OLLI SAVOLA

BRAIN INJURY AND HAZARDOUS ALCOHOL DRINKING IN TRAUMA PATIENTS

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2004
Oulu, Finland

Abstract
Head injury is the leading cause of death and disability in trauma patients, and alcohol misuse is often associated with such injuries. Despite modern diagnostic facilities, the extent of traumatic brain injury (TBI) is difficult to assess and supplementary diagnostic tools are warranted. The contribution of alcohol misuse to traumas also needs to be elucidated, as the role of different patterns of alcohol drinking in particular has received less attention.

We investigated the clinical utility of a novel serum marker of brain damage, protein S100B, as a tool for assessing TBI in patients with trauma. We also investigated the patterns of alcohol drinking among trauma patients and the trauma mechanisms in relation to blood alcohol concentration (BAC), with special emphasis on head traumas. Finally, we studied the early identification of hazardous drinkers among trauma patients.

Serum protein S100B was found to be a feasible supplementary method for assessing TBI, as the latter was shown to elevate its levels significantly, the highest values being found in patients with severe injuries. S100B was also found to be elevated in patients with mild head injury, where it was associated with an increased risk of developing post-concussion symptoms (PCSs). Extracranial injuries also increased S100B values in patients with multitrauma. Accordingly, S100B was not specific to TBI. The more severe the extracranial injury, the higher the S100B value that was found.

Binge drinking was found to be the predominant pattern in trauma patients. Alcohol intoxication on admission and hazardous drinking patterns were more often present in patients with head injury than in those with other types of trauma. The risk of sustaining a head trauma significantly increased with increasing BAC. The results also demonstrated that BAC on admission is the best marker of alcohol misuse in trauma patients. The BAC test depicts hazardous alcohol drinking better than conventional biochemical markers of alcohol misuse such as gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), carbohydrate-deficient transferrin (CDT), or mean corpuscular volume (MCV) of erythrocytes.

The findings support the use of S100B as a supplementary method for assessing TBI and the use of BAC as a marker of alcohol misuse in trauma patients.

Keywords: alcohol misuse, brain injury, laboratory markers, patterns of alcohol drinking, post-concussion symptoms, serum protein S100B
To my family and friends
Acknowledgements

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Oulu, April 2004

Olli Savola
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
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<tr>
<td>BAC</td>
<td>blood alcohol concentration</td>
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<tr>
<td>CDT</td>
<td>carbohydrate-deficient transferrin</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DAI</td>
<td>diffuse axonal injury</td>
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<tr>
<td>EDH</td>
<td>epidural haematoma</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<tr>
<td>GGT</td>
<td>gamma-glytamyl transpeptidase</td>
</tr>
<tr>
<td>GOS</td>
<td>Glasgow Outcome Scale</td>
</tr>
<tr>
<td>LOC</td>
<td>loss of consciousness</td>
</tr>
<tr>
<td>MAST</td>
<td>Michigan Alcohol Screening Test</td>
</tr>
<tr>
<td>MCV</td>
<td>mean corpuscular volume (of erythrocytes)</td>
</tr>
<tr>
<td>MHI</td>
<td>mild head injury</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NSE</td>
<td>Neuron-specific enolase</td>
</tr>
<tr>
<td>PCSs</td>
<td>post-concussion symptoms</td>
</tr>
<tr>
<td>PTA</td>
<td>post-traumatic amnesia</td>
</tr>
<tr>
<td>RGA</td>
<td>retrograde amnesia</td>
</tr>
<tr>
<td>SAAST</td>
<td>Self-Administered Alcoholism Screening Test</td>
</tr>
<tr>
<td>SDH</td>
<td>subdural haematoma</td>
</tr>
<tr>
<td>SMAST</td>
<td>Short Michigan Alcohol Screening Test</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
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List of original publications

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


Reprints are included with the permission of the publishers: Blackwell Science Ltd (I), Lippincott Williams & Wilkins (II) and Oxford University Press (IV).
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References
1 Introduction

Head injury is a serious health burden, being a leading cause of death and disability among teenagers and young adults, and resulting in enormous financial costs for society (Alexander 1995, Thorhill et al. 2000, Thompson et al. 2001). Alcohol is a major cause of traumas of this kind, and alcohol misuse and its consequences are currently one of the major health problems world-wide (Lieber 1995, Hadfield et al. 2001).

Despite modern diagnostic and monitoring methods, it remains difficult to assess the extent of primary brain damage after head injury and the development of secondary damage (Raabe et al. 1999b). Most of the diagnostic process nowadays is based on neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), although in practice only CT is often available in the acute stage. CT is sensitive for detecting fresh blood inside the skull, but has a low sensitivity for diffuse axonal injury (DAI) (Bešenski 2002). There is a major need for supplementary diagnostic tools in cases of acute head injury, e.g. a simple biochemical marker of brain damage.

The protein S100B is the most promising candidate for a biochemical marker of brain damage to date (Ingebrigtsen & Romner 2002), having been found to correlate with the extent of brain damage and the outcome after severe head injury (Raabe 1999b). It has also been shown to be elevated in approximately 20–38% of patients with mild head injury (MHI) (Ingebrigtsen et al. 1995, Ingebrigtsen et al. 2000b). Its clinical utility among such patients is unresolved, however. S100B is also expressed in non-nervous tissues, and extracranial injuries may confound its use as a specific marker of brain damage (Haimoto et al. 1987, Anderson et al. 2001). The contribution of extracranial injuries to the elevation in S100B levels observed after head injury also remains to be elucidated.

Most patients with MHI recover well (Binder 1997), although a small but significant proportion develop persistent post-concussion symptoms (PCSs) that may prevent optimal recovery and impair return to work and psychosocial functioning (Alexander 1995, Bernstein 1999). Routine follow-up of all patients with MHI is not warranted (Wade et al. 1997), but it might be beneficial and cost-saving to follow up subjects who are likely to develop PCSs. After identification of these patients, appropriate rehabilitation services could prevent the condition from becoming chronic and avoid financial costs and social and human suffering. No methods have been proposed to date for the early detection of patients at risk of developing PCSs.
Alcohol and injuries are closely linked (Rivara et al. 1993a, Corrigan 1995, Porter 2000). Approximately 50% of trauma patients have alcohol in their blood on admission, and even higher proportions have been reported in series consisting specifically of patients with head injuries (Brismar et al. 1983, Rivara et al. 1993a, Dikmen et al. 1995). Chronic alcohol misuse is also common in trauma patients, approximately 45% of whom have been reported to be misusers (Nilssen et al. 1994). The prevalence of chronic alcohol misuse among head injury patients has varied from 16% to 66% (Corrigan 1995).

Little is known of the different patterns of alcohol drinking in patients with trauma, and more attention should be paid to binge drinking in particular, because the dangers of alcohol are not restricted to regular drinking. The social, health and economic costs of acute alcohol-related problems may even exceed those due to chronic drinking (Chikritzhs et al. 2001). It would be important to know the prevalence of different patterns of alcohol drinking and their contribution to traumas, and whether a certain drinking pattern is associated specifically with head injuries.

There have been several reports of a positive effect of brief alcohol intervention as means of reducing alcohol intake and injury recurrence (Walsh et al. 1991, Fleming et al. 1997, Gentilello et al. 1999), but there continues to be a lack of attention paid to alcohol misuse in accident and emergency departments, so that patients with alcohol misuse tend to escape specific treatment. This is likely to be due to the lack of practical tools for identifying the optimal target group for alcohol interventions. Laboratory tests such as gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), carbohydrate-deficient transferrin (CDT) and mean corpuscular volume (MCV) of erythrocytes have been suggested to help the physician to detect alcohol misusers on admission (Mihas & Tavassoli 1992), but their clinical utility remains to be elucidated. In particular, no attempt has been made to correlate laboratory markers of alcohol consumption with patterns of alcohol consumption in trauma patients.

The present study was aimed at assessing the clinical utility of S100B as a specific marker of brain damage and as a factor that predicts poor recovery after MHI, and also at elucidating the role of different drinking patterns in trauma patients and how alcohol drinking increases the risk of head trauma. Methods were sought for identifying hazardous drinkers among trauma patients, in the hope that improved identification and assessment of brain damage and alcohol misuse may lead to a better understanding of the risks of injury and of a poor outcome after injury and may help us to develop treatments and preventive medical and social policies.
2 Review of the literature

2.1 Epidemiology of head injury

The annual incidence of head injury is estimated to be between 150–300 per 100 000 of population (Annegers et al. 1980, Jennett & MacMillan 1981, Klauber et al. 1981, Kraus et al. 1984, Tiret et al. 1990, Durkin et al. 1998, Marshall 2000). Men have approximately twice as high a rate as women (Kraus et al. 1984, Lundar & Nestvold 1985), and the highest age-specific incidence is found among young adults (Kraus 1993).

These incidence figures are based on studies of hospital discharges after diagnoses of brain injury or at least skull fracture (Klauber et al. 1981, Kraus 1993), and are likely to be underestimated. Thornhill et al. (2000) reported that 20% of all head injury patients admitted to hospital were not recorded in the health service statistics, and found the total incidence of such admissions to be 326 per 100 000 of population. McGuire et al. (1995) reported an incidence of 607 per 100 000 of population when all medically treated head injury patients were taken into account, but according to an extensive survey by Fife (1987), approximately 10% of patients who reported having had a head injury were never treated for it medically. Finally, Segalowitz & Lawson (1995) found that approximately one third of high school and university students had a history of at least one head injury, and only one fifth of them had been admitted to hospital.

MHI explains approximately 80–90% of all head injuries, while moderate and severe head injuries explain the rest (McGuire et al. 1995, Thornhill et al. 2000). The annual incidence of fatal head injuries is consistently found to be between 17–30 per 100 000 of population (Kraus et al. 1984, Sosin et al. 1989, Tiret et al. 1990). Almost 60% of all fatal trauma cases admitted to hospital are due to head injury (Gennarelli et al. 1989), and traffic accidents account for approximately 60% of all severe head injuries (Sosin et al. 1989, Tiret et al. 1990), while falls and assaults are the most common causes of milder head injuries (Thornhill et al. 2000).

Disability due to head injury is a poorly studied entity. Kraus (1993) estimated the rate of disability, i.e. severe or moderate disability according to the GOS (Jennet & Bond 1975), to be 33 to 45 per 100 000 of population/year, but a recent study from Glasgow
area has reported the annual incidence to be much higher, 154 per 100 000 of population (Thornhill et al. 2000).

The financial costs associated with head injury are enormous. Max et al. (1991) assessed the total costs per year in the US as exceeding $38 billion. Thompson and her co-workers (2001) suggested that the estimate presented by Max et al. (1991) is conservative, capturing only part of the total costs, and estimated that the figure may well exceed $62 billion. In fact, the true financial costs due to head injuries are probably incalculable, as family members may develop physical and mental symptoms, for example, and the overall financial impact is unknown (Thompson et al. 2001).

### 2.2 Classification of head injuries

Head injuries are traditionally classified as mild, moderate or severe (Vos et al. 2002), the purpose being to evaluate the risk of complications and assess the probable outcome (Ingebrigtsen et al. 2000a, Thornhill et al. 2000). In practice, the classification is often performed by assessing the level of impaired consciousness on the Glasgow coma scale (GCS), which is based on eye opening and motor and verbal responses, as presented in Table 1 (Teasdale & Jennett 1974). MHI is defined as a state with scores of 13 to 15, whereas moderate and severe head injuries are defined by scores of 9 to 12 and 3 to 8, respectively. In addition, the presence and duration of post-traumatic amnesia (PTA) are often used as tools for classifying head injuries (Russell & Smith 1961, Kurup et al. 2000), and a head CT scan-based classification has also been developed especially for moderate-to-severe head injuries (Marshall et al. 1991).

*Table 1. The Glasgow Coma Scale.*

<table>
<thead>
<tr>
<th>Aspect of behaviour</th>
<th>Response score</th>
</tr>
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<tbody>
<tr>
<td>Eye-opening (E):</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td>To voice</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Best motor response (M):</td>
<td></td>
</tr>
<tr>
<td>Obey commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws (flexion)</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion (posturing)</td>
<td>3</td>
</tr>
<tr>
<td>Extending (posturing)</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Verbal response (V):</td>
<td></td>
</tr>
<tr>
<td>Oriented conversation</td>
<td>5</td>
</tr>
<tr>
<td>Confused, disoriented</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

Glasgow Coma Scale score = E + M + V
The International Classification of Diseases (ICD) (1992) can also be used for classifying head injuries. This includes diagnoses indicating the clinical features of head and brain injury, but does not classify them in terms of severity. Its clinical utility is thus limited when assessing the possible outcome, for example. The ICD classification has proved to be practicable for epidemiological studies, however (Sosin et al. 1989). Head injuries can also be classified in other ways, into impact versus deceleration/acceleration injuries (Elson & Ward 1994, Aikuisiän aivovammojen käypä hoito 2003), or penetrating versus closed head injury (Bayston et al. 2000).

2.2.1 Mild head injury (MHI)

MHIs constitute a significant medical problem for several reasons. Firstly, approximately 80 to 90% of all head injuries are mild (McGuire et al. 1995, Thornhill et al. 2000). Secondly, 0.01 to 3% of patients initially assessed as having MHI will develop life-threatening complications requiring immediate neurosurgical intervention (Dacey et al. 1986, Stein & Spettell 1995). Thirdly, great attention and financial resources have to be spent on the evaluation of these patients because of this minimal risk of possible intracranial complications (Stiell et al. 2001a). Fourthly, a small proportion of MHI patients do not achieve a good recovery (Thornhill et al. 2000) and may be left neuropsychologically impaired (Binder et al. 1997) or develop long-lasting PCSs (Alexander 1995).

2.2.1.1 MHI without brain injury

Although there certainly exist head injuries without brain injury, the terms MHI and mild TBI are often used synonymously (de Kruijk et al. 2001b). This confusion is due to the fact that there are no specific measures available for detecting the presence of negligible brain damage or for separating head injury patients with mild TBI from those without (Bernstein 1999). In two current articles, head injury patients without TBI are characterised as having a GCS score of 15 and no loss of consciousness (LOC), PTA, focal neurological deficits, or physical symptoms such as headache, dizziness or vomiting (de Kruijk et al. 2001b, Vos et al. 2002).

2.2.1.2 MHI with mild brain injury

MHIs with mild brain injury applies to a subset of patients with MHI in whom brain damage is evident but mild. These patients have a GCS score of 13 to 15 on admission to hospital and may also have one or more symptoms and/or signs of TBI. The presence of PTA (duration < 24 hours) and unconsciousness (duration < 30 minutes) are such signs (Rimel et al. 1981, Alexander 1995, Bernstein 1999, Aikuisiän aivovammojen käypä hoito
2003), and the most frequent symptoms are headache, nausea, vomiting and dizziness (de Kruijk et al. 2001a, de Kruijk et al. 2001b). Patients having a focal neurological deficit or structural damage visible in a head CT scan or MRI are assessed as having more severe TBI (Williams et al. 1990, Alexander 1995, Aikuisiän aivovammojen käypä hoito 2003).

The terms commotio cerebri and cerebral concussion, which are often used in clinical work to denote mild TBI, were initially defined as referring to a state of functional disturbance of the brain due to trauma without any tissue damage (Ward 1966). Controversy exists, however, over whether diffuse brain dysfunction can occur without structural damage, because it has become clear that brain damage is often present in patients with cerebral concussion (Ommaya & Gennarelli 1974, Vos et al. 2002). It is currently suggested, therefore, that the severity of TBI forms a continuum from negligible to clinically significant, and there is simply less brain damage in mild TBI than in more severe cases (Alexander 1995, Ingebrigtsen 1998).

Mild TBIs can be further subclassified into several grades (Dacey et al. 1993, Ingebrigtsen et al. 2000, Kurup et al. 2000, Vos et al. 2002) in order to assess the risk of intracranial complications and to predict the outcome (Ingebrigtsen et al. 2000, Vos et al. 2002). These grades are also frequently used in sports medicine as a guide to when it is appropriate to return to action (Kurup et al. 2000).

### 2.2.2 Head injury with moderate brain injury

Russell & Smith (1961) proposed a four-grade scale of TBI severity based on the duration of PTA, moderate TBI being defined as a state with PTA between 1 and 24 hours. After the introduction of the GCS, moderate TBI has been defined as a GCS score of 9 to 12 on admission (Teasdale & Jennett 1974, Rimel et al. 1982). A current Finnish guideline defines moderate brain injury as a GCS score of 9 to 12 and/or PTA between 24 hours and seven days (Aikuisiän aivovammojen käypä hoito 2003).

Moderate TBI patients may have focal deficits in clinical examination (Aikuisiän aivovammojen käypä hoito 2003), one third actually have structural lesions in the brain visible on a head CT scan, and MRI may reveal some additional lesions (Rimel et al. 1982, Kelly et al. 1988, Stein & Spettell 1995, Ingebrigtsen et al. 2000a). Moderate TBI patients without a lesion in the brain are considered to have diffuse axonal injury (DAI) (Rimel et al. 1982). Approximately one tenth of patients with moderate TBI need a neurosurgical operation (Rimel et al. 1982).

### 2.2.3 Head injury with severe brain injury

Patients are deemed to have severe TBI if they have an admission GCS score of 8 or less (Teasdale & Jennett 1974), although some who “talk and deteriorate” may have a GCS score of over 8 initially or at some moment (Lobato et al. 1991). Severe TBI can also be characterised by a duration of PTA of at least 7 days (Aikuisiän aivovammojen käypä hoito 2003). Some investigators recognise a separate group of critical brain injuries (Vos...
et al. 2002) consisting of patients who have a GCS score of 3 to 4 and evident brain stem damage, characterised by diminished or no pupillary reactions and decerebrate motor posturing, or an absence of pupillary and motor reactions (Vos et al. 2002).

Approximately 5 to 30% of patients with severe TBI have a normal head CT scan initially (Lobato et al. 1986, Eisenberg et al. 1990, Stein & Spettell 1995) with lesions frequently seen later, or else brain atrophy may develop during the subsequent months, indicating that the initial trauma type had been DAI (Lobato et al. 1986).

2.3 Clinical features of brain injury

2.3.1 Diffuse axonal injury (DAI)

Brain injuries are commonly divided into focal and diffuse injuries (Gennarelli 1993). Diffuse brain injury is a widespread or global disruption of brain tissue and often involves only microscopically visible lesions (Adams et al. 1989). Typical microscopic findings are small focal brain lesions, clusters of microglia in the white matter, axonal bulbs, and axonal swelling and degeneration (Adams et al. 1989). This is called diffuse axonal injury (DAI) (Povlishock et al. 1983, Maxwell et al. 1997).

Strich originally reported two autopsy studies of closed head injury patients, all of whom had died in a comatose condition (Strich 1956, Strich 1961). Her postmortem findings showed that there were only a few lesions visible to the naked eye, mostly in the corpus callosum or in one or both of the superior cerebellar peduncles. The cerebral cortex appeared normal. In contrast, Strich (1961) found a widespread diffuse degeneration of the white matter in all cases, and concluded that this was due to mechanical stresses and strains which lead the nerve-fibres to tear and degenerate.

More recently, DAI has been found to be a common type of brain damage both in experimental studies of primates (Jane et al. 1985, Xiao-Sheng et al. 2000) and in studies dealing with humans (Adams et al. 1982). DAI is often present in cases of severe TBI, Adams et al. (1989) reporting that 122 out of 434 non-missile head injury patients autopsied had some evidence of DAI, although in 24 cases the DAI could be found only after microscopic examination. Oppenheimer (1968) also found DAI in five autopsied mild TBI patients, although the majority of the evidence for an association between mild TBI and DAI has come from experimental studies (Gennarelli et al. 1982, Jane et al. 1985). Povlishock et al. (1983) demonstrated that mild TBI does not always disrupt the axons mechanically but can lead to axonal swelling, it is currently thought that this non-disruptive axonal injury may result in secondary DAI some hours after injury, and that such a situation may be more common than was previously appreciated (Maxwell et al. 1997).

Although small lesions in the white matter, corpus callosum, or brain stem can be detected in the head CT scan in some cases of more severe DAI (Zimmerman et al. 1978, Levi et al. 1990), CT is in general insensible for detecting DAI, whereas MRI may be more sensitive (Bagley 1999). Thus Mittl et al. (1994) found some evidence of DAI in 30% of MHI patients with normal CT scans, and it is likely that there are a lot of head
injury patients with DAI who do not have any detectable CT lesions (Adams et al. 1989, Bagley 1999), although neuroimaging may reveal diffuse brain atrophy during follow-up (Ito et al. 1997).

### 2.3.2 Cerebral contusion

Cerebral contusions are bruises and lacerations of the brain tissue which may either be limited to the cortex or extend into the white matter and typically include haemorrhage, infarction, necrosis and oedema (Adams 1975, Levin et al. 1988). Cerebral contusions have traditionally been described as a result of coup (at the site of impact) or contracoup injuries (opposite the site of impact, where the brain strikes the skull) (Jallo & Narayan 2000). Cerebral contusions are frequent in patients with TBI, and are mostly found in the temporal and frontal regions of the brain (Mattson & Levin 1990, Gentry et al. 1988a, Stiell et al. 2001b), the areas especially prone to injury being the anterior and inferior portions of the temporal and frontal lobes, where the brain contacts the rough surfaces of the sphenoid wings, the petrous ridges, the cribriform plate and the planum sphenoidale (Bagley 1999), although cerebral contusions regularly occur in other regions of the brain as well (Hesselink et al. 1988). Cerebral contusions may swell and cause increased intracranial pressure (Bullock et al. 1991).

Contusions are characterised in head CT scans by areas of hypodensity, hyperdensity and oedema (Bešenski 2002). If there are haemorrhagic components, CT may be slightly more sensitive for detecting cerebral contusions than MRI (Hesselink et al. 1988), whereas MRI is more sensitive in depicting non-haemorrhagic contusions (Gentry et al. 1988b, Hadley et al. 1988), contusions in the brain stem (Gentry et al. 1988b) and contusions at the subacute and chronic stages (Groswasser et al. 1987, Kelly et al. 1988).

The prognosis for patients with cerebral contusions varies according to the localization and size of the lesions. MHI patients with a small frontal lobe contusion may have only minor neuropsychological disturbances (Mattson & Levin 1990), whereas mortality among patients with multiple or extensive contusions may exceed 40%, which is the overall mortality for severe TBI patients (Murray et al. 1999).

### 2.3.3 Intracerebral haematoma (ICH)

Traumatic ICH, bleeding in the brain parenchyma (Jallo & Narayan 2000), may develop primarily as a result of trauma or secondarily within the subsequent days after injury (Clifton et al. 1980, Soloniuk et al. 1986, Mertol et al. 1991). Cerebral contusions and traumatic intracranial haematomas represent a continuum, so that if there is a clear blood clot present this is called an intracranial haematoma (Jallo & Narayan 2000). There are also non-traumatic ICHs, which may be spontaneous or due to bleeding from vascular or arterial abnormalities (Caplan 1988).

As with contusions, most traumatic ICHs are located in the temporal and frontal lobes (Adams 1975). Traumatic ICH is seldom found alone, but is often associated with contu-
sions, other haematomas and oedema (Caroli et al. 2001). Siddique et al. (2002) found that only 90 out of 5686 head injury patients had isolated ICH. A head CT scan is sensitive for detecting intracranial haematomas, and it also works as a tool for assessing the need for surgical treatment (Bullock et al. 1989). An unfavourable outcome after ICH is associated with the presence of other brain lesions, a prolonged increase in intracerebral pressure and more advanced age (Caroli 2001, Siddique et al. 2002), and mortality following traumatic ICH still remains high, varying from 11 to 50% (Soloniuk et al. 1986, Mertol et al. 1991, Caroli et al. 2001).

2.3.4 Epidural haematoma (EDH)

The most common locations for EDH, bleeding between the skullbone and dura (Adams 1975), are the temporal and frontal areas of the skull, often with the middle meningeal artery as the source (Reale et al. 1984). The typical patient with EDH is a young adult male (Reale et al. 1984, Miller et al. 1990). Skull fractures significantly increase the risk of EDH (Miller et al. 1990), which usually develops rapidly after trauma. Some patients may also have delayed EDHs, however, and most of the recurrent haematomas following craniotomy for traumatic intracranial mass are EDHs (Bullock et al. 1990).

The classic symptoms of EDH include dilatation of the pupil on the haematoma side and hemiparesis of the opposite side. EDH is currently diagnosed from a head CT scan, by the typical appearance of a high-density, biconvex, lentiform, extra-axial mass, often bounded by suture lines (Bagley 1999). It may have underlying oedema, contusions, and other haematomas associated with it. Large EDHs may also have a mass effect, characterised on a CT scan by sulcal effacement, midline shift and compression of the ventricular system, and in the most severe cases herniation occurs due to increasing intracerebral pressure (Adams 1975, Stieg & Kase 1998).

Since EDH may develop even after rather low-energy trauma (Stein & Spettell 1995), considerable attention and financial resources have been devoted to the identification of cases that are likely to develop a haematoma after MHI. Ninety-eight per cent of head CT scans of MHI patients are negative for EDH (Stiell et al. 2001a). The primary therapy for acute EDH is urgent surgery (Reale et al. 1984, Miller et al. 1990), and the outcome is related to the severity of concomitant brain injuries, neurological status at the time of surgery, age and the interval between injury and surgery (Reale et al. 1984, Servadei 1997). Mortality due to EDH varies between 16 and 40% (Reale et al. 1984).

2.3.5 Subdural haematoma (SDH)

SDH, a collection of blood under the dura, is usually attributed to the rupture of small bridging veins, ruptured vessels at the site of contusions, or tearing of small branches of the cerebral arteries, particularly the middle cerebral artery (Adams 1975). SDHs are divided into acute, subacute and chronic types.
Acute SDH is present in approximately one fifth of patients with severe TBI, and almost 60% of all primarily evacuated traumatic mass lesions among these patients are SDHs (Marshall et al. 1991a). The majority of patients with acute SDHs have concomitant focal lesions such as contusions and ICHs or DAI (Tandon 2001).

Subacute subdural haematoma is found between a few days and 2 weeks after injury, whereas chronic SDH may be found weeks or even months afterwards (Adams 1975). Fogelholm & Waltimo (1975) reported the incidence of chronic SDH to be 1.72 per 100,000 of population, increasing with age to 7.35 per 100,000 of population at 70–79 years. The most frequent additional risk factors for chronic SDH are coagulopathy and alcoholism (Chen & Levy 2000).

The diagnostic examination of choice for SDHs is a head CT scan. An acute SDH is typically visible as a high-density, crescentic collection with concave inner borders which is not confined by the cranial sutures (Bagley 1999). Acute hyperdense blood becomes isodense within 4 to 7 days and hypodense within 1 to 2 weeks, after which the density increases again within 3 to 12 weeks because of fresh haemorrhage, until a reduction in X-ray attenuation is brought about during the subsequent healing process (Stoodley & Weir 2000). Subacute SDHs may occasionally be of mixed density. Isodense SDHs may be difficult to diagnose on an unenhanced CT, and such haematomas are best detected with MRI (Stieg & Kase 1998).

Surgery is the primary treatment for SDHs, being indicated when the thickness of the blood clot exceeds 10 mm. Chronic SDHs can often be drained through a burrhole, whereas craniotomy is favoured in acute cases (Tandon 2001). Mortality from acute SDH is high. In a series of 1150 patients with severe head injuries, 101 had acute SDH, and mortality among these exceeded 66% (Wilberger et al. 1991). The extent of the underlying brain injury is nevertheless thought to be more important than the SDH clot itself in dictating the outcome (Wilberger et al. 1991).

### 2.3.6 Subarachnoid haemorrhage (SAH)

SAH can occur in various clinical contexts, the most common of which are head trauma and spontaneous rupture of an intracranial aneurysm (Stieg & Kase 1998). Traumatic SAH results from the disruption of small subarachnoidal vessels or direct extension into the subarachnoidal space by a contusion or haematoma.

Traumatic SAH is usually diagnosed by means of a head CT scan, and it is often present in patients with severe TBI, the proportion varying from 33% to 39% (Eisenberg et al. 1990, Kakarieka et al. 1995, Servadei et al. 2002). The presence of traumatic SAH is often associated with a poor outcome. Eisenberg et al. (1990) reported that head injury patients with SAH had a two-fold increase in the risk of death relative to those without SAH, and other investigators have arrived at similar findings, suggesting that the poor outcome may be attributed to vasospasm due to the haemorrhage (Kararieka et al. 1995). Servadei et al. (2002) have recently reported a similar incidence of SAH among patients with head injury, a similar risk of death and a generally poor outcome, but showed in addition that death among patients with traumatic SAH was related to the severity of the initial mechanical brain damage rather than to the effects of delayed vasospasm and sub-
sequent secondary brain damage. Patients with traumatic SAHs more often had ICHs and multiple parenchymal lesions than did those without SAH (Servadei et al. 2002).

2.3.7 Secondary brain injury

Traumatic brain injuries can be divided into primary and secondary types. Secondary brain injury is important because much can be done to minimise it, whereas primary injury is unavoidable (Bullock et al. 1996, Maas et al. 1997).

Secondary brain injury may occur at any time after the initial impact, and can be either systemic or intracranial (Maas et al. 1997). The causes of intracranial secondary brain injury are infection, cerebral ischaemia, and seizures (Maas et al. 1997, Lindsay & Bone 2001), while the systemic insults are hypoxaemia, hypotension, hypercapnia, hypocapnia, hyperthermia, hyperglycaemia, hypoglycaemia, and hyponatraemia (Maas et al. 1997).

Cerebral ischaemia, which is the leading cause of secondary brain damage after TBI (Graham et al. 1989, Maas et al. 1997), may be due to systemic hypoxia or hypotension or impaired cerebral perfusion due to increased intracranial pressure (Maas et al. 1997). Mass lesions, brain swelling and oedema are all able to raise intracranial pressure. Increased intracranial pressure may not only lead to cerebral ischaemia but also to tonsillar or tentorial herniation (Lindsay & Bone 2001). Brain swelling is thought to be due to increased intravascular blood within the brain, whereas brain oedema refers to a specific situation in which there is an increase in extravascular brain water (Gennarelli 1993). Mass lesions such as EDHs, SDHs and ICHs may develop secondarily within minutes to hours after trauma, but also within the next few days (Bullock et al. 1990, Mertol et al. 1991). Infections may develop after a dural tear, which provides a route for infection into the brain (Bayston et al. 2000). Meningitis and cerebral abscess are the clinical features of secondary infection.

2.3.8 Skull and facial bone fracture

Brain injuries are often associated with skull fractures, either linear or depressed, or fractures of the facial bones. The incidence of skull fractures in MHI patients varies from 3% to 11% (Dacey et al. 1986, Stiell et al. 2001b), while Rimel et al. (1982) reported that 24% of their patients with moderate TBI had a skull fracture. Correspondingly, Shapiro et al. (2001), reviewing all trauma admissions during an 11-year period at a level I trauma centre, found that 11% of the patients had a facial bone fracture.

Skull or facial bone fracture does not directly mean brain injury. Williams et al. (1990) even suggested that TBI patients with a depressed skull fracture without an underlying lesion can be classified as mild. Patients with a skull fracture have an increased risk of intracranial haematoma, however (Mendelow et al. 1983), and it has been estimated that approximately one out of every four head injury patients with a skull fracture has an
intracranial haematoma and half of the patients who develop a haematoma have a fracture (Ingebrigtsen et al. 2000a).

Basal skull fractures can be suspected if the patient has nasal cerebrospinal rhinorrhoea, bilateral periorbital haematoma, subconjunctival haemorrhage, bleeding through a torn tympanic membrane, or bruising over the mastoid (Lindsay & Bone 2001). Most skull and facial bone fractures are diagnosed by skull radiography or a head CT scan, is the latter currently being a modality of choice if a skull fracture is suspected (Hofman et al. 2000, Salvolini 2002, Vos et al. 2002).

2.4 Diagnosing brain injury in patients with head injury

2.4.1 Clinical examination

A clinical neurological examination forms the basis for assessing head injury patients on admission, as this can reveal brain injury and help the physician to estimate the outcome (Maas et al. 1997, Vos et al. 2002).

Although typical symptoms such as headache, neck pain, nausea, dizziness and vomiting symptoms are frequent among TBI patients shortly after trauma, they are not specific to brain injury, as they may be due to a mixture of brain injury, peripheral vestibular injury and injury to the soft and bony tissues of the head or neck (de Kruijk et al. 2001b).

The relationship between amnesia and unconsciousness in patients with TBI is depicted in Figure 1. The assessment and follow-up of impaired consciousness and amnesia plays an important role in such cases as these features are known to correlate with the severity of TBI (Russel & Smith 1961, Murray et al. 1999, van der Naalt et al. 1999). The GCS (Table 1) is currently the most widely used tool among clinicians and investigators for assessing coma and impaired consciousness (Teasdale & Jennett 1974), but as it was initially developed for patients with severe head injury, there is a wide heterogeneity in the severity of TBI among patients with an admission GCS score of 13 to 15 (Williams et al. 1990, Ingebrigtsen et al. 2000a). It has been suggested that the length of PTA may correlate better with the outcome among moderate-to-mild TBI patients (van der Naalt et al. 1999), and there are few validated questionnaires available to assess the length of PTA (Fortuny et al. 1980, Shores et al. 1986, King et al. 1997). In any case, both GCS and PTA have their limitations, since they are vulnerable to confounding factors such as alcohol intoxication (Galbraith et al. 1976, Wrightson & Gronwall 1981, Jagger et al. 1984). Absence of the pupillary light reflex and/or oculocephalic reflex was also found to be associated with a poor outcome after severe head trauma (Attia et al. 1998). Expanding intracranial lesions such as EDH may be revealed by the absence of a pupillary light reflex (Lindsay & Bone 2001). Basal skull fractures can also be identified by clinical examination if the patient has nasal cerebrospinal fluid rhinorrhoea, bilateral periorbital haematoma, subconjunctival haemorrhage, bleeding through a torn tympanic membrane, or bruising over the mastoid.
2.4.2 Skull radiography

Skull radiography can detect linear skull fractures, depressed fractures, fluid in the paranasal sinuses and air inside the skull. The skull fractures diagnosed in this way carry an increased risk of intracranial haematoma (Mendelow et al. 1983), but skull radiography does not detect intracranial haematoma as such, nor does it reveal brain damage, and it has been concluded in a recent meta-analysis that skull radiography is of little value for the initial assessment of patients with head injury (Hoffman et al. 2000).

2.4.3 Computed tomography (CT)

A head CT scan is considered the gold standard for the detection of intracranial abnormalities in head injury patients (Vos et al. 2002), as it enables extra-axial haematomas such as EDHs, SDHs, and SAHs, intra-axial lesions such as cerebral contusions and some DAIIs, and secondary lesions such as brain oedema and herniation to be detected (Bešenski 2002).

A head CT scan has several important purposes when examining patients with head injury. Firstly, it is an objective method for documenting scalp, bone and brain damage (Bagley 1999), secondly, initial management decisions can be based on the CT findings (Stieg & Kase 1998), thirdly, the presence of CT abnormalities and their type can assist in assessing the severity of brain injury (Marshall et al. 1991b), and fourthly, acute head CT
findings provide a baseline from which to monitor changes in TBI over time (Bešenski 2002).

If all head trauma patients with an initial GCS score of 13 to 15 are examined, the presence of traumatic intracranial findings in the head CT scan varies from 2 to 11% (Moran et al. 1994, Nagy et al. 1999, Haydel et al. 2000, Livingston et al. 2000, Stiell et al. 2001b), but if we take those with an admission GCS score of 9 to 12, the presence of intracranial abnormality exceeds 30% (Rimel et al. 1982), and for those with a GCS score of 8 or less it may even exceed 94% (Eisenberg et al. 1990).

A normal head CT scan on admission has been found in two large multicentre studies to be good for excluding the need for neurosurgical intervention (Livingston et al. 2000, Shackford et al. 1992). The series considered by Shackford et al. (1992) included 2766 head injury patients with an admission GCS at or above 13, among whom none of those who had a normal neurological examination and normal head CT scan needed neurosurgical intervention (negative predictive value 100%). Livingston et al. (2000) studied 2152 head injury patients with an admission GCS score of 14 to 15 and reported that a normal initial head CT scan excluded the need for a neurosurgical operation with an accuracy of 99.7%. They therefore concluded that MHI patients with a normal initial head CT scan can safely be discharged from the emergency department without observation (Livingston et al. 2000).

On the other hand, the use of a head CT scan is not efficient, since almost 80% of the scans ordered on account of MHI are negative (Stiell et al. 2001a). It is regarded as mandatory for patients with moderate-to-severe head injury (Ingebrigtsen et al. 2000a), but the indications for imaging in the case of patients who are initially assessed as having MHI are controversial.

Two large prospective studies have validated a set of clinical criteria for identifying MHI patients who need to undergo head CT scanning on admission (Stiell et al. 2001b, Haydel et al. 2000). Haydel et al. (2000) studied 1411 consecutive MHI patients with an admission GCS score of 15 and found that if all those with risk factors (headache, vomiting, seizure, PTA, drug or alcohol intoxication, or age over 60) were imaged, all the traumatic intracranial abnormalities could be identified (sensitivity 100%, 95% CI 95 to 100%). On their criteria, 78% of MHI patients should undergo a head CT scan (Haydel et al. 2000).

Stiell et al. (2001b) reported two sets of clinical criteria for ordering head CT scans for MHI patients, based on a series of 3121 consecutive patients with an admission GCS score of 13 to 15. The first set of criteria included five risk factors for predicting the need for neurosurgical intervention (GCS score <15 at 2 h after injury, suspected open or depressed skull fracture, any sign of basal skull fracture, two or more episodes of vomiting, and age at or over 65). These enabled all such complications to be identified (sensitivity 100%, 95% CI 92 to 100%), and implied that only 32% of MHI patients would need to undergo a head CT scan. The second set of criteria, which included two risk factors (amnesia before impact > 30 minutes and a dangerous mechanism of injury, such as a pedestrian struck by a motor vehicle, an occupant ejected from a motor vehicle, a fall from >five stairs), predicted 98% (95% CI 96 to 99%) of all intracranial lesions depicted by a CT scan. The use of these risk factors would lead to the ordering of a CT in 54% of cases (Stiell et al. 2001b). It may be concluded that not all MHI patients need to undergo
head CT scanning and that imaging resources can be directed to those with significant risk factors, leading to a reduction in total costs (Stiell et al. 2001b, Haydel et al. 2000).

A head CT scan can also be used as a tool for predicting the outcome after head injury. Marshall et al. (1999b) reported a scale based on CT findings that, together with age and the best motor GCS score, predicted mortality with a sensitivity of 59% and a specificity of 87%. The CT is negative in some patients with severe head injury, however, the proportion being 6% according to Eisenberg et al. (1990), although Lobato et al. (1986) had reported earlier that approximately one half of such patients develop lesions during follow-up and that brain atrophy, associated with a poor outcome, often developed within the next few months (Lobato et al. 1986). The findings of Lobato et al. (1986) and Eisenberg et al. (1990) may be explained by the fact that head CT scanning is insensitive for detecting DAI, and a more sensitive imaging method, such as MRI, is warranted for such patients (Bešenski 2002).

2.4.4 Magnetic resonance imaging (MRI)

MRI is more sensitive than a head CT scan for all types of traumatic brain lesions except skull fractures and SAHs (Bešenski 2002), but it has some limitations. Firstly, the equipment is not as common as for CT, and secondly, the scanning time is longer and problems may be experienced in imaging an unstable trauma patient and organising monitoring outside the magnetic resonance field.

Most studies dealing with MRI and TBIs are small and concentrate on severe brain injuries using images obtained with only T1 and T2-weighted sequences. Acute MRI has been found to depict traumatic intracranial pathology in 25 to 57% of MHI patients and in 10% of those with a normal head CT scan (Ingebritsen et al. 1999, Voller et al. 1999, Hofman et al. 2001). In cases of more severe head injuries the presence of intracranial lesions in MRI has varied from 60 to 92%, but the image were often obtained at the chronic stage (Hadley et al. 1988, Levin et al. 1988, Fiser et al. 1998).

DAI is the most common type of brain injury seen in MRI of TBI patients, but head CT scans detected only 19% of non-haemorrhagic DAI (Gentry et al. 1988a). For the haemorrhagic subset of DAI, however, MRI was not superior to CT (Gentry et al. 1988b). Cortical contusions without haemorrhagic components are also better depicted by MRI, but if haemorrhage is present, CT may reveal all the contusions (Gentry et al. 1988b, Hesselink et al. 1988). If a contusion is located in the brain stem, MRI can detect it more sensitively (Gentry et al. 1988b). SDHs are also best detected with MRI (Gentry et al. 1988b, Kelly et al. 1988) and finally, the method is superior to a head CT scan for detecting all types of brain injury in the subacute and chronic stages (Groszweiser et al. 1987, Kelly et al. 1988).

Despite its better sensitivity, MRI does not alter the clinical management of imaged TBI patients in the acute stage (Fiser et al. 1998, Kelly et al. 1988). An acute MRI is recommended, however, if the CT is normal but the presence of TBI is suspected, and if a patient is to be imaged in the subacute and chronic stages (Aikuisiän aivovammojen käypä hoito 2003).
New magnetic resonance-based imaging methods have been developed within the last few years, e.g. diffusion-weighted imaging, perfusion-weighted imaging, proton magnetic resonance spectroscopy and fluid-attenuated inversion-recovery sequences (Ashikaga et al. 1997, Cecil et al. 1998, Ingebrigtsen 1999, Garnett et al. 2001, Sinson et al. 2001, Hammound & Wasserman 2002). Although these have not been validated in large groups of TBI patients, their use may be indicated in certain situations, at least in the chronic stages, because they may reveal some undetected small traumatic lesions (Aikuisiän aivo-vammojen käypä hoito 2003).

2.4.5 Single photon emission computed tomography (SPECT)

Unlike static neuroimaging techniques such as CT or MRI, SPECT produces functional rather than structural images of the brain. Using radionuclides, the cerebral blood flow is imaged and reconstructed as a visual data set which also indirectly describes the cerebral metabolism (Umile et al. 1998).

SPECT is generally more sensitive than CT and MRI for detecting abnormalities after TBI (Ichise et al. 1994, Ito et al. 1997, Hofman et al. 2001). Ichise et al. (1994) examined 29 patients with different degrees of head injury and found SPECT abnormalities in 66%, whereas MRI detected abnormalities in 45% and CT in 34%. SPECT detects more lesions in the acute stage than in the later stages (Abdel-Dayem et al. 1998), and the majority of SPECT abnormalities are found in the frontal and temporal regions of the brain (Abdel-Dayem et al. 1998). Some investigators have also found a correlation between neuropsychological tests and SPECT abnormalities (Ichise et al. 1994, Hoffman et al. 2001).

SPECT has many limitations. Firstly, there are limited resources for performing it routinely, and secondly, although it can detect many lesions which cannot be seen on CT or MRI, it remains to be elucidated whether these really represent traumatic lesions (Davalos & Bennett 2002). Depression may reduce perfusion and cause false positive lesions in SPECT, for example (Umile et al. 1998).

2.4.6 Electroencephalography (EEG)

The use of EEG for the acute assessment of TBI patients has become rare. EEG describes the functional response of the brain to insult, EEG abnormalities are often seen in head injury patients. Geets & Zegher (1985) studied 400 MHI patients and found abnormalities in 27%, whereas Voller et al. (1999) found MRI abnormalities in 25% of MHI patients but none showed EEG abnormalities. Thatcher et al. (1991) examined 162 closed head injury patients, most of whom had moderate-to-severe head injuries, and found that EEG was better at predicting the outcome than the GCS score or head CT scans (Thatcher et al. 1999). However, Attia & Cook (1998), in their review of all studies dealing with EEG and the outcome in patients with TBI, concluded that it is still unclear how much incremental information on clinical examination is added by EEG for predicting the outcome.
2.4.7 Biochemical markers

Despite significant progress in cerebral monitoring, it is still difficult to quantify the extent of primary and ongoing secondary brain injury after head trauma. Thus, there is a major need for a supplementary diagnostic test to follow CT and MRI, such as a biochemical marker of brain damage (Ingebritsien & Romner 2002).

Bakay & Ward (1983) defined an ideal biochemical serum marker of brain damage as one with high sensitivity to brain injury and high specificity for the brain tissue. It should also be released into the serum rapidly and only after irreversible brain damage, and it should have adequate clinical relevance.

Numerous potential biochemical markers of brain damage have been studied in patients with head injury, including creatine kinase BB (Nordby & Urdal 1985), myelin basic protein (Thomas et al. 1978), neuron specific enolase (Raabe et al. 1999a) and protein S100B (Townend et al. 2002). Glial fibrillary acidic protein has also been suggested as a potential marker of brain damage, but there are no studies dealing with it in the context of TBI (van Geel et al. 2002). The most promising markers are neuron specific enolase and protein S100B.

2.4.7.1 Neuron specific enolase (NSE)

NSE is a dimeric protein with a molecular mass of 78 kDa, the and isoforms of which are mainly expressed in neurons and peripheral neuroendocrine tissues (Cooper 1994). NSE is located in the cytoplasm of the neurons, and it is considered a possible marker of neuron damage. There are many limitations on its use, however. It is expressed in erythrocytes, for example, and is known to increase in serum due to haemolysis (Johnsson 1996). Serum values of more than 10 µg/L are considered pathological in studies dealing with head injuries (Woertgen et al. 1997).

de Kruijk et al. (2001c) measured NSE in 104 MHI patients, but failed to find any significant association between the marker and the length of PTA, reported LOC, or acute symptoms due to trauma. They did not report the number of patients above the cut-off level of 10 µg/L, but the 90th percentile of NSE was 14.4 in the patients with MHI and 13.3 in healthy controls (de Kruijk et al. 2001c).

Woertgen et al. (1997) reported that all their patients with severe head injury had elevated levels of NSE, but still had to admit that NSE neither predicted the outcome (Woertgen et al. 1997, Raabe et al. 1999a) nor correlated with head CT scan findings (Raabe 1998). Herrmann et al. (2001) found a trend between increased concentrations of NSE and neuropsychological deficits at two weeks after trauma, but not at six months, in patients with moderate-to-mild head injury, which led Ingebritsen & Romner (2002) to conclude that despite some promising findings, the sensitivity of NSE is inadequate and its clinical value as a marker of traumatic brain damage is questionable.
2.4.7.2 Protein S100B

Protein S100 is a dimeric protein with a molecular mass of 21 kDa (Zimmer et al. 1995). It was first described by Moore (1965) and its name is derived from its solubility in 100% saturated ammonium sulphate at neutral pH. Its two isoforms, ββ and αβ, referred to as S100B, have been studied as a biochemical marker of acute brain damage (Ingebrigtsen & Romner 2002).

S100B is expressed in most human tissues, but the highest concentrations are found in the astroglial cells of the central nervous system (Hidaka et al. 1983, Kato & Kimura 1985, Haimoto et al. 1987, Zimmer DB & van Eldik 1987). The second highest tissue concentration has been found in adipose tissue, where it is consistently approximately one third to one fourth of that found in brain tissue (Hidaka et al. 1982, Zimmer & van Eldik 1987). The median serum value of S100B in healthy people has been found to be 0.01 µg/L with an upper 97.5% cut-off level of 0.13 µg/L (Anderson et al. 2001). Excretion into urine is the major route for its elimination and its half-life in serum is thought to be short, between 25 and 113 minutes (Usui et al. 1989, Jönsson et al. 2000, Ytrebo et al. 2001).

Damage to glial cells and a reduced integrity of the blood brain barrier may lead to increased serum S100B concentrations (Nygaard et al. 1997), and consistent with this, elevated S100B levels have been found in patients with TBIs of varying severity. Ingebrigtsen et al. (1995) initially reported that S100B was at or above 0.50 µg/L in 20% of their MHI patients who had normal head CT scans on admission, while in a later study that included 182 MHI patients 35% had S100B values at or above 0.20 µg/L (Ingebrigtsen et al. 2000b).

Elevated S100B levels in patients with MHI have been found to be associated with prolonged hospitalisation and the presence of neuropsychological dysfunctions (Ingebrigtsen et al. 1997, Waterloo et al. 1997, Ingebrigtsen et al. 1999, Ingebrigtsen et al. 2000b, Herrmann et al. 2001), and also to predict the presence of intracranial lesions seen on a head CT scan in cases initially assessed as having MHI (Ingebrigtsen et al. 1999, Ingebrigtsen et al. 2000b, Biberthaler et al. 2001). Even more importantly, normal or low S100B has been shown to exclude the presence of intracranial abnormalities in a head CT scan with a high accuracy, since a cut-off level of 0.20 µg/L has been found to predict a normal CT scan with an accuracy of 99%.

In patients with moderate-to-severe head injury, increased S100B values have been associated with lower GCS scores shortly after trauma (Herrmann et al. 2000, Romner et al. 2000), traumatic lesion size as seen in a head CT scan (Raabe et al. 1998, Romner et al. 2000) and ongoing secondary brain injury (Raabe et al. 1999b, Woertgen et al. 1997). They have also been found to predict a poor outcome in these patients. Woertgen et al. (1997), examined 30 patients with severe head injury (GCS score of 8 or less), and found that an unfavourable outcome on discharge was associated with higher S100B values than was a favourable outcome, and later the same authors included 44 patients with severe head injury in their analysis and found that the S100B serum levels on admission predicted the outcome better than either the GCS or the Marshall Computed Tomographic Classification (Woertgen et al. 1999). Raabe et al. (1999b) included 84 patients with severe head injury in their series and found that 58% of the patients who died had a peak S100B value of at least 2 µg/L shortly after the trauma. S100B was also found to be an independent prognostic factor for survival, even when age, GCS score, intracranial pres-
sure and head CT scan findings were taken into account (Raabe et al. 1999b). Townend et al. (2002), studying 118 patients with an initial GCS score of 4 to 15, found that a serum S100B concentration above 0.32 µg/L predicted an unfavourable outcome at one month post injury with a sensitivity of 93% and a specificity of 72%, while a good recovery at the same point (extended GOS ≥7) was best predicted with a cut-off of 0.27 µg/L, giving a sensitivity of 76% and a specificity of 69% (Townend et al. 2002). In conclusion, S100B measured shortly after trauma has been shown to correlate with the severity of TBI and predict the outcome even when other prognostic factors such as the GCS score, CT findings, intracranial pressure level and age are taken into account.

Anderson et al. (2001) reported on a series of 17 trauma patients with severe extracranial injuries without evident head injury, all of whom had elevated S100B levels on admission (0.19 to 10.2 µg/L). Their observations suggest that the S100B measured in serum could also be of extracranial origin, but further research is required to demonstrate the extents to which different types of extracranial trauma contribute to the elevation in S100B.

2.4.8 Neuropsychological assessment

Neuropsychological and neurobehavioural dysfunctions often complicate the outcome after TBI. In fact, outcome studies dealing with severe TBIs have shown that chronic disability and the burden imposed on the family are primarily attributable to neuropsychological and neurobehavioural deficits, whereas motor and sensory deficits are less consequential (Levin 1993).

Neuropsychological assessment plays an important role in determining the extent and severity of the sequelae of head trauma, and the healing process after TBI can also be followed up with neuropsychological tests. A recent Finnish guideline recommends neuropsychological assessment for all TBI patients who are still suspected of having some neuropsychological or neurobehavioural deficits at one month post injury (Aikuisiän aivovammojen käypä hoito 2003). The results of neuropsychological tests are not specific to TBI, however, but are vulnerable to many confounding variables such as alcohol abuse and psychotropic drug effects (Mearns & Lees-Haley 1993). Thus, a comprehensive assessment performed by a professional neuropsychologist is the key factor in obtaining a reliable test result (Mearns & Lees-Haley 1993, Aikuisiän aivovammojen käypä hoito 2003).

In patients with MHI, information processing speed, memory and attention are the most common impaired functions, and deficits are often seen during the first weeks after trauma (Gronwall & Wrightson 1981, Levin et al. 1987, Stuss et al. 1989). In a recent meta-analysis, the prevalence of impaired neuropsychological performance among this group of patients was found to vary from 1.4 to 7.4%, and the most common single deficit was attributed to the measures of attention (Binder et al. 1997). The authors concluded, however, that neuropsychological assessment is likely to have a positive predictive value of less than 50% in patients with mild head injury, and that clinicians should exercise considerable caution before diagnosing TBI based on the findings (Binder et al. 1997).
The prevalence of neuropsychological impairments increases sharply in patients with more severe head injury. Herrmann et al. (2001), studying patients with mild-to-moderate head injury, found that 74% showed impairment at two weeks post injury and 69% still displayed disorders at six months. Typical dysfunctions were attributed to measures of attention, executive functions and memory performance (Herrmann et al. 2001). Neuropsychological impairments practically always complicate the outcome for patients with severe head injury (Levin 1993). Recovery is rapid within the first year after trauma (Levin et al. 1987, Levin 1993), but subtle changes in memory, attention and behavioural adaptation may continue for up to 2 years after injury, although the patient’s overall cognitive capacity may already have reached a plateau (Stuss et al. 1985, Levin 1993).

2.5 Treatment of head injury

Although there is very little firm scientific evidence on which to base the acute management of head injury patients (Young A & Willatts 1998, Thornhill et al. 2000), current evidence suggests that the aims must differ according to degree of the injury (Maas et al. 1997, Ingebrigtsen 2000a). The management of those who are initially evaluated as having MHI should be focused on assessing the risk of traumatic intracranial haematoma and preventing persistent PCSs (Williams et al. 1990, Stein & Spettell 1995, Ingebrigtsen et al. 2000a, Viola et al. 2000, Servadei et al. 2001, Vos et al. 2002), whereas the management of patients with moderate-to-severe head injury must be directed at minimising secondary brain damage (Menon 1999).

Three recent guidelines summarising the acute management of patients with MHI maintain that this should be based on the risk for intracranial complications (Ingebrigtsen et al. 2000a, Servadei et al. 2001, Vos et al. 2002). In the scheme shown in Table 2, MHI patients are divided into three risk groups: low-risk patients, having an admission GCS score of 15 without LOC, PTA or additional risk factors, medium-risk patients, having an admission GCS score of 15 with a history of brief LOC or amnesia, and high-risk patients, who initially have a GCS score <15. If any of the listed additional risk factors is present, the patient must be included in the high-risk group (Table 2). If a head CT scan reveals intracranial pathology with or without a need for intervention, then consultation or transfer to a neurosurgical centre is recommended. The observation stage can also be performed in a local trauma or medical centre. Instructions should always be given to patients who are sent home (Ingebrigtsen et al. 2000a).
Table 2. Complication rates and management of MHI patients by risk of intracranial lesions.

<table>
<thead>
<tr>
<th>Severity category</th>
<th>Approximate risk of lesions (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intracranial</td>
<td>Surgical</td>
</tr>
<tr>
<td>Low risk</td>
<td>Almost zero</td>
<td>Almost zero</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Send home with instructions</td>
</tr>
<tr>
<td>Medium risk</td>
<td>&lt;10</td>
<td>1–3</td>
</tr>
<tr>
<td></td>
<td>CT; If none, observe for 12 h</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>15–20</td>
<td>3–6</td>
</tr>
<tr>
<td></td>
<td>CT mandatory; observe for 12 h</td>
<td></td>
</tr>
</tbody>
</table>

Additional risk factors: prolonged unconsciousness or amnesia, anticoagulation or haemophilia, demonstrated or suspected skull fracture, post-traumatic seizures, neurological deficit, multi-injuries, age > 60 years, vomiting ≥ 2 episodes. Modified from Ingebrigtsen et al. 2000a, Haydel et al. 2000, Servadei et al. 2001, Vos et al. 2002, Stiell et al. 2001b

Inconsistent findings exist as to whether a routine follow-up and counselling should be given for every patient with MHI and whether this can prevent persistent PCSs. Some reports support reassurance and counselling (Relander et al. 1972, Alves et al. 1993, Ponsford et al. 2002), whereas others do not (Wade et al. 1997). Bed rest after head trauma has not been shown to prevent PCSs (de Kruijk et al. 2002b).

Moderate-to-severe head injuries have to be treated in trauma centres, since this has been shown to reduce overall mortality among such patients (The Brain Trauma Foundation 2000a). Two recent guidelines summarising the acute management of severe head injury patients (Bullock et al. 1996, Maas et al. 1997) both point out that management should be focused on preventing secondary brain damage. The preventable causes of such injury can be divided into systemic ones such as hypoxaemia, hypotension, hypercapnia, hypocapnia, hyperthermia, hyperglycaemia, hypoglycaemia and hyponatraemia, and intracranial ones such as mass lesions, brain swelling, oedema, seizures and infection (Maas et al. 1997). The systemic causes can be monitored and treated by maintaining the physiological conditions of the body (Menon 1999), while there are five interventions available to treat and prevent intracranial causes, namely hyperventilation, mannitol administration, cerebrospinal fluid drainage and the use of barbiturates or corticoids, but all of these have failed to reduce death or disability in controlled trials (Roberts et al. 1998). There is general agreement, however, that cerebral perfusion pressure has to be adequate in patients with head injury, between 60 and 70 mmHg, the accepted methods for maintaining it being ones which either lower the intracranial pressure or raise the mean arterial blood pressure (Menon 1999). It is accepted that all the aforementioned interventions except for corticoids either lower the intracranial pressure or raise the mean arterial pressure and thus maintain an adequate cerebral perfusion pressure (Maas et al. 1997). The indications for surgical treatment in cases of head injury are also generally accepted. If an extra-axial haematoma of thickness over 10mm or an intra-axial haematoma volume of over 25–30 ml is observed, or if a clot appears to have raised the intracranial pressure, surgery is indicated (Maas et al. 1997).

The use of prophylactic anticonvulsants in the acute stage is likely to prevent the occurrence of early post-traumatic seizures, but there is no reliable evidence to support their use for preventing late post-traumatic seizures (The Brain Trauma Foundation. 2000b). Early enteral feeding should be favoured, since it seems to be associated with a trend towards a better outcome in terms of survival and disability (Yanagawa et al. 2002).
2.6 Outcome after head injury

The Glasgow Outcome Scale (GOS) introduced by Jennett & Bond (1975) for assessing the outcome after head injury divides patients into five groups: dead, persistent vegetative state, severely disabled, moderately disabled and good recovery. This is a widely used method to describe the overall outcome after head injury, but as it is likely to be insensitive to mild disabilities, the authors later introduced an amendment called the extended GOS, in which the three highest categories of the original version are divided into better and worse levels (Jennett et al. 1981). Although the GOS and its amended version have been found to correlate with the emotional and cognitive consequences in patients with severe head injury (Wilson et al. 2000), there has been a need for a practical outcome scale, especially for MHI patients, who often suffer from subjective symptoms rather than objectively measurable deficits. Consequently, King et al. (1995) introduced the Rivermead Post Concussion Symptoms Questionnaire, which is now widely used for assessing PCSs attributable to mild head trauma (Ingebrigtsen et al. 2000b).

2.6.1 Mild head injury

Recovery from MHI is usually good and disability unusual. Binder (1997) concluded after reviewing 17 studies dealing with 2660 MHI patients (GCS ≥ 13) that 86% returned to their previous work and 7–8% had persistent PCSs. In fact, the prevalence of disability after MHI is clearly attributable to the definition of what is called “mild”. Thornill et al. (2000) studied head injury patients with an admission GCS of 13 to 15 and found that they were moderately or severely disabled (GOS: severely disabled or moderately disabled) just as often as those who were initially assessed as having a more severe head injury (GCS ≤ 13). Thus one should not pool all MHI patients with an admission GCS score of 13 to 15 together but define those with intracranial lesions in CT or MRI or with a PTA over 24 hours as having at least moderate brain injury (Williams et al. 1990, Aikuisiän aivovammojen käypä hoito 2003).

MHI patients have also been reported to have approximately a 1.5 times higher risk of epileptic seizures than healthy persons, a situation that can last for up to 4 years after trauma (Annegers et al. 1998).

2.6.1.1 Post-concussion symptoms (PCSs)

MHI may result in a subjective symptom complex known as PCSs (Alexander 1995, Bernstein 1999), to be found both in children and adults (Lundar & Nestvold 1985, Ingebrigtsen et al. 1998). The most common PCSs are headache, fatigue, dizziness, depression, poor concentration and irritability (Szymanski & Linn 1992). Most patients recover from these symptoms within a year, but a significant minority, approximately 7–15%,

may have persistent symptoms lasting for more than a year after the trauma (Alexander 1995, Binder 1997).

PCSs were assessed earlier with the investigators’ own checklists, but there is now a standardised questionnaire, known as the Rivermead Post Concussion Symptoms Questionnaire, which includes the sixteen most commonly reported PCSs (King et al. 1995). There is no consensus as to whether one symptom or a certain number of symptoms lasting long enough should be referred to as the post-concussion syndrome (King 1997), nor is there any consensus as to whether or not the symptoms should be divided into subgroups such as physical symptoms, cognitive complaints and behavioural and affective symptoms (Bernstein 1999).

The aetiology of PCSs remains unclear. Demographic, psychogenic and organic factors have all been suggested as playing a role in their development (Lishman 1988, Gasquoine 1997), and there is some evidence that age could increase their risk (Rutherford et al. 1978). Similarly, females have been thought to develop PCSs more often than males (Rutherford 1977, Bazarian et al. 1999). Psychogenic and behavioural factors such as depression, emotional distress, alcohol or drug abuse and litigation have also been thought to increase the risk of PCSs (Miller 1961, Lishman 1988, Bohnen & Jolles 1992, Karzmark et al. 1995, Cattelani et al. 1996, King 1996). Organic factors have been poorly studied, however. PTA as a marker of the severity of TBI has been assessed in relation to PCSs (King 1996, Bazarian et al. 1999), and traumatic brain damage could be an underlying factor, at least in some patients. Mittl et al. (1994) found that 30% of their patients who had been initially assessed as having MHI with normal CT had abnormalities compatible with DAI in MRI, while Ingebrigtsen et al. (2000b) found a tendency for an increased frequency of PCSs in patients with an elevated serum S100B concentration. The relationship between PCSs and neuropsychological deficits is unclear. Although some investigators have found higher prevalences of specific deficits such as attention and reaction time tests in neuropsychological tests performed on patients suffering from PCSs, there have been a number of patients with PCSs without any deficit (Bohnen & Jolles 1992, Bazarian et al. 1999).

In conclusion, PCSs relatively often complicate recovery after MHI, and in a small but significant group of patients the symptoms may be persistent. The clinical picture of PCSs reflects a multifactorial state in which organic, psychological and socioeconomic factors may play a role (Lishman 1988). Individual symptoms may substitute for each other over time and thus the association of a single symptom with damage in a certain region of the brain may be difficult to establish (Bohnen & Jolles 1992). The role of brain injury in the development of PCSs has been poorly studied, however. In any case, the prevention of PCSs has been raised as one of the main aims in the management of MHI patients (Ingebrigtsen et al. 2000a).

2.6.2 Moderate-to-severe head injury

Moderate-to-severe head injury often leads to death or chronic disability. The GOS scores reported after severe head injury, defined by an admission GCS score \( \leq 8 \), in four large studies are summarised in Table 3.
Table 3. Glasgow Outcome Scale (GOS) at six months post injury. Findings in four large surveys of the outcome after severe traumatic brain injury.

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBIC core data survey - severe cases</th>
<th>International databank - full series</th>
<th>USA traumatic coma databank</th>
<th>UK four centres study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>481</td>
<td>2959</td>
<td>746</td>
<td>976</td>
</tr>
<tr>
<td>GOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>40%</td>
<td>49%</td>
<td>36%</td>
<td>39%</td>
</tr>
<tr>
<td>Vegetative</td>
<td>4%</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Severe disability</td>
<td>16%</td>
<td>13%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>19%</td>
<td>15%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Good recovery</td>
<td>21%</td>
<td>20%</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>Unspecified</td>
<td></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>

Modified from Murray et al. (1999)

Murray et al. (1999) also reported data on 273 patients with moderate head injury (admission GCS score 8 to 12) and found the GOS distribution at six months post injury to be 48% good recovery, 21% moderate disability, 14% severe disability, 1% vegetative state and 16% dead. Similar findings have also been reported at three months (Rimel et al. 1982) and one year after moderate head injury (Thornhill et al. 2000). Thus the contributions of patients with severe and moderate head injury to the classes of severe disability and moderate disability do not differ much, whereas the occurrence of death is more frequent in those with severe head injury and a good recovery in those with moderate head injury.

There are a number of prognostic factors which may influence the outcome in patients with moderate-to-severe head injury. Increasing age, lower GCS motor score, absence of pupillary light reflex or oculocephalic reflex, and CT findings especially marks of increased intracranial pressure or SAH, have been consistently found to be associated with a poor outcome (Choi et al. 1988, Marshall et al. 1991a, Attia & Cook 1998, Signorini et al. 1999, Wardlaw et al. 2002), as also have multiple injuries (Gennarelli et al. 1989), haemostatic abnormalities (Olson et al. 1989), female gender (Farace & Alves 2000), previous head injury (Thornton et al. 2000), apolipoprotein ε4 genotype (Teasdale et al. 1997), alcohol abuse (Corrigan 1995) and lower socioeconomic status (Binder 1997, Wagner et al. 2000).

Patients with moderate-to-severe head injury have an increased risk of post-traumatic epilepsy (Annegers et al. 1998), this being approximately 7% within 1 year after a closed severe head injury and 12% within 5 years, or approximately 1% and 1.5%, respectively, after a closed moderate head injury (Annegers et al. 1980, Annegers et al. 1998). The presence of contusion, SDH, or skull fracture marks a specific type of trauma that increases the risk of later seizures. In the case of both moderate and severe head injuries, the increased risk of late seizures lasts for up to approximately ten years after the trauma (Annegers et al. 1998).
2.7 Alcohol and head injury

2.7.1 General aspects

Alcoholism and hazardous alcohol drinking have an enormous impact on the productivity and quality of life in Western countries. It was estimated that the total annual costs of alcohol misuse in the US in 1985 exceeded $86–100 billion (Rice et al. 1991, Angell & Kassirer 1994), and ten years later the total costs were estimated to have increased to $175.9 billion (Rice 1999). Thirty three per cent of all economic costs attributed to motor-vehicle crashes, for example, have been estimated to be associated with alcohol (CDC 1993).

In Finland, the annual direct costs arising from alcohol misuse exceed 550–705 million euros. If all the direct medical care expenditure, indirect costs and the value of lost productivity, including persons who die prematurely due to alcohol misuse, the total annual costs are estimated to reach 2443–4563 million euros (Päihdetilastollinen vuosikirja 2003).

2.7.2 Alcohol drinking as a risk factor for trauma

Acute hospitalisations are often associated with alcohol, so that Charalambous (2002) estimated that 2–40% of all accident and emergency department attendances are of this kind, and alcohol is especially linked to traumas, approximately one half of all trauma patients being BAC-positive on admission and more than a third having a BAC at or above 100mg/dL. (Rivara et al. 1993a). A high incidence of acute alcohol abuse has also been found among adolescents, to the extent that Porter (2000) reported that 32% of a series of 2724 trauma patients aged 12–24 years were BAC-positive on admission.

There is direct evidence that alcohol intoxication increases the risk of trauma (Honkanen et al. 1976, Cherptitel et al. 1995, Rivara et al. 1997, McLeod et al. 1999, Li et al. 2001, Borges et al. 2004). Cherptitel et al. (1995) reported that the risk of injury was found to increase with an average daily consumption of one drink and with a frequency of consuming five or more drinks on one day more often than twice a year. The case-control study by McLeod et al. (1999) showed in a multivariate analysis after adjustment for demographic variables that the consumption of more than 60 grammes of ethanol (pure alcohol) in a 6-hour period produced an odds ratio of 3.4 (95% CI 1.8–6.4) on sustaining an injury. Alcohol intoxication has also been found to be associated with other forms of risk behaviour for sustaining an injury, such as suicidal ideation and violence (Field et al. 2001).
2.7.3 Alcohol drinking as a risk factor for head injury

Alcohol ingestion is often involved in head injuries, the proportion of BAC positives having been found to be over 50% in prospective head trauma series (Rimel et al. 1982, Brismar et al. 1983, Corrigan 1995, Dikmen et al. 1995), while the number of patients with BAC at or above 100mg/dL has been reported to vary from 35 to 40% (Rimel et al. 1981, Dikmen et al. 1995). Head injury patients are also often chronic alcohol misusers. Corrigan (1995) found in a review of seven studies that the prevalence of chronic alcohol abuse varied from 16% to 66%. Bias was evident in the case of the lowest rates, because the findings were based on chart reviews (Corrigan 1995). Brismar et al. (1983) found that psychiatric examination revealed alcohol dependence in 43 out of 100 consecutive head injury patients. Chronic alcohol misuse among head injury patients also seems to be associated with many forms of risk behaviour which may compound the risk of head injury. These include lower educational attainment, problems with the law, lower perceived social support, and greater prevalence of other substance abuse (Cherner et al. 2001).

2.7.4 Alcohol and trauma morbidity and mortality

Ward et al. (1982) reported that mortality after trauma was significantly lower among those with a positive BAC on admission than in sober counterparts, and suggested that alcohol may have some protective effects on the consequences of injury (Ward et al. 1982). Patients who died on the scene were not included in the series. It is known, however, that many accidental deaths occur before hospital admission (Klauber et al. 1981), so that the finding of Ward et al. (1982) may be biased. Waller et al. (1986) later found after studying more than 1 million drivers involved in motor vehicle crashes that the drinking drivers more often suffered serious injury or death than the sober ones, and similar findings have also been reported in bicycling injuries (Li et al. 2001). Thus alcohol ingestion is more likely to potentiate the primary injury than to provide protection from its consequences. Alcohol intoxication on admission has also been shown to result in an increased use of invasive diagnostic and therapeutic procedures (Gurney et al. 1992, Jurkovich et al. 1992, Melnick et al. 2000), and there is evidence that alcohol abusers often suffer recurrent traumas (Rivara et al. 1993b).

2.7.5 Alcohol and traumatic brain injury morbidity and mortality

The pathophysiological changes associated with acute and chronic alcohol exposure in the setting of TBI are complex. Alcohol intoxication can cause haemodynamic and respiratory depression, blood-brain barrier disruption and haemostatic impairments (Zink et al. 1993, Kelly 1995). Kelly et al. (1997a) found in an experimental setting involving brain injury in rats that high-dose acute alcohol ingestion (3g/kg) increased mortality after trauma, whereas better recovery rates were recorded in the low (1g/kg) and moderate (2.5g/
kg) alcohol dose groups. Theoretically, alcohol may also be neuroprotective, since it causes inhibition of N-methyl-D-aspartate (NMDA) receptors (Kelly 1995). On the other hand, chronic alcohol exposure results in up-regulation of NMDA receptors and down-regulation of -aminobutyric acid receptors, and this adaptation may result in hyperexcitability during withdrawal and thus exacerbate TBI (Lovinger 1993, Kelly 1995). There is no clear experimental evidence that chronic alcohol administration exacerbates TBI, however. Neither 6 weeks nor three months of alcohol ingestion in rats was found to have any significant exacerbating effects on neurological motor deficits or sizes of morphological brain lesions (Shapira et al. 1997, Masse et al. 2000).

The contribution of acute alcohol intoxication to the outcome after human head injury remains to be elucidated. There are studies in which alcohol intoxication on admission has been found to predict either a favourable (Kraus et al. 1989) or an unfavourable outcome (Brooks et al. 1989, Sparadeo & Gill 1989, Kelly et al. 1997b, Bombardier & Thurber 1998), and studies in which alcohol has not been found to correlate with the outcome at all, or else the correlation has been lost when other prognostic factors have been taken into account (Choi et al. 1988, Ruff et al. 1990, Signorini et al. 1999, Wagner et al. 2000). In contrast, chronic alcohol misuse has quite consistently been found to be associated with a poor outcome. Corrigan (1995) concluded after reviewing seven studies dealing with this relationship that only one had failed to find such an association. Separate associations between alcohol abuse and more severe primary injury, higher mortality rate and poorer neuropsychological and overall outcome have also been reported (Corrigan 1995).

2.8 Identification of hazardous alcohol drinking

Hazardous alcohol drinking often means frequent drinking aimed at intoxication. The identification of alcohol misuse has been based on a clinical history, specific questionnaires and various laboratory tests or combinations of tests (Ewing 1984, Skinner et al. 1986, Ross et al. 1990, Mihas & Tavassoli 1992, Hartz et al. 1997). In the case of trauma patients, the results of clinical histories, questionnaires and laboratory tests of alcohol misuse have been compared with clinical diagnoses of alcohol dependence (Soderstrom et al. 1997, Ryb et al. 1999), or with each other (Rivara et al. 1993, Nilssen et al. 1994, Dikmen et al. 1995, Bombardier et al. 1997b, Cherner et al. 2001), but there have been no studies dealing with the identification of different patterns of alcohol drinking.
2.8.1 Tools for identifying hazardous alcohol drinking

2.8.1.1 Questionnaires and interviews

There are a number of questionnaires designed to identify and assess alcohol misuse and dependence, of which the most common are the Michigan Alcoholism Screening Test (MAST) (Selzer 1971), the self-administered Short Michigan Alcoholism Screening Test (SMAST) (Selzer et al. 1975), the Alcohol Dependence Scale (Skinner & Allen 1982), the CAGE questionnaire (Ewing 1984), Self-Administered Alcoholism Screening Test (SAAST) (Hurt et al. 1980) and the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al. 1993). Most of these have been validated with materials consisting of alcoholics and non-alcoholics, and they have been shown to distinguish between them with high sensitivity and specificity (Davis et al. 1987, Ross et al. 1990).

There is also a structured interview for assessing the amount of alcohol drinking and its pattern. The Timeline Followback technique is a retrospective survey which includes memory aids to enhance patient recall and is thought to allow the collection of reliable information on a period of at least 12 months (Sobell & Sobell 1995, Allen et al. 1997).

2.8.1.2 GGT

Gamma-glutamyl transpeptidase (GGT) is a membrane-bound glycoprotein found in the membrane fractions of many tissues, including liver, kidney, brain, spleen, pancreas and heart (Mihas & Tavassoli 1992). Chronic alcohol consumption leads to elevated serum GGT values, and the sensitivity of GGT for detecting alcohol misuse has been reported to vary between 34 and 85% (Sillanaukee 1996). The suggested mechanisms for the increase of GGT in serum due to alcohol ingestion include induction of hepatic GGT, increased permeability of hepatic plasma membranes and hepatocellular injury. An increase in GGT calls for heavy drinking for several days or weeks (Rosman 1992, Sillanaukee 1996). Values above 80 U/L (men) and 50 U/L (women) are considered indicative of alcohol misuse. The half-life of GGT in serum is approximately 2–3 weeks.

Elevated serum GGT may also be due to non-alcoholic conditions, however. Non-alcoholic liver diseases, diabetes, obesity, heart failure, the use of anticonvulsants and severe trauma are such conditions (Sillanaukee 1996).

2.8.1.3 AST & ALT

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are enzymes that are abundant in the liver, and AST is also found in the heart, muscle, brain, pancreas, kidney and lungs (Mihas & Tavassoli 1992, Rosman 1992). These enzymes may increase in serum after alcohol-induced liver damage, but also in cases of non-alcoholic liver diseas-
es, muscle disorders and myocardial infarction (Sillanaukee 1996). AST values above 50 U/L (men) and 35 U/L (women) are considered indicative of alcohol misuse. The sensitivity of AST for detecting alcohol misuse has varied between 15 and 69%, but the specificity has been low (Sillanaukee 1996). ALT is not as useful as AST as a marker of alcohol misuse, but a ratio of AST to ALT of over two may be useful, and may indicate alcoholic hepatitis (Mihas & Tavassoli 1992).

2.8.1.4 CDT

Transferrin is the iron transport protein, which includes two globular domains and several polysaccharide side chains (Mihas & Tavassoli 1992). When transferrin is exposed to alcohol, abnormal side chains result and carbohydrate-deficient transferrin (CDT) is produced (Lesch & Walter 1996).

CDT is a promising marker of excessive alcohol use. Serum CDT was found to be increased after a daily intake of 50–80 grammes of pure alcohol for at least one week and was normalised slowly during abstinence, with a half-life of approximately 15 days (Stibler 1991). Values above 20 U/L (men) and 26 U/L (women) are considered indicative of alcohol misuse. After pooling approximately 2500 individuals from relevant studies, Stibler (1991) found that CDT had a sensitivity of 82% and a specificity of 97% for detecting alcohol misuse. Meerkerk et al. (1998), however, reported that in studies dealing with more general populations the sensitivity of CDT varied from 12% to 45% and the specificity from 87% to 96%. False positive findings have been reported at least in patients with primary biliary cirrhosis, chronic hepatitis C, hepatic malignancies, a genetic variation in transferrin and certain rare inborn glycoprotein disorders (Sillanaukee 1996). Common chronic diseases such as hypertension, asthma/bronchitis, diabetes, angina pectoris, depression and disorders of the digestive tract have not been found to cause unspecificity (Meerkerk et al. 1998).

2.8.1.5 MCV

The mean corpuscular volume (MCV) of erythrocytes may be elevated as a result of excessive alcohol consumption, but also in response to many other conditions such as liver disease, folate deficiency and hypothyroidism (Sillanaukee 1996). Values above 96 fl are considered indicative of alcohol misuse. MCV returns to normal values within 3 months after the beginning of abstinence. Its sensitivity for alcohol misuse is relatively low, since MCV detects only 30–40% of subjects with a drinking problem (Mihas & Tavassoli 1992).
2.8.1.6 BAC

Blood alcohol concentration (BAC) can be measured directly from a blood sample or be estimated from breath, saliva or urine measurements. Urine measurements often show higher concentrations than measurements in blood, whereas breath measurements give an accurate estimate of the real BAC (Bendtsen et al. 1999).

BAC of at least 150mg/dL without gross evidence of intoxication, 300mg/dL at any time or 100mg/dL in routine examination are first-level criteria for alcoholism (Criteria Committee, National Council on Alcoholism, New York 1972).

2.8.2 Detecting hazardous alcohol drinking

2.8.2.1 In patients with trauma

CAGE has been found to be the best questionnaire for predicting chronic alcohol dependence in trauma patients (Nilssen et al. 1994, Soderstrom et al. 1997), where it predicted life-time alcohol dependence with a sensitivity of 84% and a specificity of 90% (Soderstrom et al. 1997). By contrast, laboratory tests such as GGT, AST, MCV and serum osmolality seem to lack sensitivity and specificity for detecting alcohol dependence in trauma patients. Ryb et al. (1999) compared the above four tests in 684 male trauma patients and found relative low sensitivities (0.51, 0.43, 0.27, and 0.74, respectively) and specificities (0.78, 0.74, 0.89, and 0.70, respectively) for detecting current alcohol dependence. BAC on admission nevertheless appeared to be associated with recent alcohol dependence better than any of the conventional biochemical markers (Ryb et al. 1999).

2.8.2.2 In patients with head injury

Although the prevalence of hazardous alcohol drinking may be high in patients with head injury, the identification of alcohol misuse among such patients has not been studied greatly (Corrigan 1995). Dikmen et al. (1995) found that 45% of patients with head injury reported 2 or more items on the SMAST, a level considered indicative of problem drinking. Bombardier et al. (1997b) studied 50 head injury patients admitted to an inpatient rehabilitation programme and found that MAST showed alcohol problems in 74% of these cases, while Brismar et al. (1983) found that 43 out of 100 consecutive head injury patients were alcohol-dependent, and GGT was elevated in 37%, AST in 35% and ALT in 28% of the total series. No relationship between alcohol dependence and biochemical markers was reported (Brismar et al. 1983).
2.9 Alcohol interventions as means of preventing injuries

Although alcohol is thought to be a significant cause of trauma, there still continues to be a lack of attention to hazardous drinking in accident and emergency departments (Soderstrom & Cowley 1987, Schermer et al. 2003), although these could be optimal places for commencing alcohol interventions and thus reducing its detrimental effects (Charalambous 2002).

Alcohol interventions are aimed at reducing alcohol drinking and alcohol-related effects such as violence, injuries and illnesses. There are many intervention protocols, but a brief alcohol intervention is thought to be the most practicable in accident and emergency departments (Dunn et al. 1997). Holder et al. (1991) found a negative relationship between the effectiveness and costs of alcohol interventions, which further supports the use of inexpensive, easy methods of alcohol counselling.

Evidence is accumulating that brief interventions are effective in reducing alcohol drinking and may thereby also reduce the risk of alcohol-related accidents (Antti-Poika I et al. 1988, Walsh et al. 1991, Fleming et al. 1997, Holder et al. 2000). Two recent meta-analyses have concluded that alcohol interventions may be associated with reductions in suicide attempts, domestic violence, drinking-related injuries and injury hospitalizations, and with reductions in deaths ranging from 27% to 65% (Dinh-Zarr et al. 1999, Dinh-Zarr et al. 2000).

In a study of 2524 consecutive trauma patients, including 1153 who were screened as positive with respect to alcohol problems, Gentilello et al. (1999) randomised 366 patients to a counselling group (a brief alcohol intervention) and 396 to a control group. A significant decrease in alcohol consumption was found in the former at 12 months, accompanied, interestingly, by significant reductions in injuries requiring emergency or trauma centre admissions (47%) or hospital admissions (48%) within three years of the original trauma (Gentilello et al. 1999).

Even though hazardous alcohol drinking is a major problem affecting patients with head injury, there are no studies dealing with a brief alcohol intervention as a means of reducing alcohol consumption in this group. On the other hand, the consumption of alcohol has been found to decrease after the occurrence of head injury even without structured interventions (Kreutzer et al. 1991, Dikmen et al. 1995). Dikmen et al. (1995) found that alcohol consumption had decreased most compared with the pre-injury level at 1 month, after which it increased significantly, but the patients were not followed-up for more than 12 months. The reduction in alcohol consumption early after trauma may be due to lack of access to alcohol (still hospitalised), non-structured advice given by health care providers, decreased tolerance of alcohol, or rethinking in the aftermath of a major trauma (Dikmen et al. 1995).
3 Aims of the research

The purpose of the present research was:

1. to find simple clinical measures that predict the development of PCSs in patients with mild head injury and to validate serum protein S100B as a prognostic marker. (I)
2. to evaluate the clinical utility of protein S100B as a marker of brain damage in patients with multitrauma, and to find out whether its usefulness is confounded by extracranial injuries. (II)
3. to study patterns of alcohol drinking in trauma patients and assess whether there are specific risk patterns for head trauma. (III)
4. to investigate how hazardous alcohol drinkers among patients with head injuries and other types of trauma can best be identified on admission. (IV)
4 Subject and methods

The work was carried out in the Department of Neurology, University of Oulu, during the years 1998–2004. The protocol was approved by the Ethics Committee of the Medical Faculty, University of Oulu, and carried out according to the principles of the Declaration of Helsinki. All the patients or their relatives gave informed consent before inclusion in the series.

4.1 Subjects

The series comprised 385 consecutive acute trauma patients aged 16 to 49 years admitted to the emergency department of Oulu University Hospital between June 1998 and July 2000, comprising 224 having head injuries with or without extracranial injuries and 161 patients having extracranial injuries only. Patients admitted more than 6 hours after the trauma event were excluded. None of the patients reported suffering from cancer, multiple sclerosis, stroke, or treated epilepsy.

Paper I involved 172 MHI patients, of whom 129 were men and 43 women. These represented the 199 out of the 224 head injury patients who fulfilled the following criteria for MHI: Glasgow Coma Scale (GCS) score of 13–15 on admission, loss of consciousness for ≤ 30 minutes, if at all, and no focal deficits in a neurological examination performed on admission. Twenty-seven of these 199 MHI patients had to be excluded because they were not reached, so that no interview to determine post-concussion symptoms (PCSs) could be performed.

Paper II covered a total of 379 trauma patients, of whom 224 were head injury patients and 155 patients with extracranial injuries only. Fifty-four of the head injury patients had simultaneous extracranial injuries. Six patients with extracranial injuries only were omitted because they reported PTA, so that the presence of TBI could not be convincingly excluded. Additionally, we examined whether the exposure of healthy individuals to high +Gz forces without actual impact on tissues could increase serum S100B values. For this purpose, we recruited eight flight crew members of the Finnish Air Force, seven of whom performed two flight missions seated in the back seat of a BA Hawk Mk 51 A aircraft and
wearing an extended coverage anti-G suit. The detailed characteristics of the flight missions and management of these subjects have been described elsewhere (Siitonen 2000).

Paper III included all the 385 trauma patients, and paper IV included those who were interviewed for patterns of alcohol drinking (n=349).

4.2 Methods

4.2.1 Clinical examination

4.2.1.1 Emergency room

The patients included in the series were carefully examined on admission by emergency room physicians according to a structured checklist designed for this purpose. Clinical data, including neurological examinations, the presence of clinical symptoms such as unconsciousness, amnesia, dizziness, headache, neck pain, nausea and vomiting, and the type and extent of the head and extracranial injuries were carefully recorded. A history of infections (HIV/AIDS, hepatitis B and C) and other diseases was also recorded. The level of alcohol intoxication was assessed clinically and graded as none, slight, or severe intoxication. Venous blood samples were obtained from each patient for biochemical determinations.

The injured body parts of each patient were divided into six categories: head, spine, thorax, abdomen and upper and lower extremities. The presence of injury was recorded when there was distinct physical evidence of trauma as assessed by the emergency room physician. The Injury Severity Score (ISS) was also used as an index of trauma severity (Baker et al. 1974, Copes et al. 1988), and the GCS to assess the level of consciousness (Teasdale & Jennett 1974).

The physician decided on admission which of the additional examinations (imaging modalities) were needed, and the patients were subsequently treated according to the hospital’s routine protocols. Sixty-six head injury patients underwent a head CT scan within 24 hours from the trauma, and the resulting scans were evaluated twice, first as part of the routine clinical evaluation and later in a re-evaluation of all the scans by a trained neuroradiologist. Thirty-three patients were further examined by skull radiography.

The patients with head injury discussed in paper II were classified on the basis of their symptoms and signs as follows: 1. 35 patients having head injury without brain injury, 2. 165 patients having head injury with mild brain injury, and 3. 24 patients having head injury with moderate-to-severe brain injury. The groups fulfilled the following diagnostic criteria:
1. Head injury without amnesia, unconsciousness, headache, dizziness or vomiting
2. Head injury with amnesia and/or unconsciousness (duration ≤ 24 hours), headache, dizziness or vomiting
3. Head injury with amnesia and/or unconsciousness (duration > 24 hours), intracranial lesion visible in the head CT scan or focal deficits in the neurological examination.

The extracranial injuries were divided in paper II into two groups: small (soft tissue contusions, wounds, sprains, luxations and small fractures) and large (large fractures and abdominal injuries). Vertebral, pelvic, femoral and brachial fractures and fractures of both forearm bones were assessed as large and all other extracranial fractures as small.

4.2.1.2 Alcohol data

Blood alcohol concentration (BAC) on admission was determined either from exhaled air (n=206) or from serum samples (n=179). Personal interviews were conducted with 349/385 (91%) of the patients by the same interviewer throughout using a structured questionnaire to gather data on their alcohol consumption. The interviews were performed blind to any knowledge of the determinations of BAC levels or other biochemical markers of alcohol consumption. The interviews took place within 2–6 weeks of the injury.

The history of alcohol consumption included the following information: how many drinks of alcohol (one standard drink = 12 g of ethyl alcohol, corresponding to one beer, one glass of table wine or four centilitres of proof spirit) the patient had consumed during (i): 24 hours, and (ii): one week preceding the injury. Daily alcohol consumption during a period of one year prior to the trauma was also assessed using a time-line follow back technique (Sobell & Sobell 1995, Allen et al. 1997). Based on the resulting data, the patients were classified into dependent drinkers, binge drinkers, light-to-moderate drinkers and non-drinkers. The dependent drinkers were those who showed clinical evidence of pathological alcohol use, social impairment and tolerance/withdrawal. Their daily alcohol consumption had exceeded 80 g. Binge drinking (i.e. heavy episodic drinking) was defined as an intake of 6 or more (men) or 4 or more (women) standard drinks of alcohol in one session. Binge drinkers were further divided into frequent binge drinkers, who reported this type of drinking at least once a month, and infrequent binge drinkers, who reported that it occurred 1–11 times per year. Light-to-moderate drinkers did not drink for intoxication, but consumed 1–2 standard drinks per day either daily or less frequently. Non-drinkers had not drunk any alcohol during the year preceding the injury, and included both life-long abstainers and ex-drinkers. The dependent drinkers and frequent binge drinkers together made up the group referred to as hazardous drinkers.

4.2.1.3 Follow-up interviews

The follow-up interviews were carried out twice, a face-to-face interview within 2–6 weeks of the trauma, but not before full recovery from amnesia, and a second, telephone interview 8–30 months after the injury.

The first interview included questions on the trauma, education and employment status, previous diseases, use of medicines, lifestyle factors and a modified Rivermead Post
Concussion Symptoms Questionnaire (King et al. 1995) in which the answers were dichotomized to yes or no. Questions were also added regarding decreased alcohol tolerance and the occurrence of panic attacks. The presence and duration of post-traumatic amnesia (PTA) at the time of injury was assessed according to the Rivermead Post-Traumatic Amnesia Protocol (King et al. 1997), and educational status was recorded in terms of the number of years of schooling. The patient was also asked whether he or she had insurance that covered the accident. Previous diseases such as TBIs, psychiatric illnesses and contacts and HIV, hepatitis or other liver diseases were also ascertained, and medications were carefully recorded.

The second interview was a telephone interview (8–30 months after the injury), which aimed at ensuring that the patients with PCSs really fulfilled our criteria (I). This was done because the first interview had been performed 2–6 weeks after trauma, and according to our definition of PCSs, symptom(s) had to last at least one month post injury before the criteria were fulfilled.

### 4.2.2 Laboratory procedures

Venous blood samples were obtained from each trauma patient as soon as possible after admission, but no later than six hours from trauma. The samples were centrifuged and stored at −20°C until analysed, except that the mean corpuscular volume (MCV) of erythrocytes was determined as soon as possible after admission. Protein S100B, serum gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST) and carbohydrate-deficient transferrin (CDT) were measured for each patient, whereas MCV was determined in 302/385 cases (78%).

The concentration of protein S100B was measured using a commercially available monoclonal two-site immunoluminometric assay (LIA-mat® Sangtec® 100; AB Sangtec Medical, Bromma, Sweden) with a detection limit of 0.02 µg/L. Blood alcohol concentrations were measured on a Vitros 250 clinical chemistry analyser (Johnson & Johnson Clinical Diagnostics, Rochester, New York), and the ALCO-SENSOR III (Intoximeters Inc., St. Louis, Mo) was used for the breath analyses. Serum CDT was measured with a competitive radioimmunoassay after microcolumn separation (CDTect, AxisShield, Oslo, Norway), and the measurements of MCV, GGT and AST were carried out using standard clinical chemical methods.

Normalised S100B values for paper I were calculated according to a half-life of 120 minutes as follows: normalised S100B = 2 (time from trauma to blood sampling in minutes / 120 minutes) x measured S100B. The following cut-off values were used in the analyses for the diagnostic characteristics of the laboratory tests: in paper I: S100B 0.50 µg/L, in paper IV: MCV >96 fL for women and men, GGT >50 U/L for women and >80 U/L for men, AST >35 U/L for women and >50 U/L for men and CDT >26 U/L for women and >20 U/L for men.
4.2.3 Statistical analysis

Categorial variables were compared by means of Fisher’s exact 2-tailed test or the Pearson $\chi^2$ test. Continuous variables were compared among groups using Student’s t-test, the Mann-Whitney U-test, or the Kruskall-Wallis test. Univariate associations of continuous variables were tested by means of Spearman’s rank correlation coefficients ($r_s$). Receiver operating characteristic (ROC) curves for the S100B values were also drawn in paper I for detecting PCSs patients with and without S100B normalisation, and sensitivities, specificities, positive and negative predictive values, and 95% confidence intervals (CIs) were calculated for each marker of alcohol consumption in paper IV for detecting hazardous alcohol drinking.

Odds ratios (OR) and 95% confidence intervals (CI) before and after adjustment for possible confounding variables were calculated by logistic regression for paper I, and the hypotheses were tested and 95% CI determined using standard error estimates for the logistic coefficients. Stepwise multiple logistic regression ($p<0.1$ for entry limit and $p>0.15$ for removal limit) was used to test the significant independent risk factors for PCSs. In paper III, relative risk (RR) estimates and 95% CIs were calculated before and after adjustment for confounding factors, and in paper II, a two-way analysis of variance was used to assess the effects of head injuries and other types of trauma on S100B values.

All the analyses in papers I and II were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0, for Windows, SPSS Inc, Chicago, IL USA), and in papers III and IV using the CIA statistical software (Gardner & Altman 1989) and SPSS.
5 Results

5.1 Protein S100B as a predictor of PCSs in MHI patients (paper I)

A total of 172/199 (86%) MHI patients were included in this series, 129 men and 43 women, with a mean age of 31.3 years (SD 10, range 10–49) (I; Table 2). Thirty-seven of them (22%) reported PCSs, i.e. at least one PCS lasting at least one month following the trauma event. The most common PCSs were depression, dizziness, fatigue and headache (I; Table 1). Thirty of these patients (81%) had suffered from at least two symptoms, and the mean number of symptoms amounted to 5.0 (SD 3.6, range 1–14). Thirty-nine of the 172 patients (23%) underwent a head CT scan on admission, and eight had traumatic intracranial lesions visible. Of the 164 patients who did not have any evidence of intracranial lesions, 32 (20%) reported PCSs.

Significant risk factors for PCSs emerging in univariate analysis were the presence of skull or facial bone fracture, elevated serum protein S100B (0.50 µg/L), the presence of dizziness and headache on admission, psychiatric illness in childhood, loss of consciousness and PTA (I; Table 2). There was also a correlation between the number of symptoms and the S100B values (Spearman correlation, p < 0.001), but no statistically significant correlation between PCSs and age (as a continuous variable), psychiatric illness in adulthood, use of psychotropic drugs, current smoking, prior use of illicit drugs, or neck pain on admission.

The ROC curves for S100B in the 172 MHI patients with and without S100B normalisation are presented in Figure 2. Serum protein S100B with a cut-off level of 0.50 µg/L showed a high specificity for PCSs (93%) but a rather low sensitivity (27%). The sensitivity with a cut-off value of 0.20 µg/L was 68% and the specificity 67%, but the negative predictive value was as high as 88%.
Skull fracture, elevated protein S100B ($\geq 0.50\ \mu g/L$), dizziness and headache on admission and age were identified as independent risk factors for PCSs (Table 4). The model remained unchanged after normalisation of the S100B values. This model gave ORs of 6.1 (1.9–19.6) for skull fracture, 6.0 (2.3–15.2) for protein S100B, 3.0 (1.1–7.9) for dizziness, 2.3 (0.9–5.9) for headache and 1.05 (1.00–1.10) for age.

**Table 4. Multivariate ORs for PCSs in mild head injury patients ($n=172$). Table from paper I.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull fracture</td>
<td>8.0</td>
<td>2.6–24.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Protein S100B $\geq 0.50\ \mu g/L$</td>
<td>5.5</td>
<td>1.6–18.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Dizziness on admission</td>
<td>3.1</td>
<td>1.2–8.0</td>
<td>0.021</td>
</tr>
<tr>
<td>Headache on admission</td>
<td>2.6</td>
<td>1.0–6.5</td>
<td>0.043</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.01–1.10</td>
<td>0.027</td>
</tr>
</tbody>
</table>

ORs represent comparisons between patients with and without at least one symptom lasting for one month or more and are adjusted for sex, educational status and the other variables listed in the table.

Loss of consciousness, post-traumatic amnesia, presence of extracranial injury, prior head injury, employment status, insurance, psychotropic drugs, current heavy drinking, smoking and prior use of illicit drugs were not independent risk factors for PCSs.
5.2 Effects of extracranial injuries on S100B levels (paper II)

A total of 379 trauma patients were included in this series, of whom 224 had head trauma and 155 had extracranial injuries only. Fifty-four (24%) of the 224 head trauma patients also had extracranial injuries.

The median serum concentration of protein S100B among the patients with head trauma was 0.17 µg/L (0.07–0.36, Q1–Q3), whereas the corresponding value for those without head trauma was 0.07 µg/L (0.03–0.13, Q1–Q3) (Mann-Whitney U-test: p < 0.001). When the head trauma patients were classified into those with no brain injury, mild brain injury and moderate-to-severe brain injury, the median levels (n, Q1–Q3) of S100B were 0.10 µg/L (35, 0.06–0.18), 0.16 µg/L (165, 0.07–0.32) and 1.27 µg/L (24, 0.32–3.3), respectively (Kruskall-Wallis test: p < 0.001). The median S100B concentration (n, Q1–Q3) was 0.35 µg/L (7, 0.20–0.64) for the patients with large extracranial injuries only and 0.07 µg/L (148, 0.03–0.12) for those with small extracranial injuries (Mann-Whitney U-test: p < 0.001).

The effects of the severity of brain injury and the size of extracranial injury on S100B levels (logarithmic modification of S100B values) are illustrated in Figure 3. Both brain injury and extracranial injury independently increased the serum S100B concentrations in the trauma patients, since two-way analysis of variance showed that the two variables and their interaction were statistically significant (p < 0.001).

A comparison of S100B cut-off levels showed that there were only a few head trauma patients without brain injury or patients with extracranial injuries alone above the highest cut-off level (0.50 µg/L) (II; Table 4), whereas the head trauma patients with moderate-to-severe brain injury exceeded this cut-off in 67% of cases. Likewise, 61% (136/224) of the head trauma patients and 26% (41/155) of those with extracranial injuries only had S100B above 0.13 µg/L (Pearson $\chi^2$ test: p < 0.001).

Fig. 3. Effects of the severity of brain injury and the size of extracranial injury on S100B levels. Logarithmic modification of S100B concentrations: Ln (1 + S100B). Figure from paper II.
Of the different types of extracranial injuries, large extracranial injuries such as large fractures and abdominal injuries elevated S100B values significantly (II; Table 3), whereas soft tissue contusions, wounds, sprains, luxations and small fractures (i.e. small extracranial injuries) did so only slightly (II; Table 3). We did not find any significant increase in serum S100B in healthy individuals after exposure to high +Gz forces, the median S100B level (Q1–Q3) in blood samples taken 5 and 60 minutes after the 22-minute flight missions with a maximal acceleration of + 6 Gz being 0.00 µg/L (0.00–0.03).

5.3 Binge drinking as a risk factor for head trauma (paper III)

Eight per cent of the trauma patients were found to be dependent drinkers, 61% frequent binge drinkers and 17% infrequent binge drinkers (Table 5). Thus a total of 78% of the patients reported binge-type drinking. The light-to-moderate drinkers and non-drinkers represented 8% and 6% of the population, respectively. The dependent drinkers tended to be older than the patients with other drinking patterns, and they also had the highest BACs on admission (Table 5). The proportion of women among the dependent drinkers and frequent binge drinkers was found to be low.

Table 5. Characteristics of the patients classified according to the history of alcohol consumption (n = 349).

<table>
<thead>
<tr>
<th>Pattern of drinking</th>
<th>Patients n (%)</th>
<th>Women n (%)</th>
<th>Age (years) Mean ± SD</th>
<th>BAC (mg/dL) on admission Mean ± SD</th>
<th>Clinically intoxicated on admission n (%)</th>
<th>Alcohol consumption during the preceding year, g/day Mean ± SD, women/men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent drinkers</td>
<td>26 (8)</td>
<td>0</td>
<td>38 ± 9</td>
<td>210 ± 160</td>
<td>20 (77)</td>
<td>137±45†</td>
</tr>
<tr>
<td>Frequent binge</td>
<td>214 (61)</td>
<td>51 (24)</td>
<td>30 ± 10</td>
<td>120 ± 110</td>
<td>124 (58)</td>
<td>16±15 / 27±20</td>
</tr>
<tr>
<td>drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infrequent binge</td>
<td>59 (17)</td>
<td>25 (42)</td>
<td>33 ± 10</td>
<td>20 ± 70</td>
<td>5 (8)</td>
<td>6±3 / 6±6</td>
</tr>
<tr>
<td>drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light-to-moderate</td>
<td>28 (8)</td>
<td>14 (50)</td>
<td>31 ± 12</td>
<td>0 ± 10</td>
<td>1 (4)</td>
<td>2±1 / 4±4</td>
</tr>
<tr>
<td>drinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>22 (6)</td>
<td>7 (32)</td>
<td>30 ± 12</td>
<td>0</td>
<td>0</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>

BAC, blood alcohol concentration. † Men only

Dependent drinking and frequent binge drinking were found to be common patterns among the head trauma patients (Table 6), in whom they occurred significantly more often than in those with other types of trauma (77% versus 59%, RR, 2.38; 95% CI, 1.50 to 3.77).

Fifty-one per cent of all the patients had alcohol in their blood on admission and most of the intoxicated subjects (86%) had reached a level of 100 mg/dL. When the patients were classified according to the type of trauma, the incidence of elevated BAC was significantly higher in the head trauma patients than in those with other types (65% versus 32%, RR, 3.92; 95% CI, 2.55 to 6.03). The relative risk of sustaining a traumatic head
injury increased sharply with increasing BAC, being significantly higher than that for other types of trauma above the level of 150 mg/dL (Figure 4). The RRs were as follows: 0 mg/dL (0.51; 95% CI 0.42–0.63), 1–99 mg/dL (0.67; 95% CI 0.32–1.38), 100–149 mg/dL (0.84; 95% CI 0.40–1.76), 150–199 mg/dL (1.71; 95% CI 0.93–3.17) and > 199 mg/dL (4.87; 95% CI 2.82–8.40).

Table 6. Drinking patterns of the trauma patients interviewed (n=349), by type of trauma.

<table>
<thead>
<tr>
<th>Pattern of drinking</th>
<th>All N=349</th>
<th>Head trauma N=192</th>
<th>Other trauma N=157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent drinkers</td>
<td>26 (8%)</td>
<td>24 (12%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Frequent binge drinkers</td>
<td>214 (61%)</td>
<td>124 (65%)</td>
<td>90 (57%)</td>
</tr>
<tr>
<td>Infrequent binge drinkers</td>
<td>59 (17%)</td>
<td>27 (14%)</td>
<td>32 (21%)</td>
</tr>
<tr>
<td>Light-to-moderate drinkers</td>
<td>28 (8%)</td>
<td>8 (4%)</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>22 (6%)</td>
<td>9 (5%)</td>
<td>13 (8%)</td>
</tr>
</tbody>
</table>

Fig. 4. Crude relative risks for head injury at various level of blood alcohol concentration (BAC). Above the level of 150 mg/dL, the risk for head injury was greater than the risk for other types of injury. The bars indicate the 95% confidence intervals at different BACs, and if the bar does not cross the level one, it is statistically significant.

The main causes of trauma under the influence of alcohol were assaults, falls on the ground and biking accidents, so that these together accounted for 68% (135/198) of all the trauma patients who had alcohol in their blood. Ninety-four per cent of the assault victims were BAC-positive on admission and most of their traumas (92%) were head injuries (III; Table 3). The patients injured in falls on the ground and biking accidents also frequently had alcohol in their blood, 60% and 61%, respectively. The BAC-positive subjects sustained head traumas significantly more often both in falls on the ground (RR, 3.50; 95% CI, 1.32 to 9.26) and bicycling injuries (RR, 8.26; 95% CI, 1.48 to 45.45) than
their sober counterparts (III; Table 3), but the BAC-negative bicyclists had injuries to their extremities (50%, 9/18) significantly more often than the BAC-positive ones (7%, 2/28) (RR, 12.99; 95% CI, 2.35 to 71.43).

5.4 Laboratory markers of hazardous alcohol drinking in trauma patients (paper IV)

Sixty-nine per cent (240/349) of the trauma patients interviewed reported hazardous alcohol drinking (i.e. they were dependent drinkers or frequent binge drinkers). BAC (blood/breath alcohol) proved to be the most sensitive marker of hazardous drinking and a highly specific one (Table 7), so that 137 (57%) of the hazardous alcohol drinkers had a reading above 100 mg/dL. When a cut-off level of > 0 mg/dL was used, the sensitivity for identifying hazardous drinkers increased to 68% (95% CI, 61 to 73%) with a positive predictive value of 96% (95% CI, 92 to 98%). Thus, 96% of the BAC-positive trauma patients proved to be hazardous alcohol drinkers.

We further analysed the usefulness of various combinations of biochemical markers. BAC (>0 mg/dL) together with CDT was the most sensitive combination, correctly identifying 73% of the target population, but even though both CDT and GGT slightly improved the sensitivity when combined with BAC, the additional effect did not reach significance.

Table 7. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) of markers of alcohol consumption for detecting hazardous alcohol drinking (including dependent drinkers and frequent binge drinkers) among the trauma patients (n=349). Table modified from paper IV.

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAC &gt;0 mg/dL, (95% CI)</td>
<td>68% (61 to 73%)</td>
<td>94% (87 to 97%)</td>
<td>96% (92 to 98%)</td>
<td>57% (49 to 64%)</td>
</tr>
<tr>
<td>BAC &gt;100mg/dL</td>
<td>57% (51 to 63%)</td>
<td>94% (89 to 98%)</td>
<td>96% (91 to 98%)</td>
<td>50% (43 to 57%)</td>
</tr>
<tr>
<td>GGT</td>
<td>11% (8 to 16%)</td>
<td>97% (92 to 99%)</td>
<td>90% (74 to 97%)</td>
<td>33% (28 to 39%)</td>
</tr>
<tr>
<td>MCV</td>
<td>18% (13 to 24%)</td>
<td>94% (88 to 98%)</td>
<td>88% (75 to 95%)</td>
<td>34% (28 to 40%)</td>
</tr>
<tr>
<td>CDT</td>
<td>33% (28 to 40%)</td>
<td>88% (81 to 93%)</td>
<td>86% (78 to 92%)</td>
<td>38% (32 to 44%)</td>
</tr>
<tr>
<td>AST</td>
<td>17% (13 to 22%)</td>
<td>94% (89 to 98%)</td>
<td>87% (74 to 94%)</td>
<td>34% (29 to 40%)</td>
</tr>
</tbody>
</table>

BAC = blood alcohol concentration (100 mg/dL = 22 mmol/L); cut-off values: CDT (20/26 U/L, men/women), GGT (80/50 U/L, men/women), AST (50/35 U/L, men/women), MCV (96 fl, men and women). MCV was measured for 288 (83%) of the patients interviewed (n = 349).
6 Discussion

6.1 PCSs in patients with mild head injury

The reported incidence rates of PCSs in patients with MHI vary widely, but a significant minority, approximately 7–15%, may have persistent symptoms lasting more than a year after trauma (Alexander 1995, Binder 1997). In our series, 22% of the MHI patients had PCSs one month after the trauma, and if those with intracranial lesions visible in CT are excluded, the corresponding figure is 20%.

Skull or facial bone fracture, elevated serum protein S100B (≥ 0.50 µg/L), dizziness and headache on admission were found to be independent predictors of PCSs in the MHI patients. Elevated serum protein S100B was a significant predictor even when the patients with intracranial lesions verified by a head CT scan were excluded. The association between elevated protein S100B serum concentrations on admission shortly after head injury and PCSs strongly suggests an organic aetiology for PCSs. Serum S100B was elevated on admission in 27% of the MHI patients who developed PCSs, but only in 7% of those who did not.

Previous studies have also observed an association between elevated S100B and PCSs among MHI patients (Ingebritsen et al. 2000b, de Kruijk et al. 2002a), but the association was even more distinct in the present case, possibly because we had a rather low proportion of PCSs patients (22%). Ingebrigtsen et al. (2000b) identified a relatively high proportion of PCSs among MHI patients (62%), but their timing and methods of interview differed from ours. In a recent study, de Kruijk et al. (2002a) found that elevated S100B and NSE values on admission predicted more severe PCSs at six months post injury, and those who had headache, dizziness, or nausea shortly on admission also reported more severe PCSs (de Kruijk et al. 2002a). Our results are in good accordance with these findings, since we also found headache and dizziness on admission to predict the development of PCSs, although we also found skull or facial bone fracture to be an independent and important risk factor for PCSs.

Our results do not support the notion of an association between heavy alcohol drinking or illicit drug use and PCSs, although it has been suggested that alcohol misuse could play a role in their development (Lishman 1988), neither did we find significant associa-
tions between other possible risk factors such as gender, prior disease, and factors predisposing to malingering (insurance, unemployment, etc.) and PCSs. Litigation is also often thought to be a risk factor for PCSs (Bernstein 1999, Mickeviciene et al. 2002), but our findings do not support this hypothesis, although they do not exclude the possibility that litigation may exacerbate the symptoms.

6.2 Protein S100B as a marker of brain damage

Serum protein S100B has recently been an object of increasing attention in the identification of brain damage because of its high brain tissue specificity. Its clinical utility with head trauma patients has not yet been fully elucidated, however.

Acute traumatic brain injury has been found to cause a leakage of S100B into the serum (Ingebrigtsen et al. 1999, Raabe et al. 1999b, II), and the severity of brain injury has been found to correlate positively with S100B values, the highest levels being reported in patients with moderate-to-severe injuries (Raabe et al. 1999b, Romner et al. 2000, II). Brain lesions found in head CT scans have also been shown to be associated with elevated S100B (Raabe et al. 1999b, Ingebrigtsen et al. 2000b). Romner et al. (2000), studying 278 acute head injury patients with minor, moderate and severe injuries, found that S100B was elevated (>0.20 µg/L) in 92% of those with intracranial lesions in their head CT scans and 34% of those without. In fact, serum S100B with a cut-off of 0.20 µg/L was extremely good at excluding intracranial pathology visible in a head CT scan, since its negative predictive value was as high as 99%.

A positive correlation has also been reported between elevated S100B values and poor recovery in patients with head injury (Raabe et al. 1999a, Woertgen et al. 1999, Townend et al. 2002). Townend et al. (2002) studied 119 such patients (with an initial GCS score of 4–15) and found that a serum S100B concentration of > 0.32 µg/L predicted severe disability (extended GOS < 5) at one month after trauma with a sensitivity of 93%, a specificity of 72%, and a negative predictive value of 99%. Thus, patients with a concentration of S100B > 0.32 µg/L and poor recovery at one month post injury must be extremely rare.

S100B levels have been shown to be elevated in 20–42% of patients with MHI (Ingebrigtsen et al. 2000b, de Kruijk et al. 2001c, de Kruijk et al. 2002a, I, II). In addition, a poor neuropsychological outcome has been reported to be associated with increased S100B concentrations in MHI patients (Waterloo et al. 1997, Herrman et al. 2001), and S100B levels have been shown to be higher in patients who will develop PCSs than in those who will not (Ingebrigtsen et al. 2000b, de Kruijk et al. 2002a). Furthermore, we showed in paper I that S100B was an independent and good predictor of PCSs. When a cut-off value of 0.50 µg/L was used, the sensitivity, specificity and negative predictive value for PCSs were 27%, 93% and 82%, respectively, while if a lower cut-off value (0.20 µg/L) was used, the corresponding figures were 68%, 67% and 88%. The MHI patients with S100B values of < 0.20 µg/L shortly after trauma rarely developed PCSs.

One of our objectives was to study the effects of extracranial injuries on S100B levels in serum (II). We showed that not only brain damage but also extracranial injuries, includ-
ing small ones, increased serum S100B values in patients with multitrauma, although only large extracranial injuries elevated S100B values significantly, as reported by others (Andersson et al. 2001). Although small extracranial injuries (i.e. wounds, soft tissue con-
tusions, distensions, luxations and small fractures) also increased serum S100B values, the effect was not found to be clinically significant (II). Thus it is evident that extracranial injuries cause some false positive findings related to S100B, at least if a large extracra-
nial injury is present. However, normal S100B values (< 0.20 µg/L) predict the absence of intracranial damage and good recovery after trauma with a high accuracy. Thus, S100B can be used as a marker to exclude intracranial pathology (Romner et al. 2000), poor out-
come (Townend et al. 2002) and the development of PCSs (I) in patients with head trauma.

6.3 Alcohol and trauma

6.3.1 Hazardous alcohol drinking in patients with trauma

There is no doubt that alcohol and injuries are closely linked to each other. Approximate-
ly one half of all trauma patients are BAC-positive on admission, and more than a third have a BAC at or above 100mg/dL (Rivara et al. 1993a, III). The proportion of BAC-pos-
itive cases among patients with head injury has been found to be over 50%, and the pro-
portion of those with a BAC at or above 100mg/dL has been shown to vary from 35 to 40% (Rimel et al. 1982, Brismar et al. 1983, Corrigan 1995, Dikmen et al. 1995, III).

The methods used to detect heavy alcohol drinking and alcoholism in previous studies of trauma patients have varied greatly (Corrigan 1995, Nilssen et al. 1994), the lowest incidences, 16% (Rimel et al. 1982), 25% (Sparadeo & Gill 1989) and 36% (Wong et al. 1993), having been found in studies where the assessments were based on retrospective chart reviews, while the highest ones, 66% (Kreutzer et al. 1991) and 58% (Kreutzer et al. 1990), have been reported from rehabilitation centres. Nilssen et al. (1994) reported an approximately 45% incidence of alcohol abuse in trauma patients based on screening with the CAGE and SMAST questionnaires.

We found that binge-type drinking was the predominant pattern among the trauma patients. Patterns of alcohol consumption have so far not received much attention. We fur-
ther showed, however, that a total of two-thirds of our trauma patients reported hazardous drinking (i.e. they were dependent drinkers or frequent binge drinkers), and hazardous drinking was found to be more frequent in the patients with head injury that in those with other types of trauma (III).

The high prevalence of binge drinkers among trauma patients is alarming. It suggests that more attempts should be made to reduce this type of drinking. If alcohol consumption is assessed in terms of grammes of ethanol consumed per day, most binge drinkers will be classified as moderate drinkers and not as hazardous ones (Naimi et al. 2003), but it is precisely this pattern of binge drinking that is closely associated with alcohol-impaired driving (Liu et al. 1997), and there is growing evidence that the social, health and eco-
nomic costs of acute alcohol-related problems may even exceed those arising from the chronic effects (CDC 1993, Chikritzhs et al. 1993). The highest prevalence of binge drinking has been found among young adults, but it is also a frequent and favoured drinking pattern among adolescents (American Academy of Pediatrics Committee on Substance Abuse 1995, Naimi et al. 2003). Binge drinking is an increasing problem worldwide (Mäkelä et al. 2001, Naimi et al. 2003), and the present findings suggest that it is a substantial, and growing medical hazard, and that more interventions should be employed in attempts to prevent it.

Fleming et al. (1997) found that brief advice from a physician reduced binge drinking by approximately 40% in a randomised controlled trial, and the reduction was found to last for at least 12 months. Thus, if alcohol interventions are to be used, they should be focused on this group, because most of them are young adults and not heavy drinkers, and therefore the intervention could come before the patients have reached a stage of severe alcohol dependence.

6.3.2 Alcohol as a risk factor for head trauma

Previous reports have emphasized the high prevalence of alcohol intoxication among trauma patients, but not the high frequency of binge drinkers. Our data emphasise the adverse consequences of binge drinking, which may cause severe intoxication in individuals who are not regular drinkers and who do not have increased alcohol tolerance. Thus the more frequent binge drinking is, the greater is the risk of trauma. Accordingly, the lower incidence of trauma observed here in infrequent binge drinkers than in frequent ones is apparently due to their fewer occasions of alcohol intoxication (III). Where Mäkelä et al. (2001) found that the mean frequency of binge drinking in Finland was approximately 11 times a year, 61% of all our trauma patients reported at least 12 such episodes a year prior to injury. The high binge drinking rate among trauma patients supports the view that this type of drinking is a more significant risk factor for trauma than has been previously acknowledged.

We showed that the risk of sustaining a head trauma increased as a function of increasing blood alcohol level, and significantly so above the level of 1.5‰ (III). The most common causes of injury among the BAC-positive patients were assaults, falls on the ground and bicycling injuries. Alcohol is likely to cause deleterious effects on psychomotor skills and the preventive mechanisms to respond to situational hazards which, in turn, may favour the occurrence of head trauma. Consistently, BAC-positive patients injured by falls on the ground or in bicycling accidents injured their head significantly more often than did their sober counterparts (III). In contrast, sober bicyclists more often avoided head trauma and injured their extremities (III).

McLeod et al. (1999) reported that consuming more than 60 grammes of alcohol in a 6-hour period conferred an odds ratio of 3.4 (95% CI 1.8 to 6.4) for sustaining an injury in general, and increased risks of more severe injuries under the influence of alcohol have also been found in certain specific traumas such as bicycling injuries (Ollkonen & Honkanen 1990, Li et al. 2001), motor vehicle crashes (Waller et al. 1986), motor vehicle-

6.3.3 Identification of alcohol misuse in patients with trauma

A positive effect of a brief alcohol intervention as a means of reducing alcohol intake and the adverse health effects has been reported in several studies (Walsh et al. 1991, Fleming et al. 1997, Gentilello et al. 1999, Dinh-Zarr et al. 2000), but there still continues to be a lack of attention to hazardous alcohol drinking in accident and emergency departments (Soderstrom & Cowley 1987, Charalambous 2002). One apparent reason for this is that hazardous drinkers usually remain unrecognised by the clinicians. A simple and inexpensive method for the early identification of hazardous drinkers would thus be of the utmost importance.

Ryb et al. (1999) reported that the BAC test is the best detector of alcohol dependence in trauma patients, while GGT, AST and MCV are of little value as screening tests. We also found that the conventional biochemical markers (GGT, MCV, CDT, and AST) lacked sensitivity and specificity, especially for detecting binge drinkers, but were of the opinion that the BAC test, performed either on exhaled air or on a blood sample, is the best method of detecting hazardous alcohol drinking (i.e. dependent drinking and frequent binge drinking) among trauma patients (IV). BAC not only identifies acute alcohol drinking but also provides a good estimate of chronic patterns of hazardous drinking. BAC (\(> 0 \text{mg/dL}\)) on admission was found to be a sensitive (68%) and specific (94%) marker of hazardous drinking, and 96% of all the BAC-positive trauma patients turned out to be hazardous drinkers. Thus, the BAC test can be recommended as a primary screening tool to guide patients for alcohol interventions without subjecting them to an unacceptable degree of stigma as problem drinkers and before they have reached a stage of severe dependence.

6.4 Strengths and weaknesses

The material was collected from the emergency department of a hospital which is the only trauma centre for Oulu, a city with approximately 120,000 inhabitants. The patients were recruited consecutively seven days a week and 24 hours a day, but with certain exclusion criteria applied.

Firstly, patients representing the age range 16–49 were recruited. This was done, because the highest rates of morbidity, mortality and persistent functional and psychological impairment due to trauma are known to occur in this group. Secondly, many common diseases such as cardiovascular and neurological diseases are frequent in the elderly, and little is known about their effect on S100B levels. Additionally, life-style factors such as alcohol drinking habits are likely to differ between our material and cases of children or elderly people, and as our material includes acute trauma patients, the results of series derived from out-patient clinics may differ from ours.
The interviews were always performed by the same person. The first interview to place face to face, and the second, which occurred 8 to 30 months post injury was a telephone interview aimed at ensuring that the PCSs had lasted long enough to fulfil our criteria (i.e. one month post injury). The long interval between trauma and the interview may have caused underestimation of certain symptoms, particularly impairment of cognitive functions.

Of the 385 patients, 349 (91%) were interviewed within 2–6 weeks of the trauma (including alcohol data) and PCSs data was collected from 86% of the MHI patients (172/199). Thus, the percentage of patients who were interviewed was high, higher than in many other studies concerning PCSs or alcohol drinking (Ingebrigtsen et al. 1998, Ryb et al. 1999, Ingebrigtsen et al. 2000b).

In conclusion, the material represents a good spectrum of consecutive Finnish trauma patients in a general hospital, excluding children and elderly people. Because the results concerning protein S100B and the alcohol literature from other countries is quite comparable to ours in this respect, it can be assumed that the results can also be generalised worldwide.
7 Conclusions

1. PCSs often complicate recovery after mild head injury. Skull or facial bone fractures, elevated serum protein S100B and headache or dizziness on admission are associated with an increased risk of developing PCSs. These simple criteria may help the physician on duty to identify patients for counselling and follow-up.

2. Serum protein S100B is a feasible supplementary method for detecting traumatic brain damage. In particular, normal levels of S100B after head injury predict normal head CT scan findings, good overall recovery and the absence of PCSs in the follow-up.

3. In addition to brain injury, extracranial injuries also increase serum S100B levels and may cause false-positive findings. S100B is not a specific marker of brain injury.

4. Alcohol intoxication indicative of hazardous alcohol drinking (i.e. dependent drinking and frequent binge drinking) is a common finding in trauma patients, and more common in head injury patients than in those with other types of trauma. Binge drinking is the predominant pattern of alcohol drinking in trauma patients, and particularly in head trauma patients.

5. The risk of sustaining a head injury significantly increases with increasing BAC, and is significant if BAC exceeds 150 mg/dL.

6. Hazardous alcohol drinkers, i.e. dependent drinkers and frequent binge drinkers, can best be identified by means of a BAC test on admission. The conventional laboratory markers of alcohol consumption such as CDT, GGT, AST, or MCV do not offer any significant benefit in patients with trauma.

7. BAC should be measured, either from exhaled air or blood, in the case of all the trauma patients on admission. If there is an option for brief alcohol intervention, all BAC-positives should be guided for such counselling.

8. The results point to the usefulness of the BAC test as a marker of alcohol misuse and protein S100B as a marker of brain damage in patients with trauma.
References


