CLINICAL ASPECTS OF PEDIATRIC HEAD INJURY

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An idea not coupled with action will never get any bigger
than the brain cell it occupied
~Arnold H. Glasgow

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List of Papers

This thesis is based upon the following papers, referred to in the text as Paper I-IV:

I. Astrand R, Unden J, Bellner J and Romner B. Survey of the management of children with minor head injuries in Sweden. Acta Neurol Scand. 2006;113:262-266.

II. Astrand R, Unden J, Hesselgard K, Reinstrup P and Romner B. Clinical factors associated with intracranial complications after pediatric traumatic head injury: an observational study of children submitted to a neurosurgical referral unit. Pediatric Neurosurgery. 2010;46:101-109

III. Astrand R, Unden J, Reinstrup P, Lidén A, Friis-Hansen L, Romner B. Comparison between capillary, venous and arterial levels of protein S100B in severe brain pathology. *In manuscript.*

IV. Astrand R, Romner B, Lanke J, Unden J. Age and gender specific reference values for venous and capillary S100B in children. *Submitted.*

Abbreviations

BBB	Blood brain barrier	CBF	Cerebral blood flow
CK-BB	Creatine kinase, isotype BB	CNS	Central nervous system
CPP	Cerebral perfusion pressure	CSF	Cerebrospinal fluid
CT	Computed tomography	DAI	Diffuse axonal injury
ED/ER	Emergency department/room	EDH	Epidural hematoma
EVD	External ventricular drain	GCS	Glasgow coma scale
GFAP	Glial fibrillary acidic protein	GOS	Glasgow outcome scale
HISS	Head Injury Severity Scale	ICH	Intracerebral hematoma
ICI	Intracranial injury	ICP	Intracranial pressure
ICU	Intensive care unit	LOC	Loss of consciousness
MAP	Mean arterial pressure	MBP	Myelin basic protein
MHI	Minor/mild head injury	MRI	Magnetic resonance imaging
NAHI	Non-accidental head injury	NICU	Neurointensive care unit
NF (L, M, H)	Neurofilament (low, medium, high)	NSE	Neuron specific enolase
PCS	Postconcussion syndrome	RLS	Reaction level scale
SAH	Subarachnoid hemorrhage	tSAH	traumatic SAH
SBI	Shaken baby impact	SBS	Shaken baby syndrome
SDH	Subdural hematoma	SHI	Severe head injury
TBI	Traumatic brain injury	iTBI	inflicted traumatic brain injury

AAP	American Association of Pediatrics
CCHR	Canadian Head CT Rule
CHALICE	Children’s head injury algorithm for the prediction of important clinical events
CHIP	CT in Head Injury Patients
EFNS	European Federation of Neurological Societies
NEXUS-II	National Emergency X-Radiography Utilization Study II
NICE	National Institute of Clinical Excellence
NOC	New Orleans Criteria
OCTOPUS study	Observation or Computed Tomography of Mild Head Injury in Sweden
PECARN	Pediatric Emergency Care Applied Research Network
RCS	Royal College of Surgeons
SNC	Scandinavian Neurotrauma Committee

Abstract

Traumatic head injury is one of the leading causes to severe morbidity and death among children. Specific and national management guidelines for pediatric head injuries are lacking in Sweden, and management routines are consequently based on adult guidelines or local guidelines. The objectives of this thesis were to investigate the current management of pediatric head injury in Sweden and to explore the possibility of introducing a brain injury marker, protein S100B, for optimizing pediatric head injury management.

Paper I, a survey in 51 Swedish hospitals, shows that the management routines vary from hospital to hospital, especially concerning criteria for computed tomography, admission, and discharge. The children are initially managed by general surgeons and pediatricians, although several other departments are involved after the admission of the child. Less than one third of the hospitals reported the use of a standardized observation scheme. The study concludes the urgent need for standardized and updated routines for pediatric head injury management. Paper II shows that children admitted to a neurosurgical unit after head injury do well. However, pediatric head injury management based solely on adult guidelines, loss of consciousness or amnesia is not reliable, since there is a non-negligible risk of missing a clinically relevant intracranial hematoma.

Before a serum marker can be properly evaluated in clinical trials, there is a need for knowing the reference levels of the marker. Capillary sampling in young children is sometimes easier and less painful and time consuming than venous sampling. In Paper III simultaneous capillary, venous and arterial samples were drawn and compared. The results show that analysis of capillary S100B is possible, but differ from venous concentrations by an average of 0.08 µg/L, while arterial and venous samples can be considered nearly equal. Hence, separate reference levels for capillary and venous S100B are required. Paper IV therefore investigates both capillary and venous reference values for S100B in 465 neurologically healthy children. Pediatric S100B reference levels are age-related and higher than those set for adults (venous S100B: 0.14 µg/L for 3-16 year old vs. 0.10 µg/L for adults), while capillary S100B for 3-16 year old is 0.40 µg/L. These reference levels should be used in the evaluation of future studies.

Introduction

Traumatic brain injury (TBI) is commonly used as synonym to head injury, acquired brain injury and brain injury. It is a common occurrence in the pediatric population and accounts for the largest cause of acquired disability in childhood. The field of pediatric head injury is broad and versatile. Recommendations and opinions are deviating and proposed management regimes are not always optimal or easily applied.

This thesis will try to summarize some of the basic facts, present the research performed, discuss the challenges in the management of pediatric head injuries and introduce other possible methods of optimizing current management routines.

Classifications of head injury

To estimate the severity of brain injury after head trauma, various classification systems of head injury have been proposed and modified throughout the years; particularly the definition of minor head injury. Most of them are, however, based on the patients' level of consciousness according to Glasgow Coma Score (GCS).[1]

In 1981 Rimel and colleagues defined minor head injury as a head trauma with patient's GCS score of 13-15 at admission, loss of consciousness (LOC) less than 20 minutes and a duration of hospital admission less than 48 hours.[2] About a decade later Stein and Spettell introduced a modified classification system; the Head Injury Severity Scale (HISS) which is a five-interval severity scale (minimal through critical) based primarily on initial GCS score. The HISS scale also include the aspects of retrograde amnesia, loss of consciousness and focal neurological deficits for each severity interval.[3]

In 2000, the Scandinavian Neurotrauma Committee (SNC) presented guidelines for management of adult head injury[4] using a modified version of the HISS classification. SNC classified head injuries into minimal, mild, moderate and severe. Minimal head injury is defined as a patient with GCS 15 at admission and with no LOC or focal neurological deficits. Mild head injury is defined as initial GCS of 14 to15, brief LOC (< 5 min) and no focal neurological deficits. The definition of moderate head injury defines patients with initial GCS of 9-13 and/or focal neurological deficits or LOC > 5 min after head trauma, while severe head injury includes all patients with a GCS score of 8 or below.

Scales

Immediate triage and assessment of the severity and probable survival of the traumatized patient are made whenever possible already at the scene of the injury. A useful help are the trauma assessment scores that have been developed and that are easily used and understood.

Glasgow Coma Scale

The Glasgow coma scale (GCS) has been the most valuable and frequently used scoring system for assessing the severity of neurologic injury after head trauma. It was initially designed by Teasdale and Jennett for assessment of the comatose patient.[1] The scale is divided in three parts: eye response, verbal response and motor response, each part with a score range from 1-4, 1-5 and 1-6 respectively. The total score of all three parts adds to a sum between 3 to 15 points.

The GCS scale has, however, been considered difficult to apply on especially preverbal children[5] since their ability to express themselves verbally or non-verbally in a consistent manner are limited. Reilly et al were the first to design the pediatric version of the GCS, where verbal responses were reported as appropriate words or social smiles, cries, irritability and agitation.[6, 7] Some modifications of the scale have been made to suit even the youngest children and infants. The pediatric GCS scale has been proven to be accurate in evaluating preverbal children with head trauma with regards to the need for acute intervention.[8] A combined standard GCS score and pediatric version is presented below.

Swedish Reaction Level Scale

In Sweden, the most practiced scale for assessment of the level of consciousness is the Swedish Reaction Level Scale 85 (RLS).[9-11] This scale evaluates the consciousness in an inverted manner to the GCS, with a scoring range from 1 (best) to 8 (worst). It excludes the specific focus on the verbal response, which makes the score more practical to use, particularly in neurologically traumatized patients (who also may suffer from aphasia) or children, and is more easily remembered in acute situations.

Glasgow Coma scale

Score	Standard GCS	Pediatric version	
		1-4 years	**< 1 year**
	Eye opening		
4	Spontaneous	Open	
3	To speech	To voice	
2	To pain	To pain	
1	None	No response	
	Verbal response		
5	Orientated	Oriented, speaks, Interacts	Coos, babbles
4	Confused conversation	Confused speech, consolable	Irritable cry, consolable
3	Words (inappropriate)	Inappropriate words, inconsolable	Persistent cry, inconsolable
2	Sounds (incomprehensible)	Incomprehensible, Agitated	Moans to pain
1	None	No response	No response
	Best Motor response		
6	Obey commands	Normal spontaneous movement	
5	Localizes pain	Localizes pain	
4	Flexion, withdraws to pain	Withdraws to pain	
3	Flexion, abnormal to pain	Decorticate flexion	
2	Extension (to pain)	Decerebrate extension	
1	No response	No response	
3-15	TOTAL SCORE		

Swedish Reaction Level Scale

RLS	Score
Fully awake. Oriented	1
Lethargic. Confused. Contact after mild stimuli	2
Stupor. Confused. Contact after rough stimuli or pain	3
Unconscious. Localizes to pain	4
Unconscious. Withdraws to pain	5
Unconscious. Abnormal flexion to pain	6
Unconscious. Abnormal extension to pain	7
No response to painful central stimuli	8

Epidemiology

Incidence

The incidence of TBI has been estimated to 200-300/100000/year in the western world, the highest incidence in the ages 10-29 years (567/100000/year) and the lowest for children younger than 5 years (117/100000/year).[12] Head injury rates are slightly higher in males than females.[12] The majority of patients are so called minor head injured patients (80%), while the more severely head injured account for 5-10 percent.

Children with suspected head injuries are a common sight at the emergency departments, accounting for about 40 percent of the attendants with suspected head injury. The majority of them (90%) has a mild head trauma, while the rest are moderately and severely head injured children.[13] In Sweden about 17000 patients annually seek emergency care due to head injury.[14, 15] Of these, 7200 are children admitted for observation due to suspected brain injury.[16]

Mortality

TBI is one of the leading causes to morbidity and mortality in the western world[17] and the major cause of death under the age of 45.[18] Most trauma victims die without reaching assistance (87%)[19] and up to 65% of patients with a traumatic brain injury die before reaching a hospital.[12] According to Health Statistics in the Nordic countries (2007) death from accidents range from 26 to 79 per 100000 inhabitants.[20] Estimated death rates for TBI per 100000 are 11.5 for Denmark, 21.2 for Finland, 10.4 for Norway and 9.5 for Sweden.[17]

According to a former epidemiological study on severe pediatric TBI in Sweden, the mortality rate was significantly lower than compared with northern England or Switzerland (2.6 vs. 5-6.8/100000).[21] The overall mortality due to head injury has been reported to be about 2% or less,[22] though the mortality for children with severe head injuries are higher (above 20%),[21, 23] especially among the youngest ones.[24]

Morbidity and outcome

Morbidity rates are high among the moderately and severely brain injured patients. About 20% end up with severe disabilities or even a vegetative state (4%). Favorable outcome is estimated to 40-50%.[23, 25] The pediatric patients have been reported to have a higher percentage of good outcomes and lower mortality rates compared to adult patients,[26] however less so for younger children.[27] Outcome is assessed according to a few standard scales, the Glasgow Outcome Scale (GOS)[28] being one of the most commonly used (as shown below). Rehabilitation of both motor and cognitive skills are required and even if some patients fully recover in their neurological functions many still suffer from memory problems, psychological and social problems. This results in difficulties of resuming a normal social life.[29]

Glasgow Outcome Scale

Score		Description
5	Good outcome	Resumption of normal life; there may be minor neurological/psychological deficits.
4	Moderately disabled	Able to work in sheltered environment and travel by public transportation
3	Severely disabled	Dependent for daily support due to mental or physical Disabilities
2	Vegetative state	Persistently unresponsive and speechless
1	Death	

Even the mildly head injured patients may suffer from longer lasting (> 3 months) symptoms such as persistent headache, memory and concentration problems, fatigue, dizziness or blurred vision.[30, 31] These symptoms or other neurobehavioral sequelae are described in 15-50% of the adult population after 1 year following mild head injury.[32] Concerns about similar problems with persistent physical, psychological and cognitive impairment among the pediatric population have been addressed. However, there is still a considerable controversy regarding the so called postconcussion syndrome (PCS) in children after MHI.[33-36]

Mittenberg et al have studied postconcussive symptoms in children with mild and moderate-severe TBI and compared them to children with orthopedic injuries. The autors found significantly more symptoms in the TBI group. At 6 weeks post MHI there were considerably more symptomatic children than adults, which was quite the opposite of what had previously been found. The authors stated therefore that postconcussion syndrome exists in children.[33] Others state that the occurrence of postconcussive symptoms after MHI in children reflects a combination of outer factors; premorbid vulnerability, family adjustment, post-injury adjustment of the child, and changes in brain function.[37]

Another study found that about 14% of school-aged children were symptomatic after 3 months post head-injury, and a study by Barlow and colleagues found that 11% of the children were symptomatic after 3 months post head injury, compared to 0.5% of pediatric patients with only external injuries.[38, 39]

Mechanism of injury

The etiology of pediatric TBI varies with age. Accidental trauma is most common in all age groups. Non-accidental trauma usually occurs in the younger age groups; the majority of inflicted TBI occurs in infants younger than 1 year of age.

Traffic accidents, especially those involving motor vehicles and high-energy trauma, are large contributors of severe injuries and deaths.[21] Children are commonly injured by being struck by a motor vehicle either as pedestrians or bicyclers, or injured in motorcycle accidents which often are considered as high-energy trauma.[40, 41] Falls are more common

among the younger (< 2 years) and older population.[18] Fall from lower height (< 1 m) or from stairs are common among younger children. High-energy trauma falls are commonly defined as falling from a height of 3 m or more. This has been linked to a higher mortality rate.[42] Sports and leisure related head injury and concussion are often associated with football and ice-hockey playing among older children.[43, 44]

Child abuse and inflicted traumatic brain injury (iTBI) can be difficult to detect. Many different definitions have been used for describing the occurrence of brain injury and mechanisms by which the harm is done by e.g. non-accidental head injury (NAHI), inflicted childhood neurotrauma, shaken-baby-syndrome (SBS), shaken baby impact (SBI), inflicted TBI, or battered child.[45] Brain injuries are often related to direct blows to the head, whereas only a minority of iTBI is caused by violent shaking.[46] Subdural hematoma is the most common type of intracranial injury, particularly among infants, and followed by subarachnoid hemorrhage, diffuse axonal injuries (DAI) and cerebral contusions, but even cerebral edema and infarcts as a result of anoxia/hypoxia.[45, 47-49] Reports of outcome for iTBI children seem to show a less favorable outcome. According to an Australian study, 29% of the iTBI children had a favorable outcome while 6% died and 64% survived with a severe outcome.[47] Another study by Bonnier et al showed similarly that 61% ended up with severe disabilities, while 35% had moderate disabilities. Only 1 child was normal at follow-up.[50]

The true number of children with iTBI is difficult to determine, but the incidence of serious or fatal iTBI has been estimated to be as high as 30–40 per 100000/year among children younger than 1 year of age.[51-53] According to a former American study, the majority of children with iTBI (85%) are younger than 2 years. The incidence of abusive head injury in the pediatric population in Sweden is today unknown. However, according to a retrospective study by Tingberg et al less than 0.2% of the head injured children were further investigated for child abuse, indicating a very low figure of iTBI compared to other studies. When medical attention is sought, clinical symptoms presented might be acute and often combined with a decreased level of consciousness/encephalopathy, seizures, apnea, external bruising over the head and face, retinal hemorrhages or skeletal or skull fractures.[45] Indicators of suspected child abuse are: a history of injury inconsistent with the clinical presentation (e.g. fall from low height), delay in seeking medical attention, a changing history of injury and radiological evidence of head injury.

Primary and secondary brain injury

Primary brain injury refers to the immediate brain damage caused upon impact. This includes cerebral contusions, shearing lesions (diffuse axonal injuries), lacerations from a foreign body, acute subdural and epidural hematomas. The occurrence of primary brain injuries can only be influenced by preventive measures, such as increased helmet use during bicycling or motorcycle driving.

Secondary brain injury refers to progressive cerebral edema, which is more commonly seen in children, cerebral ischemia, expansion of cerebral contusions and the surrounding

focal edema which can cause an increase in intracranial pressure (ICP) within the confined skull. This can eventually lead to cerebral herniation and death.

The risk of developing an intracranial lesion after mild head injury is low, but not negligible, and the effect of an intracranial hematoma can be detrimental. Former studies have found a prevalence of 1.2 - 14% for intracranial injuries after pediatric MHI,[54-58] and up to 36% after severe head injury.[59]

Risk factors and clinical symptoms

There are various factors based on the type of trauma, clinical symptoms and neurological findings, which upon management rely. Evaluation of life-threatening signs, such as altered level of consciousness, pupillary dysfunction (size, shape, reactivity to light), Cushing's syndrome (hypertension and bradycardia) and a bulging fontanel in infants, is vital and these symptoms may be signs of increased ICP and herniation.

Differentiation of the risk factors in a conscious patient is more challenging since more than 90% of children seen in the emergency department after head injury belong to this group. LOC and the duration of loss of consciousness are not always easy to assess in children and infants. Although the overall risk of intracranial hematoma after head trauma is considered to be lower in children, the risk within the different levels of consciousness have been demonstrated being the same as in adults.[60] Physical signs of a depressed skull fracture, skull base fracture, posttraumatic seizures, focal neurologic deficits or shunt-treated hydrocephalus are also considered as increased risk of intracranial hematoma.[4, 61] Coagulopathy is an important risk factor for the development of hematoma and secondary complications.[4] The role of other clinical symptoms such as headache, nausea, vomiting and blurred vision have been conflicting in adults and some former studies suggest that these symptoms are not predictive of intracranial hematoma in children. The presence of scalp contusion or hematoma, irritability, behavioral changes, age younger than 2 years, and the number of vomits are other factors which are being discussed as risk factors for intracranial hematoma after head injury.[62]

It is also known that particularly younger children have an increased risk of intracranial injuries after head trauma, even without the presence of a skull fracture or other symptoms.[63] Greenes and Schutzman also stated in 1998 that physicians cannot rely on the absence of clinical signs of brain injury to exclude intracranial injury in infants during their first year of life.[63] As there are continuously concerns about the predictive relevance of these symptoms in children, management recommendations tend to be more conservative and liberal for computed tomography (CT) than for older children and adults.

Radiology

Early radiologic routines in minor head injuries included skull radiography to identify skull fractures due to the increased risk of intracranial injury if such fracture was present.[64] Skull radiography also identified depressed fractures, presence of a foreign body or intracranial air, and in some cases midline shift of a calcified pineal gland. The result of the skull radiography helped in determining whether the patients would be admitted or not.[65] In the 1970's CT of the head was reserved to the severely head injured patients. The clinical use of skull radiography in head injuries correlated poorly with skull fracture and clinically important intracerebral hematomas.[66, 67] As CT was becoming more and more available, discussions lay in whether or not to perform a skull X-ray on low-risk patients. Masters et al stated in 1987 that omitting skull radiography in low-risk patients who are asymptomatic, who have headache, dizziness, scalp hematoma, laceration, contusions or abrasions was safe and that the strategy would decrease unnecessary exposure to radiation and reduce costs.[68] The revisions of management recommendations aimed in reducing the number of skull X-rays without affecting the detection rate of intracranial hematomas.[65] Nevertheless, in some cases increased diagnostic use of head CT and hospitalization were warranted.[60, 69]

During the following decades the number of CT examinations rapidly increased. According to a Swedish study CT was shown to be more cost-effective for the acute management of patients with mild head injury, since the cost of a single CT is about one third less than admission for observation.[70] In the subsequent OCTOPUS study the authors also stated that early CT scanning was as safe as admission for observation in mild head injured patients,[71] which also applied on children older than 6 years. In 1989 approximately 4% of all CT examinations performed were on children under the age of 15. By 1993 the number was estimated to 6% and in year 2000 about 10%.[72, 73] An international multicenter study on pediatric traumatic brain injury reported in 1998 a CT ordering rate of 14.3%, while 89% of the children received a skull X-ray. In Canada the reported CT ordering rate for pediatric head injuries varied from 6% to 26% in year 2000,[74] in Sweden around 10% for MHI (2002)[16] and in Australia around 19% (2006).[75] In America, the use of CT had increased substantially in the evaluation of children with head trauma, with figures from 12.8% to 22.4% during 8 years.[76] UK seem to have had the lowest figures for CT ordering, 2.1-4.4%,[33] but with the newer recommendations this rate is estimated to increase to an order of 14-18%, if fully complied.[55, 77]

With growing use of diagnostic CT came a growing concern about its associated risks, especially concerns about radiation-induced cancer. In a debated and well cited study Brenner and colleagues aimed to assess the lifetime cancer mortality risks attributable to radiation from pediatric CT. The authors predicted that approximately 170 deaths would be attributable to 1 year of head CT examinations in the US for children < 15 years.[72] The estimated cancer mortality risk increases with decreasing age and the estimated risk of dying of cancer due to a single CT radiation exposure in a 1-year-old child was approximated to be 1 in 1500 (0.07%) for a head CT, and 1 in 550 (0.18%) for an abdominal CT. These numbers were calculated from several assumptions and approximations, especially assuming the same exposure for children as for adults.

In a similar study from Sweden, Hall et al estimated the risk of CT induced malignancies among children < 18 years and found a risk of inducing 2.4 cases of cancer per 1000 CT examinations.[78] Head CTs were the most common type of CT examination performed (50%), while abdominal CTs were 24%. Among children < 5 years of age, 59% of all CTs performed were head CTs. In order to try to decrease this risk, some radiologists call for a reduction of exposure settings for infants and children by 30-50%; a decrease of the organ dose which can be done without jeopardizing the quality of the scan.[79, 80]

With the nearly exponential increase in the number of CT examinations performed it is essential for clinicians to continue the search for more optimized guidelines in pediatric head injury.

Management guidelines

In 1981 Teasdale and Jennet published their book on the management of head injuries, describing the evidence for treatment regimes and a detailed summary of the clinical features and challenges.[81] Most of their focus was set on severe head injuries and there were no clear differences between adult or pediatric management. Mainly retrospective studies on minor head injury had been performed. Patients seeking the emergency departments after a head injury were frequently admitted for observation to identify those with an evolving intracranial hematoma, and skull radiography was frequently performed.

One of the first guidelines published was “The Provision of Surgical Services to Patients with Head Injuries” by The Royal College of Surgeons of England (RCS) in 1986. In 1999 the RCS updated the guidelines with the so called “Galasko Report”[82] recommending skull radiography to patients with mild head injury and/or head CT if a skull fracture was present. An immediate CT was warranted for patients with impaired consciousness or neurological symptoms. Severe head injuries (defined as patient in coma or with deteriorating level of consciousness) were to be urgently referred to a neurosurgical unit or a CT if available. The report also noted that children were, compared to adults, more likely to need a CT in certain situations.

In 2000 the Scandinavian Neurotrauma Committee published guidelines for initial management of traumatic head injuries. Based on an extensive MEDLINE search, they recommended that patients with so called minimal head injury (GCS 15 and no LOC) could be discharged without further radiological investigations. Routine CT was recommended for patients with mild head injury; GCS 14-15 and a history of brief LOC. CT was mandatory on patients with moderate head injury, GCS 9-13, brief LOC or focal neurologic deficits. Patients with certain additional risk factors, such as anti-coagulant therapy or depressed skull fracture were recommended a CT and admission. The risk, however, of developing an intracranial complication after minimal head injury was considered almost zero and patients were recommended discharge without further radiological investigation.[4]

The use of CT for minor head injury was becoming increasingly common, especially in North America. In 2000 Haydel and colleagues presented the so called New Orleans criteria (NOC): seven clinical criteria for identifying patients with positive CT after minor head injury.[83] They estimated that by restricting CT scanning to patients with at least one of the following criteria: headache, vomiting, an age over 60 years, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicles and seizure, would reduce the use of CT by approximately 22 percent.[83]

The Canadian Head CT rule (CCHR), published in 2001, is a decision rule for the use of CT in patients with minor head injury (GCS 13-15). Five high-risk factors have been identified as substantially increasing the risk for a neurosurgical intervention and two medium-risk factors for a clinically important intracranial lesion.[84] The potential CT ordering factor was estimated to 32-46%. Comparison studies between the CCHR and the NOC show that the CT ordering rate decrease only marginally for NOC, but up to 37% for the CCHR, due to its higher specificity for clinically important brain injury.[57, 85] These rules, however, only apply to adult patients.

In 2003 the NICE guidelines, based on a modified Canadian Head CT rule, were introduced in the UK,[86] replacing the previous "Galasko Report" guidelines and significantly reducing the number of performed skull radiographies.[87] Concerns for increased work load particularly to the radiological departments[88, 89] and contemporary versions (2007) also try to account for the present service structure and resource limitations.[90] Due to the lack of derivation rules for children, recommendations for the management of children with head injury were also based on the CCHR, until around 2007.[91]

During the last decade several attempts have been made for deriving highly sensitive prediction rules for patients with minor head injury, e.g., the National Emergency X-Radiography Utilization Study II (Nexus-II) decision rule,[92] the guidelines of European Federation of Neurological Societies (EFNS)[93] and the CT in Head Injury Patients (CHIP) prediction rule.[94] The risk factors differ and vary in number, but the sensitivity for identifying intracranial lesions on CT or patients requiring neurosurgical intervention are high.[95] Some of these rules have yet to be internally and/or externally validated and the majority of these guidelines only apply on adult patients. Some also point out the problem of assessing children and infants and recommend the use of pediatric GCS for children aged 5 years or younger.[93] The EFNS guidelines also addresses the interest in further exploring the utility of biochemical brain markers.[93]

Pediatric head injury management guidelines

Minor head injury

Despite the extensive research in the management of head injuries in adults, the pediatric guidelines for minor head injury was not introduced until 1999, the same year Homer and colleagues stated that there were not enough scientific studies to produce evidence based recommendations for management of pediatric MHI.[96, 97]

The American Association of Pediatrics (AAP) was the first to publish recommendations for management of closed head injury in children.[98, 99] The guidelines defined a group of children older than 2 years with normal mental status at first examination, no focal neurological deficits or physical evidence of skull fracture. LOC was set to less than 1 minute. Due to an estimated low risk of developing an intracranial injury and an even smaller risk of a neurosurgical relevant injury in this patient group, observation for at least 24 hours was mainly warranted. In case of LOC < 1 min the option of additional CT scanning was to be considered.[98] For children < 2 years CT was to be promptly considered for patients at an intermediate risk-level (LOC < 1 min, extensive vomiting, history of lethargy, non-acute skull fracture, or parental concern) or otherwise admitted for observation and CT after 4-8 hours if symptoms had not resolved.[99] Children with low-energy trauma and asymptomatic 2 hours after the injury could be considered discharged for home observation.[99] The proposed guidelines were based on a MEDLINE search and panel discussions, and gives physicians the possibility of individualizing care by adoption of a variation of the recommendations.

In another observational study of 2043 children done by Palchak and colleagues[100] several clinical factors identifying children at low risk for TBI after head trauma were presented. The absence of abnormal mental status, clinical signs of skull fracture, history of vomiting, scalp hematoma (in children ≤ 2years), and headache had a sensitivity of 98% for intracranial complications. The specificity was 44.7%. The negative predictive value was 99.6% for CT verified intracranial complications and 100% for brain injuries requiring intervention.

In the UK, modified NICE guidelines had been applied to children due to lack of other pediatric guidelines. In 2006, the “children’s head injury algorithm for the prediction of important clinical events” (CHALICE)[55] was recommended instead, however, with certain caution since the decision rule had not been validated. This decision rule by Dunning and colleagues is a large multicenter study including more than 22000 children younger than 16 years old, that lists 14 criteria, among others, vomiting ≥ 3 times, LOC > 5 minutes, GCS < 14 or fall from > 3 meters, as separate risk factors for intracranial pathology after head trauma. A CT was required if any of the 14 criteria were present. The sensitivity for a clinically important head injury was 94-99% and the specificity about 87%. The negative predictive value for clinically significant intracranial pathology was 99.9%. The CT ordering rate was estimated to 14%; an increase from the earlier management guidelines, but a decrease in the admission rate. There have also been reports that the application of the decision rule could double the use of CT in other sites.[75, 77]

In 2009 the North American PECARN group published a prediction rule for identifying children at very low risk of TBI for whom CT could routinely be obviated.[101] A total of 42212 children younger than 18 years with head trauma and GCS 14-15 were enrolled in the study. Separate rules were derived for children below 2 years of age and those 2 years and older. Six factors were found being predictive for a clinically important TBI. These were, for children younger than 2 years: altered mental status, LOC, mechanism of severe injury, suspected skull fracture, scalp hematoma and “not acting normal according to parents”. For older children the latter three factors were exchanged for: clinical signs of

basilar skull fracture, history of vomiting and severe headache. Children with none of the six variables for whom CT could have been avoided accounted for 25% of CTs in the younger age group and 20% of CTs in the older. The negative predictive values for clinically important TBI in the validation group were 100% and 99.95% respectively for the both age groups. The estimated CT ordering rate following these rules was 14%, which is significantly less than the actual CT use (35%) in the study. The decision rule has not been validated externally yet.

There are no specific pediatric management guidelines for minor head injury currently recommended in Scandinavia.

Moderate head injury

The definition of moderate head injury varies in literature with regards to the level of consciousness of GCS 13. In most adult recommendations, an initial GCS of 13 is considered to belong to mild head injuries. In the SNC recommendations patients with GCS 9-13 are regarded as having a moderately increased risk of intracranial complications and are therefore recommended a routine CT scanning and hospital admission.[4] This is more in line with other studies on pediatric trauma patients with mild alterations in consciousness (GCS 13-14), who have a relatively high incidence of intracranial injuries (19-27%) and for which routine CT is also recommended.[102]

Deterioration can occur quickly with confusion, development of focal neurology or decrease in the level of consciousness. Moderately head injured patients are therefore recommended hospitalization and close observation. The majority of moderately head injured patients will recover within 24-36 hours without further treatment. However, according to earlier recommendations for pediatric head injuries, the effect of an epidural hematoma might be overtly expressed first after 48 hours (the phenomenon commonly known as “talk and die”), whereas in adults it is expressed often within 24 hours.[103] Continuous re-examinations and re-evaluations for performing a second CT are advocated, even when symptoms of concussion such as headache, nausea and dizziness are persistent or only slightly worsening during the observation period.

Severe head injury

Previous management strategies and decision making were mainly based on adult treatment recommendations or clinical experience.[103] In 2003 the first evidence based pediatric guidelines for the management of severe TBI were published by Adelson et al.[104] During the past decades, advances in the management of severely head injured children have been made, especially regarding treatment strategies within the intensive care setting to optimize outcome and outcome prediction.[105, 106]

Severe head injuries are defined as GCS 8 or less (RLS4-8). Immediate resuscitation, establishment of free airway, oxygenation and restoration of normal blood volume are crucial factors to assure adequate perfusion to the brain and hence, minimize secondary intracranial complications before referral to a trauma center. All therapeutic strategies

post-trauma focus on the prevention or reduction of secondary brain injury by optimizing cerebral blood flow (CBF). Severely head injured children receive an urgent CT scan to identify those in need of immediate neurosurgical evacuation of an intracranial hematoma. Thereafter the identified children are referred to a neurointensive or pediatric intensive care unit for optimal treatment.

Cerebral perfusion pressure (CPP) is so far the best surrogate marker for estimating CBF, measured by mean arterial pressure (MAP)-ICP. The ideal level of CPP for children is not fully known, however there are studies that show favorable outcome associated with CPP between 40 mmHg and 65mmHg and poor outcome with CPP < 40mmHg. The pediatric guidelines for severe head injury (2003) recommend a CPP > 40mmHg and a slightly higher CPP with increasing age.[107] There are two different schools for the treatment of intracranial hypertension: the CPP targeted therapy and the ICP targeted therapy (Lund concept). The CPP targeted therapy aims at lowering the ICP by adding vasopressors, to increase the CPP by increasing MAP, which only works as long as autoregulation is intact. The ICP targeted therapy uses aggressive treatment for reducing ICP to 20 mmHg or below by usage of systemic anti-hypertensive agents and maintenance of normovolemia, which has shown favorable outcomes.[105] The main counter argumentation for the Lund concept is the potential risk of hypotension, which could consequently lead to secondary brain injury and worse outcome.

For continuous ICP monitoring on sedated children, intraparenchymal ICP monitoring or external ventricular drains (EVDs) are possible options, which aid in estimating CPP and CBF. An EVD can sometimes be difficult to place correctly in case of diffuse cerebral edema and very small ventricles. However, an EVD has the advantage of the possibility of CSF drainage, which decreases the intracranial volume and possibly also the ICP.

Elevation of the head, intravenous analgesics and increase in sedatives are non-invasive methods of lowering the ICP. Rapid infusion of hypertonic saline, osmotic agents (e.g. mannitol) and hypocapnia (pCO_2 3.5-4.0 kPa) are options when other measures have not affected the ICP, or when there are signs of cerebral herniation (Cushing effect). Prophylactic use of osmotic agents or hyperventilation is not recommended because of the risk of a rebound effect, increased brain edema and excessive cerebral vasospasm. This could consequently lead to reduced cerebral blood flow and ischemia.[108] The use of steroids has been controversial for a long time and does not have a place in current head injury management.[109] Anti-convulsive therapy should be given only in presence of seizure.[110]

Second line treatment, when intracranial pressure seems resistant to the above regime, is change of anesthesia to e.g. barbiturate coma and prolonged sedation. According to the pediatric guidelines from 2003 continuous infusion of propofol (prolonged for 24 hours) is not recommended in the treatment of pediatric TBI, due to the risk of metabolic acidosis and death (the so called propofol infusion syndrome).[111, 112] Decompressive craniectomy can be meaningful in certain situations.[113, 114] The use of hypothermia in severe head injury has been one of the last possibilities in former guidelines,[103] although there have not been any evidence of a favorable effect in children with TBI. In previous studies there have even been a tendency towards worse outcome in patients receiving hypothermia treatment

after TBI,[115-117] which has recently been verified in a large randomized multicenter study on adults.[118] Hence, early hypothermia cannot be considered as a neuroprotective strategy in patients with severe traumatic brain injury.

Biochemical markers for brain injury

Biochemical markers are constantly being used as diagnostic tools for injuries in specific organs, such as troponin for myocardial infarction, creatinine for renal dysfunction and pancreas amylase and lipase for acute pancreatitis. Since 1965 much research has been done on potential biochemical markers specific for injuries in the central nervous system (CNS),[119] but the complexity of the brain, its physiological function and the severity of an eventual injury of the brain, has set the criteria and standards high for an upcoming brain injury marker. The previously defined criteria for an ideal biochemical brain marker are:[120, 121]

1. Central nervous specificity
2. Rapid and significant release into the blood after injury, within minutes
3. Elimination within a few hours
4. Rapidly and readily obtainable assay results
5. Predictability of serious injury from an early sample
6. Relationship of maker concentration to the degree of injury
7. Inexpensive

Several biochemical markers have already been investigated and some are still under investigation for usage in different neurological and neuropsychiatric diseases. However, none of them have been accepted as an ideal marker with a sufficient relevance in brain injury.

Creatine kinase, isotype BB (CK-BB) shows great activity in the brain, mainly astrocytes. It is normally not present in the CSF, but is released into the cerebrospinal fluid (CSF) after hypoxic brain injury after cardiac arrest[122] and traumatic brain injury. Former studies found a correlation between CSF levels and neurologic outcome after cardiac arrest.[123] Skogseid et al showed a correlation between the severity of brain injury and the volume of contusions to the maximum concentration of CK-BB in serum.[124] However, CK-BB is also found in the large intestine and prostate with a concentration up to one third of that seen in brain tissue.[125]

Myelin basic protein (MBP) is an 18.5 kDa myelin specific protein found in growing oligodendroglial cells. It can be released into serum after brain damage or in demyelinating diseases. Despite a high specificity, the sensitivity of MBP in serum is low and the utility of the protein in brain injury is therefore limited.[126]

Neurofilament protein (NF) belongs to the intermediate filament family (NFH, NFM, and NFL) and constitute the major component of the neuronal cytoskeleton, mainly in thick myelinated axons. NFL is so far only measurable by enzyme-linked immunosorbent assay in CSF in e.g. Alzheimer's disease, amyotrophic lateral sclerosis and stroke. The marker increases very late in the process, with maximum level several weeks after the insult.[127]

Glial fibrillary acidic protein (GFAP) is one of the brick-stones in glial filaments, hence a cytoskeleton structure in astrocytes. GFAP in CSF is increased in disorders causing astrogliosis and in e.g. stroke causing leakage from damaged cells to CSF. The CSF concentration correlates to the extent of damage and is seen to be extremely high in e.g. herpes-encephalitis and large cerebral infarcts. There is only a slight increase in GFAP in chronic diseases, such as Alzheimer's and multiple sclerosis due to astrogliosis. Serum levels of GFAP have also shown to be highly elevated in severe TBI and are related to increased mortality and poor outcome.[128-130]

Neuron specific enolase (NSE) is a cytoplasmic enzyme of glycolysis with a subunit consisting of $\gamma\gamma$-enolase or $\alpha\gamma$-enolase. It is normally found in neurons and neuroectodermal cells. NSE can be detected in both CSF and serum and is therefore a potential biochemical marker under investigation. Serum concentrations of NSE are known to increase in small-cell lung carcinoma, medulloblastoma and in brain injury. Nowadays its clinical usage is as a marker for tumors of the amine precursor uptake and degradation. The marker has also been investigated as a predictive marker of neurological outcome after cardiac arrest and cardiac surgery.[131, 132] However, one major drawback of NSE is its prevalence in erythrocytes and its release in the blood by hemolysis.[133]

Protein S100B is a small (21kDa) calcium binding protein expressed mainly in astroglial cells and Schwann cells in the CNS, exerting both intracellular and extracellular effects.[134-136] Protein S100B can be detected in both CSF and blood. The marker concentration has been shown to increase in CSF and/or serum after a vast number of cerebral diseases, e.g. traumatic brain injury,[137-140] cerebral infarction[141] and subarachnoid haemorrhage.[142] Previous studies have shown that serum S100B levels of patients with severe and minor head injuries correlate to both neurological findings at admission and to long-term outcome.[138, 143-146] However, increased concentration of serum S100B has also been found in patients suffering from extracranial injuries, especially long-bone fractures[147, 148] and after cardiopulmonary bypass surgery.[149, 150] Nevertheless, today protein S100B is still the most promising diagnostic biochemical marker used in MHI.

Protein S100B and its functional roles

BW Moore was the first to identify the S100 protein in 1965.[119] It was purified from bovine brain and named S100 due to its solubility in 100% saturated ammonium sulphate.[119] The S100 protein was at that time determined to be brain specific, since bovine brain was thought to contain only nervous-system specific proteins. However, subsequent studies showed that bovine brain contained predominantly two different polypeptides, S100B and S100A1.[151] Nowadays there are more than 20 proteins belonging to the S100 family, a multigenic family of non-ubiquitous Ca^{2+}-modulated proteins of the EF-hand type (helix-loop-helix).[135] S100 proteins are low molecular weight proteins, existing within cells as homodimers, with the exception of the monomeric protein calbindin D_{9k}. Dimerization of the S100 proteins is important for their biological activities, though in some cases even S100 heterodimers are formed, e.g. S100A1/S100B.[135, 136] S100 proteins are thought to be involved in intracellular activities, such as the regulation of protein phosphorylation, enzyme activities, Ca^{2+} homeostasis, cell proliferation and differentiation, and inflammatory response. Extracellular effects have only been described for some of the S100 proteins, e.g. stimulation of neurite extension activity, neuronal apoptosis, inhibition of the extrinsic pathway of blood coagulation and proinflammatory activity on endothelial and inflammatory cells. In vitro studies have shown that secreted S100B exerts neurotrophic effects in nanomolar concentrations by stimulating neurite outgrowth and toxic effects in micromolar concentrations due to increased expression of the proinflammatory cytokine IL-6 and induction of apoptosis.[152]

S100B is primarily produced by astrocytes, but is also found in Schwann cells, adipose tissue[153] and malignant melanoma cells.[154, 155] However, the concentration of S100B in tissues outside the nervous system is normally much smaller than in brain tissue and nearly negligible.[156]

S100B can be detected in both CSF and serum. There are still some uncertainties about the release mechanism of S100B into the blood. The most accepted theory is that of extracellular S100B passing into the blood due to a disrupted blood brain barrier (BBB). Serum protein S100B is an early marker of the disruption of BBB after a blow to the head, though not always as a sign of neuronal damage.[157, 158]

The protein is metabolized and excreted by the kidneys[159] and its biological half-life has been estimated to about 30 minutes[160] even though other studies have found S100B half-life up to 130 minutes.[161] The stability of protein S100B in serum has been investigated by Raabe and colleagues, who found no effects of storage time and temperature before analysis.[162] The stability of urine S100B seem to be less stable.[163]

Serum S100B has in a few studies been measured in the jugular vein and compared to the arterial concentrations. The studies have found contradicting results, one finding a significantly higher concentration in jugular blood[164] and the other with almost equivalent levels.[165]

Methods of analysis

During the past years there have been various commercially available methods from several manufacturers used in research for measuring S100B concentrations in both CSF and serum. Differences between the analytical methods should be considered when interpreting results from different studies.[155, 163, 166] The more commercially available methods are: the two-site immunoradiometric assay Sangtec®100 IRMA, the immunoluminometric assay LIA-mat®Sangtec 100 and LIAISON®Sangtec 100 (DiaSorin AB, Bromma, Sweden), the ELISA Nexus DX™ S100 (SynX Pharma Inc., York, UK.), the enzyme-linked immunosorbent assay (Nanogen), the enzyme-linked immunoassay Elecsys® S100 and the more recent electrochemiluminescence immunoassay Elecsys170 (Roche Diagnostics, Mannheim, Germany).[154, 167]

Reference values of S100B in children

CSF concentrations differ between males and females and are also seen to increase with growing age.[168, 169] Wiesmann et al showed that plasma S100B concentration in healthy adults was both gender- and age-independent, concluding that there is no need for corrected reference values for measurements in the blood of adults (age 18-65).[170]

Portela and colleagues (2002) were the first to determine normal levels of S100B in 19 neonates and 25 children (4-16 years). The authors also compared these findings to serum S100B measured in 85 healthy adults. They found a negative correlation between S100B and age in individuals < 20 years, but not in individuals > 20 years old, which indicated that S100B decreases considerably during the first two decades of life and remains relatively constant in adulthood.[171] Gender differences were not found.

A study by Gazzolo et al found a negative correlation between serum S100B and age in children, as well as gender differences. The median S100B concentration in females was higher especially in the first 3 years of life. Reference values of serum S100B in infants (younger than 1 year) were significantly higher than in children aged 2-7 years (75th percentile 2.55 and 1.06 µg/L respectively). Reference values were increased again after the age of 9-10 years, possibly due to the neurotrophic effects of the protein at these ages.[172]

In 2008 Castellani et al also investigated the reference values in children and found an upper reference level of 0.16 µg/L for children 3-18 years-old.[173] Castellani analyzed the S100B levels using Elecsys electrochemiluminescence assay, a different method than the one used in Portela and Gazzolo's studies (LIA-mat immunoluminometric assay). This could be one of the reasons for yielding different absolute values.

Pediatric studies on S100B

There are by far fewer studies performed on pediatric TBI and biomarkers, but similar to studies on adults, most studies have focused on S100B's ability to predict outcome after TBI. In a study by Spinella et al, serum S100B levels measured at admission on children with TBI and intracranial lesion seemed to be associated with outcome measured 6 months post-injury. Serum levels ≥ 2 µg/L (Liaison) was associated with poor outcome, with a sensitivity of 0.86 and specificity of 0.95.[174] Berger and colleagues showed in a study with 152 children that mean S100B concentrations in children with both mild and severe TBI were significantly greater than normal control concentrations and that peak S100B concentrations correlated more strongly to outcome.[175, 176]

Berger et al have also tried to identify inflicted traumatic brain injury from non-inflicted TBI in infants and children, using biochemical serum markers as screening tools. The biomarkers studied were NSE, MBP and S100B. Although the biomarkers increased in the majority of children with acute TBI, none were able to sufficiently discriminate between non-inflicted TBI and iTBI.[177]

In a recent study Bechtel and colleagues described the use of serum S100B as a screening tool to detect intracranial injuries in children admitted to the emergency department after closed head trauma. Although children with intracranial injuries had significantly higher S100B concentrations than children without ICI, the ability of S100B levels to detect ICI was found to be poor.[178]

Children are more likely to have scalp hematomas and this has been proposed as a predictive sign for intracranial injury in small children.[101] The influence of extracranial sources on S100B levels has also been addressed, mainly concerning scalp hematomas or lacerations. In a small study by Geyer et al the presence of scalp lacerations did not influence significantly on serum S100B concentrations.[179]

In one of the more recent and more encouraging studies from Austria, Castellani et al (2009) investigated the correlation of S100B to CT results after mild TBI (GCS 13-15). Serum S100B concentrations were significantly higher in patients with abnormal CT (mean 0.64 µg/L) compared with patients with normal CT (mean 0.50 µg/L) and even though specificity was poor (0.42), the sensitivity and negative predictive value was 1.00. The authors concluded that normal S100B levels (< 0.16 µg/L, Elecsys) safely rules out CT pathologies in minor head injured children.[180] This study encourage further research on this topic in pursue of optimizing routines and management in pediatric head injury.

Serum biomarkers (S100B, NSE and CK-BB) have also been studied in newborn asphyxiated children as indicators of hypoxic ischemic encephalopathy and neurodevelopmental outcome. The authors concluded however that all the biomarkers sampled on the first day of life were of limited value in predicting severe brain damage after birth asphyxia.[181] Gazzolo and colleagues have also been investigating urine S100B concentrations at first urination and up to 72 hours after birth in asphyxiated infants. They found it to be a useful tool to identify asphyxiated children at risk of hypoxic ischemic encephalopathy.[182] S100B has also been found in urine of older children with head injury,

as well as other sites such as saliva and maternal fluids. Nevertheless, the clinical usefulness of measurements in these sites have been limited.[183, 184 185, 186]

Clinical relevance of S100B in head injury management

The intense research on protein S100B has been providing hope for clinicians for a new diagnostic tool in various types of brain injuries, both primary and secondary, as well as prediction of outcome. Studies on severe TBI in adults have found high levels of S100B correlating to intracranial pathological findings on CT and MRI[138, 146] and strong associations between high levels of S100B (> 2.0- 2.5 µg/L) and unfavourable outcomes in both adults and children.[143, 174]

Romner and Ingebrigtsen showed early that S100B in serum correlated well to contusion volume on CT and magnetic resonance imaging (MRI) findings in mild head injury.[137, 146] The major drawback has long been the low specificity (0.65) of S100B for identification of a pathological CT scan or intracranial injury. However, the sensitivity has always been proven high (> 0.90). Serum S100B was later introduced in the field of minor head injury, in pursue of categorizing patients into a high or low probability category of having a intracranial injury,[121] which could lead to a significant reduction of MHI patients undergoing CT scanning. Already in year 2000 Ingebrigtsen and colleagues commented on a high negative predictive value (0.99) of S100B related to pathological CT.[145] It was not until 2005 that Muller et al discussed the possibility of accepting a minor risk (1.5%) of missing patients with clinically insignificant intracranial lesions in favour of safely reducing unnecessary CT scans in MHI patients. The present cut-off level for S100B is set to 0.10 µg/L for adults. Used in conjunction with existing guidelines, such as the Scandinavian guidelines, serum S100B could reduce the need for CT scans by 30% and still maintain a high sensitivity and negative predictive value for detection of clinically relevant intracranial complications.[187] In a recent extensive meta-analysis by Undén et al, the authors show that low serum S100B levels accurately predict normal CT findings after MHI in adults and recommend protein S100B as a complementary decision tool in the present Scandinavian guidelines.[188]

Recent pediatric decision rules (CHALICE, PECARN) have been proposed in order to reduce the number of CTs and hospitalizations among MHI children with very low risk of developing an intracranial complication. These are based on several clinical symptoms and predictive factors such as severe headache, vomiting, LOC and signs of skull/basilar skull fracture . Although the yield of a CT frequency of 14% was approximated, there have been concerns about the guidelines being too complicated to use on the intended population,and that the CT rate in other countries would be increased.[75] Accordingly, introduction of a serum biomarker for brain injury in pediatric mild head injury would be most welcome.

Aims of the studies

I. To investigate the present management of pediatric minor head injury in Swedish hospitals

II. To identify clinical factors associated with intracranial complications after traumatic head injury in children and to investigate the reliability of the present management routines for initial handling of traumatic head injury in children.

III. To investigate the relation between capillary, venous and arterial levels of protein S100B.

- Can capillary S100B measurements substitute venous S100B measurements, and if not,
- how much does a capillary S100B measurement differ from a venous?
- Can venous S100B concentrations be successfully predicted from capillary measurements?
- Can arterial measurements of S100B substitute venous measurements?

IV. To determine reference values for venous and capillary S100B in children.

Patients and methods

Paper I

Survey of the management of children with minor head injuries in Sweden

In this study we wanted to investigate how children with mild head injuries in Sweden were handled, and to get a basic knowledge about the possible clinical problems in this field.

The study was performed by a cross-sectional mail survey, including all 51 hospitals with an accident and emergency department treating children with head injuries. Eight were university hospitals, 20 central hospitals and 23 district general hospitals.

A questionnaire based on the management of MHI in children was sent to 131 hospitals in Sweden during the spring of 2004. A reminder with the questionnaire was sent to non-responders during the spring of 2005, and a 100% respondent-rate was achieved after telephone contact to those who had failed to respond even to the second initiative. Fifty-one hospitals replied that they accept and treat children with head injuries. The questionnaire included 25 questions about the hospital and the management of children with MHI. Routines concerning clinical and radiological examinations, in-hospital observation, discharge criteria and follow-up were outlined in detail.

The questionnaire was a revised version of the questionnaire developed by our research group, used for similar studies in adult patients in Norway and Sweden.

Paper II

Clinical factors associated with intracranial complications after pediatric traumatic head injury: an observational study of children submitted to a neurosurgical referral unit

This study aimed to describe the clinical problems and outcome of children admitted to neurosurgery after head trauma. We looked for symptoms and factors associated with the head trauma and related these to the presence of intracranial complications on CT or need for neurosurgery.

This was a retrospective descriptive study, including patients below 18 years of age with TBI and admitted to the Neurointensive Care Unit (NICU) at Lund University Hospital between the years 2002 and 2007. Children with any S06 diagnosis, according to ICD-10 (International Classification of Diseases) system, were included in the study.

With this design, we expected to register all children with clinically relevant complications (i.e. requiring neurosurgery and/or neurointensive care) from head injury in southern Sweden. The study design was reviewed and approved by the Regional Ethical Review Board. Medical records registered in paper files and electronically in CareVue (Philips medical system) and Melior (Siemens medical record system) were reviewed for neurological and neurosurgical data, patient history, present injury, radiological data, symptoms, treatments and clinical outcome. All relevant data were in anonymous form collected in a database (FileMaker Pro 7), and analysis was performed in SPSS version 13.0.

Paper III

Comparison of capillary, venous and arterial levels of protein S100B in patients with severe brain pathology

In this study we wanted to investigate the possibility of measuring capillary and arterial samples of protein S100B and to relate the concentrations to venous measurements.

Capillary, venous and arterial blood samples for S100B measurement were collected from adult patients (age ≥ 18 years) with severe brain pathology and admitted to the NICU at Lund University Hospital, Sweden, between 2005 and 2007. The study was continued in 2010 with similar adult patients admitted to the NICU at Rigshospitalet, Copenhagen, Denmark. Patients were not considered for inclusion if they were known to have active malignant melanoma, kidney failure or if they were multi-trauma patients with long-bone fractures. Oral and/or written consent was obtained from the patient before inclusion and if this was not possible due to unconsciousness or confusion, consent was given by the patient's next of kin.

Capillary, venous and arterial blood samples were collected simultaneously once a day and continued for a maximum of 8 consecutive days or until the patient was discharged. For further comparison, two capillary samples were drawn from different fingers on the first day of inclusion. 600 µl of capillary blood and 4 ml of venous blood were sampled and collected in SST-microtainer tubes (BD Microtainer®) and SST-tubes respectively, both containing a serum separating gel without additives. If the patient had an arterial line, an arterial sample (4 ml) was collected in a SST-tube after discarding the initial 4 ml to avoid mixing of any previous fluids from the arterial line.

The blood samples were allowed to clot for 30 minutes. After centrifugation at 2200*g* for 10 minutes, the serum was collected. For the Swedish material, immediate analysis was performed. For the Danish material, serum samples were frozen at -80°C and analyzed in batches at a later session. All samples were analyzed with an electrochemiluminescence assay (Elecsys S100B assay, Roche Diagnostics, Mannheim, Germany). The assay was performed on Roche Hitachi Modular E170. The lower detection limit for the analysis was 0.005 µg/L and the upper 39.0 µg/L.

Statistical analysis

The S100B serum concentrations were registered as 3-decimal values. Statistical analysis was performed in Stata version 9. Figures were produced in SPSS version 19. Our focus of interest was the differences in concentration between the pairs of simultaneously obtained samples and comparison analysis was performed with Student's t-test. Differences were considered statistically significant for two-sided P values <0.05. Prediction analysis was performed with linear regression analysis. The root mean square prediction error (RMSE) was calculated as a measure of the prediction success. The relation between two kinds of sampling was illustrated according to Bland-Altman.

Paper IV

Age and gender specific reference values for venous and capillary S100B in children

The study was performed at the County Hospital of Halmstad in Sweden, between the years 2007 and 2009. Neurologically healthy patients were selected for participation. Children, aged 1 to 16 years, who were scheduled for elective ear-nose or throat (ENT) surgery or microscopic otoscopy in general anesthesia, were included for participation in the study. Parental consent and a health declaration for the child were obtained for all patients. The child was excluded and none of the blood samples were drawn if the child had any of four exclusion criteria declared: (1) neurological illness (brain tumor, hydrocephalus, cerebral paresis), (2) previously treated for, or hospitalized due to brain injury, (3) recently acquired long bone fracture (within 3 months), or (4) renal failure or other disease of the kidneys.

Four serum samples were drawn from the patient. The first venous sample (3 ml) was drawn from a peripheral venous catheter immediately after application, before any fluids or sedatives had been administered. The second venous sample (3 ml) was drawn from the same catheter after sedation, immediately after about 5 ml blood first had been drawn and discarded, in order to avoid any mixing of intravenous fluids from the peripheral catheter in the second sample. Two capillary microtainer samples (600 µl) were taken after sedation of the child. The capillary samples were drawn from two separate finger pricks.

The venous samples were collected in a 3 ml SST tube and the capillary samples in a 600 µl SST microtainer tube (BD microtainer®), both tubes containing a separating gel without additives. The samples were left to clot for at least 30 minutes, centrifuged for 10 min at 2200*g*, frozen and stored at -80 °C. The two venous samples and the first capillary sample for each patient were analyzed. Analysis was performed with an electrochemiluminescence assay (Elecsys S100B assay, Roche Diagnostics, Mannheim, Germany). The assay was performed on a Roche Hitachi Modular. The lower detection limit was 0.005 µg/L and the upper was 39.0 µg/L. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

Results

Paper I

Survey of the management of children with minor head injuries in Sweden

There is a lack of specific pediatric head injury guidelines in Sweden and this study describes the variations in the management of children with mild head injury.

Fourteen (28%) of the 51 hospitals had established written criteria for the referral to and the management of children with MHI at the hospital. Children were managed by the general surgical department in 82% of the hospitals, and by a pediatric/pediatric surgical department in 8 hospitals (16%).

Management in the ER

In 96% of the hospitals initial evaluation of the head injured child was performed by assistant residents and/or residents. Only two (4%) hospitals reported that the initial evaluation was exclusively performed by consultants. Routine neurological examination for all children was performed at 96% of the hospitals. The most frequently used scale for the assessment of the level of consciousness was the Swedish Reaction Level Scale (RLS),[9] used in 44 (88%) hospitals. The pediatric GCS was used in 4 (8%) hospitals. Nine hospitals (18%) reported routine radiological examination of all children presenting with MHI. All nine used routine CT scan and 6 of the hospitals also performed radiography of the cervical spine and/or skull as a routine. All 51 hospitals reported a 24 hour access to a CT scan.

Eight (16%) hospitals consistently hospitalize all children with minor head injury, whereas 42 hospitals (84%) had established criteria for early discharge. Seven criteria were identified, and absence of focal neurological deficits, normal level of consciousness and no influence of alcohol were the three most common criteria required for discharge. Thirteen hospitals required a normal CT scan, whereas two hospitals perform skull radiography before early discharge. Six of the 42 hospitals supplied written instructions to the parents for observations at home.

Observation

Children admitted for observation were mainly admitted to a pediatric ward (63%). Ten hospitals (21%) used the intensive care unit (ICU), though some of them used the ICU for younger children only. Other wards used for observation of children were the emergency ward, the pediatric surgical ward as well as the general surgical ward.

Forty-five hospitals (90%) used a systematic assessment scale for the level of consciousness as an observation parameter. The most common was the RLS, used in 84% of the hospitals. Three hospitals (6%) reported the use of the pediatric GCS during the observation period. Most hospitals also used other observation parameters such as blood pressure, pulse rate and pupillary response. Fourteen (28%) hospitals used a standardized observation scheme.

The frequency of the assessments varied from hospital to hospital. Thirty-nine hospitals (78%) assessed patients at least once every hour. In 27 (54%) hospitals the assessment frequency was individualised, mainly depending on the type of trauma, the status of the child and the doctor's individual ordination. The duration of the observations varied from a maximum of 12 hours in 16% of the hospitals to 12 to 24 hours in 74% of the hospitals. Ten percent did not specify the duration of the observations.

Follow-up

Three hospitals offered routine outpatient follow-up after a minor head injury. Nine hospitals (18%) offered individualized follow-up for patients with persistent symptoms and/or other complications during and after hospitalization

Paper II

Clinical factors associated with intracranial complications after pediatric traumatic head injury: an observational study of children submitted to a neurosurgical referral unit

During six years, a total of 102 children were admitted to the neurosurgical intensive care unit after head injury and were initially considered for inclusion. Two patients were excluded due to the initial treatment of the head injury at a neurosurgical unit in another region. The mean age was 10.6 years (0-17 years); 20 children < 5 years of age.

Traffic accidents (50%) were the main cause of head trauma, followed by falls (36%). Thirty-two percent of all children were injured in bicycle and motorcycle accidents and of the 9 children wearing a helmet in these accidents, 1 (11%) had an EDH, 1 (11%) had a subacute SDH and 7 (78%) had other diffuse intracranial injuries, such as cerebral contusions, DAI and tSAH. Of the 17 children who were verified not to have worn a helmet during the bicycle or motorcycle accident, 12 (71%) had an EDH and 5 (29%) had other intracranial injuries.

Loss of consciousness and amnesia

Fifty-seven of the 100 children (57%) had LOC related to the head injury and 67 (67%) were verified or assumed to have post-traumatic amnesia. Fifty-two of the 90 patients (58%) with intracranial injury reported LOC, and 62 (69%) had amnesia. Both loss of consciousness and amnesia were absent in 23% of the children with intracranial injuries.

Interventions

Fifty children underwent neurosurgical intervention and 19 underwent acute neurosurgery before being admitted to the NICU (Table 1). Twelve of these 19 were children with an EDH; 2 had an evacuation of an SDH.

		ICI			**Neurosurgery**		**Outcome (GOS)**	
HISS	n	Yes	No	**EDH**	Yes	No	Good	Poor
Minimal	9	7	2	4	6	3	9	0
Mild	32	30	2	20	12	20	32	0
Moderate	36	31	5	19	17	19	34	2
Severe	23	22	1	5	15	8	18	5
Total	100	90	10	48	50	50	93	7

Table 1. Classification of head injury according to Head injury severity score (HISS) in relation to intracranial injury (ICI), epidural hematoma (EDH), neurosurgical intervention and outcome according to dichotomised Glasgow outcome scale (GOS).

ICI = Intracranial injury, i.e. one or several pathological findings such as diffuse axonal injury, EDH, subdural hematoma, cerebral contusion or traumatic subarachnoid haemorrhage. No ICI = isolated skull fracture, commotio cerebri or both.

Seven children with intracranial injury, six of them requiring neurosurgery, could according to the described symptoms at initial assessment be classed as minimal head injury, according to HISS (Table 1). Of the six children who needed neurosurgery; 4 had evacuation of their epidural hematoma, 1 received an ICP catheter and 1 had revision of a depressed skull fracture. Symptoms presented by the 9 children who were classed into minimal head injury, and leading to further investigation with a CT scan, are detailed in Table 2.

Symptoms	**n**	**Comments**	**Intervention**
Headache and vomiting Decreasing consciousness	3 (2)	all 3 with ICI	Neurosurgery
Initially fluctuating somnolence/ aggressiveness in ambulance	1	also high-force trauma patient with ICI, but GCS 15 at the ER	Observation
Open wound – type of trauma Open wound / skull fracture	3	1 of 3 with ICI, due to shot wound	1 to neurosurgery
		2 of 3 with impression / skull base fracture	1 to neurosurgery 1 to observation
Type of trauma/behaviour	1	ICI	Neurosurgery
Type of trauma/low age	1	ICI	Observation

Table 2. Symptoms presented by the 9 children classed with minimal head injury leading to further neuroradiological investigation.

Other immediate symptoms associated with head injury were headache (30%), nausea (24%), vomiting (14%) and seizures (9%). Seventeen patients complained of both headache and nausea; 15 (88%) presented with an intracranial injury. Both headache and vomiting were presented by 6 children, 5 (83%) had an intracranial injury.

Outcome

Clinical outcome was assessed according to Glasgow Outcome Scale (GOS). According to a dichotomized outcome 93 patients (93%) had a good outcome and 7 patients (7%) had a poor outcome. All 7 children with poor outcome were injured in traffic accidents. Two children did not survive; one with aSDH and the other with severe tSAH.

Paper III

Comparison of capillary, venous and arterial levels of protein S100B in patients with severe brain pathology

In this study we investigated the possibility of measuring protein S100B from capillary and arterial specimen and compared the measurements to the concentrations from standard venous sampling method. Severely brain injured patients were included in the study to get as broad variation of the S100B concentration as possible.

A total of 98 patients were included in the study; 44 females (mean age 53, range 25-77 years) and 54 males (mean age 53, range 18 to 79 years). Blood was sampled during an average of two days (range 1 to 6 days). Patients included in the study were suffering from SAH, aSDH, tSAH with cerebral contusions, hypertensive intracerebral hemorrhage, cerebral edema, cerebral malignant infarction and severe bacterial meningitis. Samples from four patients were excluded from the study: one due to suspected mix-up with other samples at analysis, one venous (0.623 µg/L) and two capillary samples due to problems at sampling (1.080 µg/L and 1.120 µg/L).

Potential outliers and excluded data

Pairs of capillary and venous samples were collected on 165 occasions from 71 patients. Venous and arterial samples were collected on 91 occasions from 36 patients and capillary and arterial samples on 125 occasions from 58 patients. In 37 patients, double capillary samples were drawn on the day of inclusion. We note from original data (Figure 1, scatter plot) that two venous samples appear extremely elevated compared to the simultaneously measured capillary samples (difference Ven-Cap: 0.898 µg/L and 0.725 µg/L). Omitting these two venous samples from the analysis (potential outliers), we gain highly improved results for both capillary-venous and venous-arterial pairs of samples. The results, with and without exclusion of potential outliers, are summarized in Table 3.

Relation between capillary and venous samples

The difference between capillary and venous S100B concentrations in the 163 measurements (71 patients), using Student's t-test, was statistically significant with a mean difference of 0.076 µg/L (95% CI 0.065-0.087, $p < 0.001$). A Bland-Altman plot (Figure 2) of all 163 paired measurements shows that capillary S100B is slightly increased relative to venous S100B. The line of regression in Figure 2 slopes slightly upwards (0.031, NS), which implies that the mean difference between capillary and venous measurements is nearly constant or slightly increased at higher serum concentrations. Linear regression

analysis for prediction of venous S100B from capillary measurements gives a slope of 0.984 and a constant –0.061µg/L. The RMSE is 0.064 µg/L.

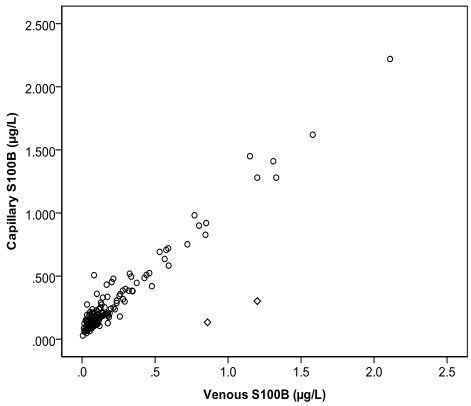

Figure 1

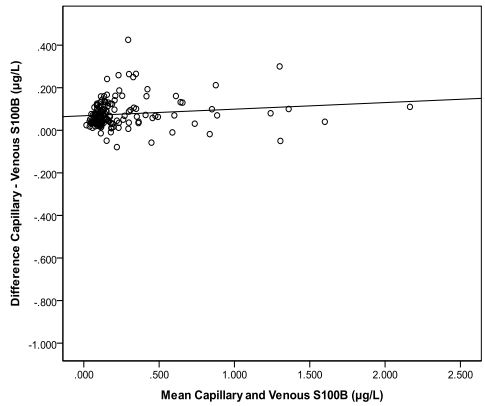

Figure 2

Relation between venous and arterial samples

The mean difference between the 89 paired venous–arterial samples was 0.013 µg/L (95%CI 0.007-0.019). A Bland-Altman plot (Figure 3) shows a slightly positive slope of regression 0.062 (p = 0.026), and prediction of venous samples from arterial samples (slope 1.029, constant +0.010 µg/L) gives an RMSE of 0.028 µg/L.

Relation between capillary and arterial samples

Capillary samples were on average 0.095 µg/L higher than arterial measurements (95% CI 0.081-0.109). The slope of the linear regression line is slightly positive 0.038 (NS, Figure 4). Prediction analysis with linear regression between arterial and capillary measurements (slope 0.938, constant -0.078 µg/L) gives an RMSE of 0.075 µg/L.

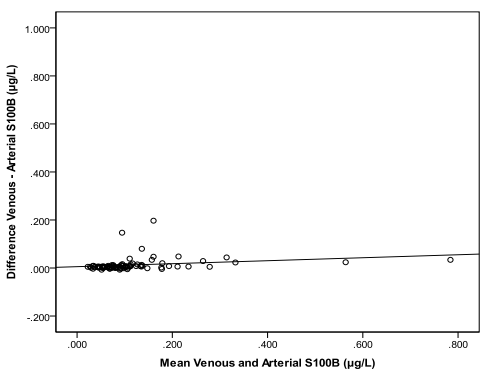

Figure 3

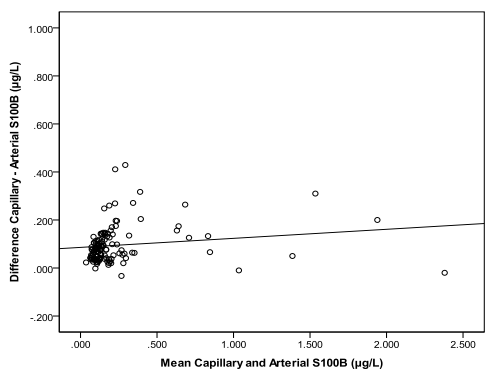

Figure 4

Analysis						Suspected outliers included				
Relations between:	N sample pairs	Mean difference (µg/L)	95% CI (µg/L)	Slope	p-value	N sample pairs	Mean difference (µg/L)	95% CI (µg/L)	Slope	p-value
Cap and Ven	163	0.076	0.065-0.086	+ 0.031	NS	165	0.065	0.047-0.083	-0.015	NS
Ven and Art	89	0.013	0.005-0.058	+0.062	0.026	91	0.031	0.007-0.019	+0.594	<0.001
Cap and Art	126	0.095	0.081-0.109	+0.038	NS					

Linear regression analysis for the prediction of:		N sample pairs	Prediction error RMSE (µg/L)	Prediction analysis	N sample pairs	Prediction error RMSE (µg/L)
Ven from Cap	Ven = 0.948*Cap - 0.061	163	0.064	Ven = 0.942*Cap - 0.049	165	0.116
Ven from Art	Ven = 1.029*Art + 0.010	89	0.028	Ven = 1.157*Art + 0.014	91	0.126
Art from Cap	Art = 0.938*Cap – 0.078	126	0.075			

Table 3. Summary of the relations between capillary (Cap), venous (Ven) and arterial (Art) S100B measurements. The right side of the table gives the relations when the two venous suspected outliers are included.

Paper IV

Age and gender specific reference values for venous and capillary S100B in children

A total of 465 children (age range 1 to 16; 260 boys, 205 girls) were included prospectively. 381 children had a venous sample drawn before anesthesia (Ven1), 446 had a venous sample drawn after anesthesia (Ven2), and 379 had a capillary sample drawn and analyzed (Cap).

The mean difference between Cap and Ven2 S100B was 0.120 µg/L (95% CI 0.107–0.132, $p < 0.001$). This difference was more pronounced in children less than 5 years than in the older ones: 0.141 µg/L vs. 0.103 µg/L ($p = 0.004$).

Influence of age and gender

Serum S100B concentrations were generally higher in younger children for both venous and capillary samples (Figure 5). The negative relation between S100B and age was also shown by negative Spearman rank correlation coefficients for both Ven1 -0.34, Ven2 -0.36 and Cap -0.29 ($p < 0.001$ in all three cases). No statistically significant gender differences for Ven1, Ven2 or Cap were found when all ages were treated jointly. However, after division of the patients into age groups, there was a statistically significant gender difference in the age group 1-2 years for Ven2 ($p = 0.028$) and Cap ($p = 0.001$), but not for Ven1: girls had a significantly higher mean S100B than boys. There were no significant gender differences in the other age groups.

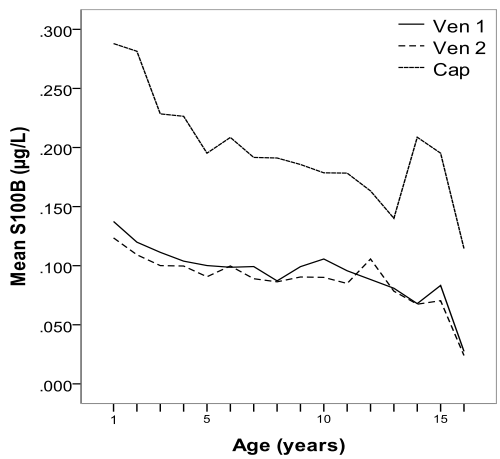

Figure 5

Reference values

For each age, reference levels for Ven1 S100B and Cap S100B are presented in Figures 6 and 7 as upper 95th quantile. The figures show that children aged 1 and 2 years have a higher S100B reference level. The reference levels of children aged 3 years and older did not vary significantly with age or gender. The reference level for children ≥ 3 years was found to be 0.144 µg/L for Ven1 and 0.400 µg/L for Cap.

Tables 4-5 show the age dependent reference levels for venous and capillary samples in children. Interestingly there was also a significant gender difference in capillary reference levels for two-year-old children (p = 0.003); girls higher than boys: 1.28 µg/L vs. 0.46 µg/L. No such gender difference was found in Ven1.

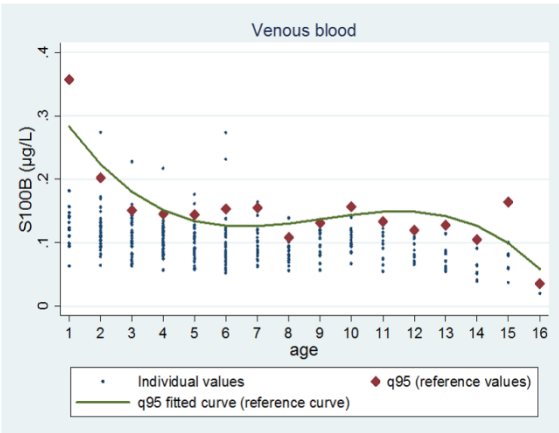

Figure 6. Summary of age-related reference values for venous S100B in children.

Venous 1	**Reference level**
Age (years)	q95 S100B µg/L (n)
1	0.36 (15)
2	0.20 (38)
3-16	0.14 (328)

Table 4

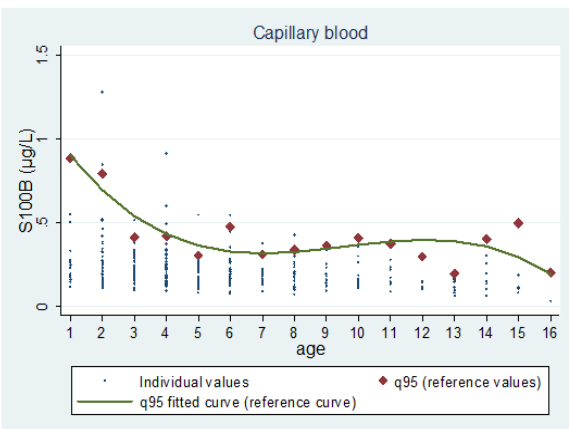

Figure 7. Summary of age-related reference values for capillary S100B in children.

Capillary		**Reference level**
Age (years)		q95 S100B µg/L (n)
1		0.89 (19)
2	Total	0.79 (47)
	Girls	1.28 (17)
	Boys	0.46 (30)
3-16		0.40 (313)

Table 5

General discussion

Pediatric traumatic head injury is a field many individuals come in contact with, either as a patient, parent, relative or as a health care professional. It is a broad and versatile area with many factors involved and with risk factors different from adults. Research has been performed for decades, especially in the UK and the US, but not until recently we have begun to see results from larger multicenter studies as an attempt to optimize the management guidelines for head injured children.[55, 101]

This thesis has its main setting in the Scandinavian country of Sweden; a country with a somewhat different prerequisite and health care system than both UK and USA. The Scandinavian research on head injuries has mainly focused on adults, though the SNC also vaguely included children in its recommendations.[4] Guidelines for adults have previously also been considered safe to use for children, although with more liberality towards CT scanning.[60] The recommendations have not been validated, but the adult guidelines are being implemented in the Scandinavian countries. However, economical and regional aspects (capacity of routine neuroradiological investigations and long distances to the nearest hospital) may have contributed to the slow implementation rate and the resuming of local regimes.

In the first two studies presented (Paper I-II) we have investigated the current status of the management of minor head injured children in Sweden, outlined clinical factors associated with intracranial complications after head injury and assessed the reliability of the current practice in Sweden. The results were not unexpected, considering the lack of specific pediatric head injury guidelines. As a probable consequence there were large local variations, especially concerning admissions and neuroradiology. This was outlined by the fact that some Swedish hospitals reported CT scanning and some skull radiography as a criteria for discharge even in the years 2004-2006, although the SNC guidelines did not recommend skull radiography (Paper I). CT performance rate in MHI children has been relatively low compared to other countries.[16, 74-76] This may be a consequence of an increased admission rate and even routine admissions for all minor head injured children in some of the hospitals in Sweden (Paper I).

In the second study (Paper II) we retrospectively studied children who had been admitted to a neurosurgical unit after head injury. By focusing on several factors considered as predictive factors for intracranial pathology after closed head injury, we could conclude that neither LOC, amnesia, initial GCS score or the HISS classification were reliable factors in children. Hence, management of MHI in children based solely on adult head injury guidelines is not enough. Other clinical symptoms for admitting a child for observation or CT scanning are e.g. persistent nausea, vomiting, headache, dizziness, presence of scalp hematoma or posttraumatic seizure.[189-191] The importance of symptoms

such as nausea, headache and vomits has in the adult population been considered conflicting and even more so in the pediatric population (Paper II). Consequently it can be difficult to make a proper decision regarding an early discharge without a CT scanning. Although the outcome after brain injury is in general more favorable among children (Paper II) than compared to adults,[192] the risk of missing a hematoma and delaying the time to correct diagnosis and treatment makes the option of observation for at least one day more attractive than an early discharge from the ED. However, the consequent extra work load and increased cost is quite obvious. According to a previous study by Holsti et al the majority of children (98%) who were observed over night at an observational unit had also received a CT scanning which were all normal. The majority of those children were safely discharged the next day.[191]

CT scanning is so far the best method of accurately diagnosing clinically relevant intracranial lesions and fractures. However, during the last decades there have been debates about the possible detrimental effect of CT scanning, especially on younger children who have a longer life expectancy and are probably more vulnerable to radiation induced malignancies due to more dividing cells.[72, 78] There is no doubt that a CT scanning has a clear benefit for the single person, but as the number of CT investigations increase (some data from the US report that up to 50% of patients with head injury receive a head CT)[101] there is a need to address this issue. Younger children can be more challenging to manage and some even require sedation before a CT can be performed, which itself is a risk and eliminates the possibility of clinical neurological observation. The awareness of this problem has spread to the clinics and newer guidelines proposed in the UK and US aim to reduce unnecessary CT examinations. The proposed guidelines are especially created for children who have a very small risk of having an intracranial bleeding after MHI.[55, 101] These derivation rules are based on clinical symptoms and findings presented at admission before a CT can be issued, but although internally validated there are still need for external validation studies before these can be implemented. As previously addressed, due to the differences in prerequisites, these studies should also be prospectively validated in Scandinavian settings before they can be safely introduced.

However, current Scandinavian routines are not fully acceptable for management of the pediatric population and we noticed a huge need and plea for national guidelines (Paper I). Decision making based upon physicians' individual evaluations should never be underestimated. Nevertheless, since younger residents are the ones most likely to be the attending physician at the ED, and this patient group is shared among several departments (pediatrics, general surgery, pediatric surgery), it is even more important to improve or develop new guidelines for the management of these children (Paper I).

The above mentioned problems and challenges were the reasons for why we began to look for other options to improve our own partially implemented guidelines. Protein S100B is the marker with the greatest potential so far in head injury management and it is now being recommended as a complement in the Scandinavian adult head injury guidelines as a decision instrument for whether a CT should be performed or not after MHI. Our final goal was to investigate the possibility of introducing this marker into the guidelines of the management of pediatric head injuries. The repeat-CT ordering rate has been estimated to

be reduced by 30% with proper use of S100B. The utilization of S100B in children could even have a greater impact as the CT rate is higher, though further studies are warranted. To date there are no blood tests drawn after suspected head injury, specific for the brain, though current research show that S100B could be a useful parameter in mild head injuries. The challenge in the management of children also includes the challenge of blood sampling; the chubby infants and the younger children require local topical anesthetics, and are in general difficult to draw a sample from. Venous sampling would not be an efficient method in these situations. Although venous sampling is the golden standard, capillary sampling is usually a good option when venous sampling seems impossible or fail.

In Paper III and IV we set out to investigate the protein S100B and specifically focused on different methods of sampling S100B and analysis; capillary and arterial measurements (Paper III). We included patients with known acute and severe brain pathologies to achieve as variable concentrations as possible, for simplicity on adult patients. We found that capillary measurements of S100B can be analyzed with Elecsys S100 assay (Roche Diagnostics), but the venous and capillary concentrations were not interchangeable and we concluded that capillary and venous measurements should be considered as separate although related variables (Paper III). The variance between two paired capillary specimen was also relatively high (0.05 µg/L), which could make the capillary method less reliable. We believe that this variation could be due to the samples being collected from adult fingers, hence mainly affected by the method of sampling, rather than biological or analytical variation (Paper III).

As a result from Paper III, we concluded that separate reference values for capillary and venous S100B in children were needed. Venous S100B reference values for children had previously been investigated using another method of analysis (Lia-mat Sangtec S100 assay, Ab Sangtec Medical). Since most hospital laboratories in Scandinavia already have the setting for Elecsys analysis, we wanted to produce reference values applicable and ready to be used for Scandinavian settings. Our study showed that capillary S100B values in children were not equal to venous, but instead elevated by a mean difference of 0.12 µg/L (Paper IV). Both capillary and venous S100B were age-dependent in children; children younger than 3 years had significantly higher reference values than children 3 years or above. The reference values for children 3 years or older was determined to 0.14 µg/L for venous samples and 0.40 µg/L for capillary samples. Compared to another recent study by Castellani, our venous S100B reference level for children 3 years and older were slightly lower (compared to 0.16 µg/L), which should be considered when future studies are performed.

Studies on capillary measurements of S100B have not been published before, although we feel that this has been an absolute necessity for investigating especially when our goals are to optimize the management of acute events such as head injuries in children. We already know that protein S100B is not an ideal marker for brain injuries, but it is the marker which so far has the best potential of being a useful tool in head injury management, even in pediatric patients. Adding a blood sample to the guidelines would be less complicated than to change and implement totally new guidelines.

Main conclusions and future aspects

- There are no specific guidelines for management of pediatric minor head injury in Sweden and routines concerning radiology and discharge criteria vary between hospitals. Several departments are involved in the acute management and observation of the head injured children, the attending physician is often a less experienced person under training and less than 1/3 of the hospitals use standardized observation schemes. There is an urgent need and plea for specific pediatric guidelines.
- Only a minor part of all children with a head injury suffer from an intracranial complication or is in need of a neurosurgical procedure. Outcome after head injury is in general favorable. Factors such as brief loss of consciousness and posttraumatic amnesia, which are considered as risk factors for intracranial complications in adults, were absent in 23% of the children admitted to neurosurgery. Hence, management based upon adult guidelines, history of unconsciousness or amnesia is unreliable in children.
- Capillary concentrations of S100B is not equal to venous, but differ in average about 0.08 µg/L. Separate reference values should be considered. Arterial S100B is only slightly lower than venous (0.01 µg/L) and can be used parallel to venous samples.
- Reference levels of venous and capillary serum S100B in children are age and gender dependent, resulting in higher levels among children aged 1 and 2 years. The reference levels for children 3 years or above is 0.14 µg/L for venous samples and for capillary samples 0.40 µg/L.

Future studies

- The upcoming study is a prospective multicenter study to test the clinical usefulness of venous and capillary S100B in pediatric head injury. In this study we would also be able to clinically evaluate and validate proposed pediatric guidelines (CHALICE and PECARN) in the Scandinavian hospitals.
- Methods for analyzing other serum markers, e.g. NSE or GFAP are now becoming more available and might be of great interest in the near future. We have the possibility of investigating other reference levels in the same children.

Sammanfattning på svenska

Summary in Swedish

En av de största orsakerna till svårt handikapp och död i västvärlden är traumatisk hjärnskada som uppstår till följd av våld mot huvudet. Utav vuxna och barn är det generellt sett barn som klarar sig bättre efter våld mot huvudet men det är ändå till stor del barn som söker akutmottagning p.g.a. skallskada. De flesta av barnen har en så kallad lätt skallskada (ca 90 %), medan resten har moderat till svår skallskada. Barnmisshandel, våld mot huvudet eller skakningar med hjärnskada som följd förekommer oftast bland de yngsta barnen (< 2 år) och dessa klarar sig oftast sämre än övriga barn.

För den primära handläggningen utgör de lätta skallskadorna också den största utfordringen; att skilja på dem med större risk att utveckla blödning i hjärnan och de utan risk. Detta bör göras utan att barnen utsätts för alltför många onödiga undersökningar, röntgenstrålning eller sjukhusinläggningar. I Sverige finns inga nationella riktlinjer för handläggning av lätta skallskador hos barn och handläggningen baseras oftast på lokala riktlinjer, vuxnas handläggningsriktlinjer och erfarenhet. De vuxna riktlinjerna baseras på den primära medvetandegrad patienten uppvisar vid ankomst till akutmottagningen, förekomst av kortvarig medvetslöshet eller minnesförlust (amnesi). Dessa symptom är speciellt svåra att värdera på yngre barn som ännu inte utvecklat sina språkfärdigheter. Datortomografi (DT) är liberalt rekommenderat på de med lätta skallskador men inte på de med s.k. minimala skallskador, d.v.s. de utan symptom.

DT är en utmärkt undersökningsmetod för att finna akuta blödningar i hjärnan, men stråldosen är hög. På senare tid har det diskuterats mycket kring DT:s risker att orsaka cancer. DT anses särskilt riskfyllt bland barn eftersom den effektiva dosen i relation till kroppsmassan är större; barn har även flera delande celler och flera levnadsår än vuxna. En del barn kan även behöva lugnande medicin eller sövning inför en DT undersökning, vilket bör undvikas såvida inte misstanken om blödning är stor.

För att ytterligare förbättra handläggningsrutinerna för de lättare skallskadade patienterna håller man nu på att införa ett blodprov för att mäta förekomst av ett protein kallat S100B. Det är en hjärnskademarkör som ökar i blodet vid hjärnskada. Vid avsaknad av detta protein förekommer ingen hjärnskada och risken att utveckla senare komplikationer eller blödningar är ytterst minimala. Forskningen kring S100B och barn med lätta skallskador har nyligen kommit igång och vissa studier har påvisat positiva resultat om att blodprovet även kan användas för att utesluta traumatisk hjärnskada på barn. Markören är inte det mest optimala proteinet men än så länge det bästa som finns på marknaden. Dock krävs ytterligare studier innan markören kan rekommenderas och introduceras i barnhandläggningen.

Denna avhandling försöker uppsummera basfakta, presentera forskning som är gjord inom skallskadehandläggningen, diskutera utfordringar inom handläggningen av barnskallskada, samt introducera andra möjliga metoder att optimera de nuvarande handläggningsrutinerna.

Den första studien är en enkätundersökning bland 51 sjukhus och akutmottagningar i Sverige som handlägger barn med skallskada. Studien visar förekomsten av stor variation i handläggning av barn, särskilt vad gäller DT, skallröntgen och inläggningskriterier. Barnen handläggs oftast av allmänkirurgerna och till mindre del av barnläkarna. Det är de yngre läkarna (AT-läkare och ST-läkare) som mottar patienterna och barn som är i behov av fortsatt observation läggs oftast in på barnavdelningen eller kirurgiavdelningen, men även i vissa fall på intensivvårdsavdelningen. De flesta sjukhus saknar ett observationsschema specifikt för dessa barn och både frekvensen och längden på observationerna varierar. Från denna studie konkluderas att svenska sjukhus är i behov av handläggningsrutiner för lätta skallskador på barn.

Den andra studien är en journalstudie som undersöker symptom och kliniska faktorer på de barn som överflyttats till en neurointensivvårdsavdelning (NIVA) efter skallskada under åren 2002-2007. Varken kortvarig medvetslöshet eller minnesförlust förekom hos 23 % av de barn som blev inlagda på NIVA, och 6 barn som senare fick påvisat en hjärnblödning hade man enligt de vuxna riktlinjerna kunnat värdera som minimal skallskada vid första undersökningen; 4 av dessa 6 barn opererades för sin blödning i hjärnan. Därmed konkluderas att handläggningsriktlinjer som baseras enbart på vuxenriktlinjer inte är pålitliga att användas i bedömningen av barn med skallskada.

Den tredje studien förflyttar fokus till hjärnskademarkören S100B för att från ett mera laboratoriemässigt perspektiv utreda om protein S100B kan mätas i kapillärt och arteriellt blod, samt jämföra dessa med ett samtidigt taget venöst prov. Kapillärt prov har den fördelen att vara något smidigare att ta, det är mindre smärtsamt för barnet jämfört med ett venöst prov och är att föredra speciellt på yngre barn. Blodprov erhölls från vuxna med svår hjärnskada för att säkerställa förhöjda värden. Den kapillära S100B koncentrationen var i medel 0,08 µg/L högre än det venösa, medan den arteriella var närmast likställt med det venösa. Skattningsfelet vid försök att förutsäga och beräkna venöst S100B från kapillära prover var 0,06 µg/L vilket är rätt högt. Därmed konkluderas att kapillärt S100B prov inte kan likställas med venöst S100B och att det kräver bl.a. separata referensvärden.

Den sista och fjärde studien i avhandlingen ger referensvärden på både kapillärt och venöst S100B på barn utan hjärnskada. Referensvärdena är indelade i åldrarna 1, 2 och 3 år och äldre, eftersom nivåerna är något högre bland de allra yngsta barnen. Referensvärdena för 3-16 åringarna är 0,14 µg/L (venöst) och 0,40 µg/L (kapillärt).

Avhandlingen har visat på problemställningar inom handläggningen av barn med skallskador och har introducerat och försökt optimera användbarheten av hjärnmarkören S100B på barn. Kommande studier bör utvärdera den kliniska rollen och säkerheten av både venöst och kapillärt S100B inom barnskallskadehandläggningen i Skandinavien.

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