $p>0.10$ for removal limit. The results of the logistic regression analysis are presented as OR (odds ratio), which indicates an increased (OR>1) or a decreased (OR<1) likelihood of the event (coded as 1) occurring. The reliability of the OR is expressed as 95% confidence intervals (CI).

The level of statistical significance was set at $p<0.05$. 

RESULTS
(Papers I and II)

Serum levels of S-100B, NSE and cortisol

Concentrations of S-100B and NSE in sera of the patients admitted to hospital due to MTBI are shown in Fig. 1A and B respectively. In both A and B, each patient is represented by a pair of symbols which are connected with a line. A majority of the patients showed higher concentrations of both S-100B (78%) and NSE (89%) in the first blood sample (sample 1: S-100B: 0.363± 0.333 µg/L; NSE: 10.93± 4.12 µg/L) compared with the second blood sample (sample 2: S-100B: 0.192± 0.134 µg/L; NSE: 7.77± 4.52 µg/L). Statistical analysis revealed a significant difference between the first and second sample, for both markers (p<0.001; Wilcoxon’s signed-ranks-test).

The results of the analysis of cortisol in serum of the patients are displayed in Fig 2A and B. For a majority of patients (78%) the concentration of cortisol decreased with time after the trauma, i.e. the concentration of cortisol in the second sample was lower than in the first sample (first blood sample: cortisol: 628.9 ± 308.9 nmol/L, range, 46-1521 nmol/L; second blood sample: cortisol: 398.2 ± 219.4 nmol/L, range, 52-1039 nmol/L) taken in the emergency room. The difference between the cortisol concentration in the first and in the second sample was statistically significant (p<0.001; Wilcoxon’s signed-ranks-test). It is well known that cortisol concentrations in serum vary with time during the day, i.e. that there is circadian variation of cortisol secretion. In order to take these physiological variations into account, cortisol concentration was also plotted against the clock time of the day, when the blood samples were taken (see Fig. 2 B). The scatter of the symbols in Fig. 2 B shows that the cortisol concentrations were generally higher (or much higher) in comparison both with reference values (shaded areas indicate the normal range of cortisol for the method of analysis used).

Occurrence and duration of post-concussion symptoms and of post-traumatic stress-related symptoms

A majority of the patients (40 subjects, 58%) showed symptoms during the first week after the trauma and the frequency of occurrence of symptoms decreased subsequently with time. At the time of the follow up, 31 patients (45%) still exhibited one or more of the post-
Fig. 1. Serum concentrations of S-100B (A) and NSE (B). Symbols representing each patient are connected with lines.
Fig. 2. Serum cortisol concentration plotted against time after trauma (A) and against clock time (B). Symbols representing each patient (n=88) are connected with lines. First blood sample: Cortisol/1: 628.9 ± 308.9 nmol/L. Second blood sample: Cortisol/2: 398.2 ± 219.4 nmol/L.
concussion symptoms and 9 (13%) showed 5 symptoms or more. In an attempt to find factors which could possibly be of importance for the prediction of persisting symptoms after MTBI, we performed a stepwise forward logistic regression analysis. Patients who reported the occurrence of at least 5 post-concussion symptoms of specific duration after the trauma were chosen as a dependent variable and coded as a binary variable (1=patients with 5 symptoms or more, 0=patients with 4 symptoms or less), as the size of the samples allowed to dichotomize in this way. Significant effects of ‘dizziness on admission’ was found for patients reporting 5 or more post-concussion symptoms lasting more than 1 week \( \text{[OR (odds ratio) } = 8.667, \text{ CI: 1.542-48.698, p=0.014]}, \text{ more than 4 weeks (OR } = 10.667, \text{ CI: 1.831-62.133, p=0.008]) and more than 12 weeks (OR } = 10.667, \text{ CI: 1.831-62.133, p=0.008]. \) No variable was entered into the equation for 5 symptoms (or more) lasting longer than 52 weeks.

In general, post-traumatic stress-related symptoms lasting longer than 1 week were reported only by about half of the patients (46 %) and they decreased in frequency with time after the trauma. In our search for factors which could possibly be of importance for prediction of patients with persisting post-traumatic stress-related symptoms, we performed a stepwise forward logistic regression analysis. Patients exhibiting some symptom of a specific duration were chosen as a dependent variable, as the size of the sample permitted to dichotomize in this way (1=patients with some symptom, 0=patients without any symptom). Interestingly, a significant effect of S-100B (sample 2) was found for patients symptoms less than 1 week after the trauma (OR per 1 µg/L S-100B increase = 5396.0, CI: 3.9-7368179.8, p=0.020). For patients with symptoms lasting more than 1 week, cortisol (sample 1) was solely entered into the equation with OR= 1.003 per 1 nmol/L concentration increase (CI: 1.001-1.005, p=0.006). For patients with symptoms lasting more than 4 weeks significant associations were encountered both for cortisol (sample 1) (OR=1.003, CI: 1.001-1.006, p=0.007) and for nausea on admission (OR=4.1, CI: 1.041-16.145, p=0.044). Patients with symptom duration longer than 12 weeks were statistically significantly associated with the presence of fractures (OR = 4.950, CI: 1.201-20.397, p=0.027). Finally, cortisol (sample 2) (OR=0.994, CI: 0.988-0.999, p=0.025), presence of fatigue on admission (OR = 17.053, CI: 1.820-159.759, p=0.013) and fractures (OR = 25.634, CI: 2.475-265.521, p=0.007) were entered into the final equation for patients showing symptoms lasting more than 52 weeks.
Levels of disability and life satisfaction

In total, 33 patients (48%) reported at least one disability on the RHFUQ. The mean RHFUQ-score was 6.5 ± 10.2 (range: 0-38, maximum possible disability score 40). The most frequently reported changes were on the disability items ‘finding work more tiring’ (reported by 24 patients), ‘ability to maintain previous work load/standard’ (22 patients) and ‘ability to enjoy previous leisure activities’ (21 patients). In a logistic regression analysis of the RHFUQ, patients exhibiting any disability were chosen as a dependent variable and coded as a binary variable (1=patients with disabilities, 0=patients with no disabilities). Stepwise forward logistic regression analysis resulted in 4 steps and in the final equation the following variables with statistically significant effects were entered: S100B (sample 1) (OR = 17.922 per 1 µg/L concentration increase, CI: 1.487-216.073, p=0.023), cortisol (sample 2) (OR = 1.004 per 1 nmol/L concentration increase, CI: 1.000-1.007, p=0.040), ‘dizziness on admission’ (OR = 54.989, CI: 3.780-799.882, p=0.003) and ‘nausea on admission’ (OR = 9.347, CI: 1.592-54.880, p=0.013).

At follow-up, life satisfaction was assessed using the LiSat-11 questionnaire. The alternatives ‘very satisfied’ and ‘satisfied’ were pooled together to give an over-all assessment of life satisfaction. Only 36% of the patients were either “very satisfied” or “satisfied” with ‘vocation’ and ‘economy’ and only 42% and 49% of the patients reached this level of satisfaction for ‘sexual life’ and ‘leisure’ respectively. The mean total LiSAT-11 score for all the 69 patients was 46.1 ± 10.8 (range: 12-62; maximum possible score = 66). There was a statistically significant negative correlation between the total score of LiSAT-11 and the total score of RHFUQ (r=-0.514, p<0.001), indicating that life satisfaction level decreased with increasing disability. Stepwise forward logistic regression analysis was also carried out (dependent variable: patients rating 6 or more items of LiSat-11 as ‘very satisfied’ or satisfied’ = 1, patients rating 5 or less variables of LiSat-11 in a similar way = 0). The analysis showed that statistically significant effects were obtained for adjusted S-100B (OR = 0.244 per 1 µg/L concentration increase, CI: 0.077-0.774, p=0.017), ‘nausea on admission’ (OR = 0.084, CI: 0.016-0.445, p=0.004) and ‘pain on discharge from hospital’ (OR = 20.502, CI: 1.938-216.889, p=0.012), implying that an increase in adjusted S-100B levels and the occurrence of ‘nausea on admission’ decreased the probability to exhibit high levels of life satisfaction.
Thirty-one patients (out of 69 participating in the follow-up) were on sick-leave for 1-2
days after the discharge from the hospital. Longer periods of sick-leave were generally due
to orthopaedic injuries. One year after the trauma 3 patients were on sick- leave because of
the head injury.

(Papers III and IV)

Serum concentrations of S-100B and NSE

For most players, post-game values of S-100B were higher than pre-game values, and the
differences between post-game and pre-game levels were statistically significant in all
sports (ice hockey: 0.072±0.108µg/L, p=0.00004; basketball: 0.076±0.091 µg/L, p=0.002;
soccer: 0.051±0.029 µg/L, p<0.001). The analysis of NSE revealed significant difference
only in soccer when the post game and pre game values were compared (post-game minus
pre-game values: 1.7±1.8µg/L, p<0.001).

S-100B, NSE and trauma events

In ice hockey, the number of body-checkings, falls and collisions was assessed and the total
number of acceleration/deceleration events was counted (mean: 2.5±1.47, range: 1-6). No
significant correlations were found between the changes in concentrations of markers and
the total number of accelerations/decelerations.

In basketball, the most frequent acceleration/deceleration event was jump (number of
jumps: 11.25±10.20, range: 0-30), while the number of other events (falls and collisions)
was much lower (number of other events: 4.43±3.16, range: 0-11).

The mean number of headers per soccer player was 3.3 (standard deviation 3.9, range 0-19,
four players did not perform any headers at all). The mean number of other trauma events
per soccer player was 3.5± 2.9 (range: 0-10).

The number of headers and the number of other trauma events for soccer players and the
number of jumps for basketball players were correlated to the changes (post-game values
minus pre-game values) of S-100 for all players and the results are shown in Figure 3 and 4.
The changes in S-100B for soccer players (post-game minus pre-game values: 0.051±0.029
µg/L) were found to be statistically significantly correlated both to the number of headers
(r=0.428, p=0.02, see Fig. 4 B) and to the number of other trauma events (r=0.453, p=0.02,
see Fig. 4 A). In contrast, no statistically significant correlation (headers: r=0.039, p=0.845, see Fig. 4 D, other trauma events: r=0.130, p=0.508, see Fig. 4 C) was found for the changes in NSE concentration (post-game minus pre-game values: 1.7±1.8µg/L). Surprisingly, a statistically significant correlation was found between the changes in S-100B for basketball players (post-game minus pre-game values: 0.076± 0.091 µg/L and the number of jumps (r=0.706, p=0.002 see Fig. 3 A), while there was no similar correlation for NSE (r=0.303, p=0.223, see Fig. 3 B).
Figure 3. Correlation between changes (post-game minus pre-game values) of S-100B (A) and NSE (B) and number of jumps during the basketball game.

A  S-100B and trauma events
Correlation: r=0.453 (p=0.02)

B  S-100 and headers
Correlation: r=0.428 (p=0.02)

C  NSE and trauma events
Correlation: r=0.130 (p=0.051)

D  NSE and headers
Correlation: r=0.039 (p=0.84)

Figure 4. Correlation between changes (post-game minus pre-game values) of S-100B (A and B) and NSE (C and D) and headers or trauma events.
DISCUSSION
(Papers I and II)
The present studies of patients with mild traumatic brain injury (Papers I and II) show that, on admission to hospital, the majority of patients had increased serum levels of S-100B, NSE and cortisol compared with serum levels a few hours later. Persistent post-concussion symptoms were frequently reported and 45 % of the patients who participated in the follow-up still reported some symptom one year after injury. The presence of 5 (or more) symptoms ‘lasting more than 1-12 weeks was found to be significantly associated with ‘dizziness on admission’. Only a minority of patients exhibited post-traumatic stress-related symptoms. Both early (mean time after the trauma: 3.0 hours) and late (mean time after the trauma: 10.3 hours) serum cortisol levels were statistically significantly associated with the presence of post-traumatic stress-related symptoms, lasting more than 1-4 weeks and more than 52 weeks respectively. Concentrations of S-100B in the blood sample obtained about 10 hours after the trauma was singled out as being the only variable statistically significantly associated with patients complaining about post-traumatic stress-related symptoms lasting less than 1 week post-trauma. The probability of suffering disability at follow-up was increased with increasing S-100B early, increasing cortisol about 10 hours after trauma and the presence of ‘dizziness on admission’ and ‘nausea on admission’. A statistically significant negative correlation was found between life satisfaction (total score on LiSat-11) and disability level (total score on the RHFUQ). The probability of exhibiting high levels of life satisfaction (LiSat-11) was statistically significantly decreased with increasing levels of adjusted S-100B and presence of ‘nausea on admission’ to hospital.

Altogether 69 (i.e. 78 %) of the 88 patients completed the follow-up fully and it seems therefore that the data are representative for the total population of patients in the present study (Papers I and II). The percentage of the patients who participated in the follow-up appears also to be comparable to other studies of patients with mild head injury and 1-year follow-up (e.g. 35% - 88%, (110, 196))

Serum levels of S-100B, NSE and cortisol
Serum concentrations of S-100B on admission are in accordance with the levels reported after mild head injury in other studies (27, 197). For a majority of the patients both S-100B and NSE decreased with time after the injury and were lower in the second blood sample (obtained about 10 hours after injury) in comparison with the first blood sample (taken
about 3 hours after injury), a finding which is similar to several previous studies ((156, 159, 161). Moreover, S-100B and NSE serum concentrations were statistically significantly (yet weakly) correlated to each other (sample 1: r=0.258, p=0.016; sample 2: r=0.212, p=0.049). Accordingly, simultaneous increases in S-100B and NSE were regularly encountered which may either indicate damage of both glial and neuronal cells or be a result of complex neuronal-glial interactions (158).

Concentrations of cortisol in blood samples obtained shortly after the trauma in our study (mean value: 628.9 nmol/L, range: 46-1521 nmol/L) are in agreement with previous studies on head injury patients including individuals with mild head injury (183, 184). However, it should be noticed that serum cortisol concentration increases of this magnitude are neither head injury specific (similar increases may be observed in injured patients without head injury, (198) and even in healthy individuals e.g. during military survival training, (186)) nor necessarily indicative of head injury severity (183, 184). A considerable number of the patients were under the influence of alcohol, which may have contributed to the rise in levels of cortisol, as alcohol is known to increase the secretion of cortisol from the adrenal cortex (182, 199).

Post-concussion symptoms
In total 31 patients (45 %) reported at follow-up 1 year after the injury some symptom related to the head trauma which is within the range of figures reported in previous studies (20-80). It should be recalled in this context that the post-concussion symptoms are not exclusively encountered in patients after mild head trauma and that they are also frequently reported by apparently healthy people (86-89) and e.g. in patients with chronic pain(90, 200), whiplash-associated disorders(91) and depression(92, 93).

Our logistic regression analysis disclosed a statistically significant association only between ‘dizziness on admission’ and the presence of 5 (or more) symptoms lasting more than 1 week, 4 weeks and 12 weeks. Thus, using our study design, we were unable to demonstrate any significant association between serum concentration levels of S-100B, NSE or cortisol and the probability to exhibit 5 (or more) post-concussion symptoms from 1 week to 52 weeks after the trauma. In a recent study, Nygren de Boussard et al. (2004) were likewise unable to demonstrate any relation between serum levels of S-100B and symptoms according to the RPQ 1-14 days post injury (201). Of particular interest is also the fact that
female gender was not singled out as a factor which would increase probability to suffer 5 symptoms or more, which is in contrast to studies showing female gender as a risk factor for developing of post-concussion symptoms (54, 98, 174, 175).

Relationship between post-traumatic stress-related symptoms, cortisol and S-100B
Rather a small number of patients reported post-traumatic stress-related symptoms lasting longer than 1 year after the trauma (17% of the patients had at least 1 symptom and 10% of the patients reported 3 symptoms or more). The gravity of the symptoms was not rated in the present study, yet it may be of interest to mention that Middleboe et al. 1992 (84) found prominent post-traumatic stress symptoms in around 20% of the patients with mild head injury one year after the trauma. In a study by Mayou et al. (2000) (202) of road traffic accident victims, the occurrence of post-traumatic stress disorder ranged between 14 and 17% at 1 year follow up. Thus, it appears that post-traumatic stress-related symptoms were less frequent and perhaps even less pronounced in the present study in comparison with these studies, which may be due to the fact that, apart from a few exceptions, most of our patients were injured at low velocities/low impacts (e.g. in falls or bicycle accidents and not car crash accidents).

We found no statistically significant correlation between reported presence of post-traumatic stress-related symptoms during the first week post-trauma and serum levels of cortisol. However, stepwise forward logistic regression analysis did reveal statistically significant association between serum cortisol (sample 1) and patients with symptoms lasting longer than 1-4 weeks, and between cortisol (sample 2) and patients suffering symptoms lasting more than one year. The association was positive for cortisol (sample 1) and patients with symptoms lasting longer than 1-4 weeks (i.e. symptoms were more likely to occur with increasing serum levels of cortisol (sample 1)). Interestingly, the association was negative for cortisol (sample 2) (OR =0.994), i.e. increased levels of cortisol in the second blood sample decreased the probability for a patient to exhibit symptoms lasting longer than 1 year after the trauma. These findings are somewhat puzzling as they are not entirely in accordance with previous studies.

Urinary secretion of cortisol (in urine collected during a 15 hour period after admission) in motor vehicle accident victims was lower in subjects subsequently (1 month post-trauma) diagnosed with post-traumatic stress disorder (187). Delahanty et al. (2000) (187) also
described negative correlation between the total amount of cortisol secreted in urine or cortisol urine concentration on the one hand and subscales of the IES-instrument on the other hand. McFarlane et al. (1997) (123) showed that motor vehicle accident victims who subsequently developed PTSD had lower blood cortisol values than the victims without subsequent PTSD. However, these authors did not account for the time between the trauma and the sampling of blood in their patients. Accordingly, it is possible that the time between the accident and sampling of blood varied a lot in their study (our study clearly shows that serum cortisol levels decrease with time after the trauma) which might have had introduced a bias. In our study, negative relation between serum cortisol level and occurrence of post-traumatic stress-related symptoms was only encountered with regard to cortisol concentration in the second blood sample and the occurrence of symptoms lasting longer than 1 year (i.e. decreasing cortisol (sample 2) increased probability for a patient to exhibit symptoms lasting more than 1 year).

Stepwise forward logistic regression analysis revealed that the association between concentrations of S-100B (sample 2) and patients exhibiting post-traumatic stress-related symptoms during the first week after the trauma was statistically significant (p=0.020) and that the probability for a patient to suffer post-traumatic stress-related symptoms greatly increased (OR = 5396 per 1 µg/L concentration increase).

Generally, in MTBI patients, serum concentration of S-100B on admission to hospital (i.e. within a few hours after the trauma) is considered in several studies as being the most indicative of late symptoms after mild head injury (162, 203). S-100B is known to be rapidly cleared from the blood (biological half-life of less than 2 hours) (134). It appears therefore surprising that the amount of this protein, considered as a “biological marker of brain injury”, in rather late samples of blood (taken 10.3 ± 3.3 hours after the trauma), provides information pertaining to the occurrence of post-traumatic stress-related symptoms during the first week after the trauma. As far is known today, two possible hypothetical explanations may be suggested.

Firstly, it has been suggested that organic damage resulting from a minor brain injury may contribute to neurobiological functions that mediate post-traumatic stress reactions (122) and an increase in S-100B late after a minor head injury may reflect such organic damage engaging neuronal circuitry involved in the formation of post-traumatic stress symptoms.
Secondly, it has been suggested that major increase in catecholamine levels without the compensatory effect of concomitant appropriate cortisol increases in association with the trauma could produce ‘superconditioned’ memories that may form subsequent PTSD-symptoms (124, 162, 203, 204). It is possible that this has been the case for the patients of our study exhibiting several post-traumatic stress-related symptoms and catecholamine levels were probably also high in these patients at the second time of blood sampling (about 10 hours post-trauma). Catecholamines are known to increase the release of S-100B from adipose tissue(205-208), and they might thereby have contributed to the late increase in serum levels of S-100B.

Disabilities
Disability level was assessed using the RHFUQ, an instrument specially designed for patients with mild to moderate head injury (188). Presence of any disability was reported by 33 patients (48 %) which corresponds well to the figure (48-56%) obtained for mild head injury patients in a study with a 6-months follow-up (107). Our finding of the most frequently reported disability item, i.e. ‘finding work more tiring’ is also in accordance with this study. Disability involving leisure activities was also very common in our study (11 patients, 30%) indicating that there was also an effect on less demanding activities with respect to performance and achievement than professional life/work. Interestingly, in contrast to these rather frequently reported disabilities involving both professional and private life, only 3 patients (2 men and 1 woman) were on sick-leave at follow-up. We dichotomised the patients into those showing disability (1) and those without any disability (0) and then did a multiple logistic regression analysis. This analysis demonstrated that increased concentrations of S-100B (sample 1), increased concentrations of cortisol (sample 2) and the presence of ‘dizziness on admission’ and ‘nausea on admission’ increased the probability of becoming patient with some persisting disability. These results indicate that it may be meaningful to explore more the possibilities of combining information on symptoms with information on several different biochemical markers shortly after a mild head injury in order to find more practical and valid instruments for the prediction of outcome in patients with mild head injury.

Life satisfaction
Altogether only 55% of the patients reported to be ‘very satisfied’/‘satisfied’ on the item ‘life as a whole’ at follow up. The corresponding figures were even lower for ‘vocation’
(36 %), ‘leisure’ (49 %) or ‘economy’ (36 %). These scores are clearly lower than the population-based reference values of the LiSat-11 described by Fugl-Meyer et al (2002) (193) (i.e. ‘life as a whole’, 72%; ‘vocation’, 54%; ‘leisure’, 58%). Thus, it appears that our sample of patients with MTBI reported decreased levels of life satisfaction in comparison with a large Swedish reference population (2533 subjects) (193). Similarly, ratings of quality of life of a cohort of MTBI patients were found to be lower than those of a gender and age matched control group by Emanuelson and co-workers (110) using SF-36 (a standardized health survey (113) with respect to the quality of life one-year post-trauma.

A negative correlation was demonstrated between the total score of LiSat-11 and the total disability score (as assessed with RFHUQ, r = -0.514, p<0.001). This negative correlation appears to depict the fact that decreased life satisfaction probably reflects increased disability levels and it may also indicate a need for rehabilitation measures, in spite of a low frequency of occurrence of sick-leave and irrespective of the pre-trauma health state of the patients. The present study provides results which indicate that the MTBI patients of our study are very rarely on sick-leave in spite of considerable symptoms and disabilities with accompanying lower levels of life satisfaction. Accordingly, it appears that litigation or malingering did not play a major role for the development of complaints and impairments after MTBI in our patients, which is in agreement with a recently published study (32). Also, a multivariate logistic regression analysis disclosed statistically significant association between life satisfaction and adjusted S-100B (OR = 0.244 per 1 µg/L concentration increase; p=0.017), showing that increased values of adjusted S-100B decreased the probability to exhibit high levels of life satisfaction. It should be recalled that increased S-100B/1 levels were also found to be associated with an increased risk of having a persisting disability (see above).

(Papers III and IV)
The serum concentration levels of S-100B and NSE found in sportsmen after the games are lower than the values found in patients shortly after mild head injury/concussion/mild traumatic brain injury (157, 179, 203, 209). The range of induced changes in S-100B in our studies (post-game minus pre-game values) corresponds to the changes observed in healthy subjects after long-distance running (210). None of the soccer players in our study was subjected to extraordinary head trauma, or showed signs or symptoms of concussion, and no value of S-100B or NSE was exceptionally raised either.
Kapural and co-workers (165) recently demonstrated, in a study using humans, that iatrogenic disruption of the blood brain barrier (in the absence of neuronal damage) using mannitol, caused a significant increase of S-100B in serum, while NSE levels were unaffected. A possible implication of these findings for the present study may be that game associated activities, in ice hockey, basketball and soccer, may have induced the opening of the blood brain barrier in the players (an increase in blood brain permeability caused by exercise has been demonstrated in animal studies) (211), which could possibly explain the rise of S-100B in sera. However, in contrast to ice hockey and basketball players, the soccer players in the present investigation exhibited also increases in the serum NSE. Because the major difference between ice hockey, basketball and soccer is heading, it is tempting to ascribe the rise in NSE found in the present study to heading and to suggest that more than solely opening of the blood brain barrier had to be involved to produce this rise.

The changes in S-100B concentrations during the soccer games were significantly correlated both to the number of headers (r=0.428, p=0.02) and to the number of trauma events (r=0.453, p=0.02). These findings are in line with some of Otto et al.’s. (2000) (210) results obtained in a study in which they compared increases in S-100B after different sport activities. They found increased levels of S-100B after jogging and running but not after cycling on a bicycle ergometer. Otto et al. (210) suggested that axial vibration of the brain is a possible mechanism for the rise of concentrations. The correlations of S-100B to the number of headers and to the number of other trauma events in our investigation may reflect that S-100B is released by vibration of the brain caused both by acceleration/deceleration of the whole body and by selective head trauma due to the heading.

CONCLUDING REMARKS

Some years ago it has been suggested that S-100B could be a rather specific tool for assessment of the amount of brain damage (157, 161). However in more recent studies it was demonstrated that S-100B in serum may be raised not only in patients with overt cerebral injuries (traumatic or ischemic), but also in patients with extra-cerebral injuries (e.g. fractures, multitrauma etc(164)) or during surgery (212), and in healthy subjects after different types of exercise, e.g. running and boxing (210). The studies accounted for in this thesis ad playing ice hockey, basketball and soccer to the list of activities, which induce
increases in serum concentration of S-100B. Thus, increases in S-100B serum concentrations associated to ordinary playing of these team sports have to be taken into consideration when S-100B is used for the detection of injury of brain tissue in sportsmen with acute/overt head trauma during sport practice. Since S-100B increases in serum were correlated to the number of headers in soccer players and since soccer play also increased serum levels of NSE (in contrast to ice hockey and basket ball), it seems that heading may have an impact on brain tissue during ordinary soccer game.

As a whole, the findings of the studies of this thesis provide support for the idea that injury of brain tissue is involved in the genesis of persisting disabilities and long-term changes of life satisfaction in MTBI. Moreover, the biochemical marker for brain damage S-100B appears (alone or together with symptoms in the acute phase after the trauma) to be a much more promising tool for prediction of disability and life satisfaction levels than for prediction of persisting symptoms after MTBI, which may be useful to single out patients in need of rehabilitation early after the head trauma.
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Appendix 1

Rivermead Post Concussion Symptoms Questionnaire

After a head injury or accident some people experience problems which can cause worry or nuisance. We would like to know if you now suffer any of the symptoms given below. As many of these symptoms occur normally, we would like you to compare yourself now with before the accident.

For each one please circle the number closest to your answer

0 = Not experienced at all  
1 = no more of a problem  
2 = a mild problem  
3 = a moderate problem  
4 = a severe problem

Compared with before the accident, do you now (i.e. over the last 24 hours) suffer from:

- Headaches 0 1 2 3 4
- Feelings of dizziness 0 1 2 3 4
- Nausea and/or vomiting 0 1 2 3 4
- Noise sensitivity, easily upset by loud noise 0 1 2 3 4
- Sleep disturbance 0 1 2 3 4
- Fatigue, tiring more easily 0 1 2 3 4
- Being irritable, easily angered 0 1 2 3 4
- Feeling depressed or tearful 0 1 2 3 4
- Feeling frustrated or impatient 0 1 2 3 4
- Forgetfulness, poor memory 0 1 2 3 4
- Poor concentration 0 1 2 3 4
- Taking longer to think 0 1 2 3 4
- Blurred vision 0 1 2 3 4
- Light sensitivity, easily upset by bright light 0 1 2 3 4
- Double vision 0 1 2 3 4
- Restlessness 0 1 2 3 4

Are you experiencing any other difficulties?  
Please specify, and rate as above:

1. ___________________________________________ 0 1 2 3 4
2. ___________________________________________ 0 1 2 3 4
Appendix 2

Rivermead Head Injury Follow-Up Questionnaire

After a head injury or accident some people experience problems which can cause worry or nuisance. We would like to know if you have difficulties with any of the activities listed below. We would like you to compare yourself now with before the accident/injury.

For each one please circle the number closest to your answer

0 = no change
1 = no change, but more difficult
2 = a mild change
3 = a moderate change
4 = a very marked change

Compared with before the accident / injury,
a) has there been a change in your…?

<table>
<thead>
<tr>
<th>Activity</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Ability to participate in conversation with one person</td>
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</tr>
<tr>
<td>Ability to participate in conversation with 2 or more people</td>
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<tr>
<td>Performance of routine domestic activities</td>
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<tr>
<td>Ability to participate in previous social activities</td>
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<tr>
<td>Ability to enjoy previous leisure activities</td>
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<tr>
<td>Ability to maintain previous work/load standard</td>
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<tr>
<td>Finding work more tiring</td>
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<tr>
<td>Relationship with previous friends</td>
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<tr>
<td>Relationship with your partner</td>
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<tr>
<td>Ability to cope with family demands</td>
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b) are you experiencing any other difficulties?
Please specify and rate

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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Would you like a follow up appointment for further advice?

YES □
NO □
Appendix 3

**LiSat - 11**

Here are a number of statements concerning how satisfied you are with different aspects of your life. For each of these statements please mark a number from 1 to 6, where 1 means very dissatisfying and 6 very satisfying.

1 = very dissatisfying
2 = dissatisfying
3 = rather dissatisfying
4 = rather satisfying
5 = satisfying
6 = very satisfying

<table>
<thead>
<tr>
<th>Statement</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>My life as whole is</td>
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<td>My vocational situation is</td>
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<td>My financial situation is</td>
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<td>My leisure situation is</td>
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<tr>
<td>My contact with friends and acquaintances is</td>
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<td>My sexual life is</td>
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<td>My ability to manage my life is</td>
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<td>My family life is</td>
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<td>My partner relationship is</td>
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<td>My physical health is</td>
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<td>My psychological health is</td>
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## Appendix 4

**Impact of Event Scale**

Below is a list of comments made by people after stressful live events such as your recent accident. Please check each item, indicating how frequently these items were true for you during the past seven days. If they did not occur at all, please mark the “not at all” column.

<table>
<thead>
<tr>
<th>Comment</th>
<th>Not at all</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I thought about it when I didn’t mean to</td>
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<tr>
<td>2. I avoided letting myself get upset when I thought about it or was reminded of it</td>
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<tr>
<td>3. I tried to remove it from memory</td>
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<tr>
<td>4. I had trouble falling asleep or staying asleep because of pictures or thoughts about it that came into my mind</td>
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<tr>
<td>5. I had a wave of strong feelings about it</td>
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<tr>
<td>6. I had dreams about it</td>
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<tr>
<td>7. I stayed away from reminders of it</td>
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<tr>
<td>8. I felt as if it hadn’t happened or wasn’t real</td>
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<td>9. I tried not to talk about it</td>
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<td>10. Pictures about it popped into my mind</td>
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<td>11. Other things kept making me think about it</td>
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<tr>
<td>12. I was aware that I still had a lot of feelings about it but I didn’t deal with them</td>
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<td>13. I tried not to think about it</td>
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<td>14. Any reminder brought back feelings about it</td>
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<tr>
<td>15. My feelings about it were kind of numb</td>
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</tbody>
</table>

**SCORE:**
- Intrusion Items
- Avoidance Items