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CEREBROSPINAL S100-B: A POTENTIAL MARKER FOR PROGRESSIVE INTRACRANIAL HEMORRHAGE IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY

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Abstract
Objective: Traumatic brain injury (TBI) is associated with cerebrovascular dysfunction and changes of the blood-brain barrier (BBB) function. Although knowledge about the function of the BBB would be of high interest, non-invasive neurodiagnostic tools are still lacking. In this context it has been shown, that the astrocytic protein S100-B is a significant parameter for neuronal damage. However, there is only poor knowledge about the dynamics of S100-B in cerebrospinal fluid (CSF) and serum of patients with severe TBI. Therefore, the aim of this study was to analyze intrathecal and systemic concentrations of S100-B in patients with severe TBI in correlation to the development of progressive intracranial hemorrhage (PIH) as well as to the CSF/serum albumin ratio (Q_{alb}), as functional parameter of the BBB.
Patients and Methods: In patients, suffering from severe TBI (GCS ≤ 8pts) and respectively healthy control patients, albumin for calculating the CSF/serum albumin ratio (Q_{alb}) as well as S100-B protein were analyzed in CSF and serum. Samples were collected immediately after placement of a ventricular catheter and 12h, 24h, 48h and 72h after TBI. S100-B was quantified using Elecsys S-100® assay (Roche® Diagnostics; Mannheim, Germany). Volume measurements of focal mass lesions based on CT images taken during the first 72 h after TBI were obtained according to the Cavalieri's Direct Estimator method.
Results: 21 TBI-patients and respectively 10 healthy controls were enrolled. In patients exhibiting a mean ICP >15mmHg (n = 15) CSF levels of S100-B were significantly increased on admission (819 ± 78 pg/ml) compared to patients with ICP ≤ 15mmHg (n = 6, 175 ± 12 pg/ml) as well as to the control group (n = 10, 0.8 ± 0.09 pg/ml). In the group with ICP >15mmHg 8 patients developed PIH A positive correlation was found between CSF S100-B and ICP (r^2 = 0.925, $p<0.001$). Furthermore a positive correlation between serum S100-B and Q_{alb} was found for each sampling point (r^2 = 0.793, $p<0.001$).
Conclusions: The cerebrospinal and serum concentration of S100-B in patients with severe TBI was evaluated. Monitoring cerebrospinal S100-B might help to prospectively identify patients with PIH.

Key-words: S100-B, traumatic brain injury, blood brain barrier, cerebrospinal fluid

INTRODUCTION

Traumatic brain injury (TBI) is one of the major reasons for morbidity and mortality especially in young trauma patients (Farin and Marshall 2004). Thus, severe TBI with an initial Glasgow Coma Scale score (GCS) of ≤8pts is associated with a mortality rate of approximately 40% (Nortje and Menon 2004). The high rate is substantially influenced by the extent of the primary impact including the mechanical injury to brain tissue as well as the development of secondary brain damage due to progressive intracranial haemorrhage (PIH) as well as immunologic reactions (Chesnut et al. 1993; Hukkelhoven et al. 2003).

In this context studies in the recent past could clearly demonstrate that initial cranial CT-scans (CCT), performed within 1 to 2h of traumatic brain injury (TBI), do not represent the later extent of intracranial haemorrhage (ICH) (Marshall et al. 1983; Lobato et al. 1997; Oertel et al. 2002). Moreover, Servadei et al. could demonstrate that 23 to 47.5% of patients develop PIH within 24 to 72h of TBI (Stein et al. 1993; Servadei et al. 2000). As patients with PIH have a greater degree of subsequent elevations of intracranial pressure (ICP), and account for almost 25% of patients who require craniotomy for haematoma removal, early recognition is potentially crucial for triggering timely medical or surgical intervention to avert irreversible neurological deteroriation (Oertel et al. 2002).

Concerning reliable biochemical markers for the assessment of the extent of TBI, especially the protein S100-B has been reported to be of major importance. S100-B protein is an acidic calcium-binding protein, which is mainly present in astroglial and Schwann cells (Pleines et al. 2001). The clinical relevance of S100-B serum assessment is widespread. For identification of high-risk patients after minor head trauma (MHT), S100-B has recently been reported by Biberthaler et al. (Biberthaler et al. 2004; Biberthaler et al. 2006). Moreover, increases in cerebrospinal fluid (CSF) S100-B concentrations have been described in patients with TBI to correlate with ICP and focal mass volume, determined from CCT (Hayakata et al. 2004). In cancer research serum S100-B serves as a parameter for evaluation of blood-brain barrier (BBB) integrity in patients with cerebral metastasis receiving iatrogenic BBB disruption by mannitol infusion (Marchi et al. 2003).

However, there is only poor knowledge about the dynamics of S100-B in CSF and serum of patients with severe TBI, developing PIH. Therefore, the aim of this study was to analyze intrathecal and systemic concentrations of S100-B in patients with severe TBI in correlation to the development of PIH as well as to an iatrogenic disruption of the BBB using mannitol infusions (Reiber and Felgenhauer 1987).

Patients and Methods

Study Design and Patient Collective

The study was conducted between November 2003 and November 2005 at our academic level-one trauma centre. The study protocol was approved by the University's Medical Board of Ethics (reference no. 330/03). All patients with a minimum age of 18, who had sustained an isolated closed TBI, presenting an initial GCS ≤8pts and radiological signs of ICH on the initial CCT (within 90min after the onset of TBI) were prospectively enrolled. Written informed consent was obtained from each patient when the patient returned to consciousness or in case of remaining unconscious a next of kin or a legal representative was asked. Demographic clinical information (i.e. gender, age, GCS) and history of systemic diseases was recorded using standardized data collection forms. For avoiding iatrogenic or pre-existing S100-B and BBB alterations, patients in whom initially (within the first 12h) surgical intervention was indicated, were excluded from the study as well as patients with a history of pre-existing neurological disease.

For assessing control values, CSF and serum samples were drawn from healthy patients, who obtained spinal anaesthesia for an elective orthopaedic intervention.

Clinical Management Protocol

After trauma resuscitation and initial CCT, intraventricular drainage catheters (TraumaCath®, Integra® Neurosciences; Plainsboro, USA) were inserted in all patients (within 90 ± 45min after admission) for continuous ICP- monitoring as well as for CSF-drainage (Krotz et al. 2004). Patients were admitted to the intensive care unit (ICU) and treated according to the guidelines of the *Brain Trauma Foundation* (The Brain Trauma Foundation 00). Management goals included maintenance of ICP at a level lower than 20mmHg and cerebral perfusion pressure (CPP) higher than 70mmHg. In case of intracranial hypertension all patients were subjected to continuous mild hyperventilation, which was induced with $PaCO_2$ at 35mmHg, mild hypothermia (35°C). All patients received high dose barbiturates. Mannitol infusions were administrated in case of further increasing ICP. No corticosteroid was administered.

In patients in whom ICP remained <15mmHg for 48h without the need for mannitol administration or CSF drainage, the intraventricular catheter was removed after 72h.

Sampling Procedures and Analysis of S100-B Protein

According to a serial protocol, 3ml drained intraventricular CSF and paired 5ml of peripheral blood were collected. The first sampling time point was immediately after insertion of the intraventricular drainage catheter (within 90 ± 45min after TBI). In a standardized manner, the remaining CSF- and serum- samples were obtained 12h, 24h, 48h and 72h after TBI. The samples were centrifuged to remove cellular debris and the supernatant was processed immediately. Concentration of S-100B in CSF and serum was determined using the commercially-available electrochemiluminescence immunoassay (ECLIA; Elecsys S-100® assay, Roche® Diagnostics; Mannheim, Germany) (Mussack et al. 2006). Synthetic human S-100B was used for standardization.

Assessment of Blood Brain Barrier (BBB) Function

In order to determine whether S100-B dynamics correlate to posttraumatic BBB disruption, the ratio of CSF and serum albumin (Q_{alb}) was calculated for each observation point separately. According to Reiber and Felgenhauer, Q_{alb} was proven as sensitive parameter for the BBB dysfunction (Reiber and Felgenhauer 1987). The disturbance of the BBB was assessed as follows: Q_{alb} values below 0.007 were considered as normal, values between 0.007 and 0.01 as mild dysfunction, values between 0.01 and 0.02 as moderate dysfunction, and levels above 0.02 as severe dysfunction. Albumin levels were measured using standardized turbidimetric assays (Cobas Integra® Albumin; Roche® Diagnostics; Mannheim, Germany).

Defining Progressive Intracranial Haemorrhage (PIH) in Consecutive CT-scans

Focal mass lesions included contusion, subdural haematoma, epidural haematoma, and intracerebral haemorrhage. Volume measurements of focal mass lesions based on serial control CT scans taken during the first 72h after TBI were obtained according to the Cavalieri's Direct Estimator method (25). PIH was de-

fined as an unambiguous increase of the lesion size amounting for 25% or greater increases in at least one dimension of one or more lesions seen on the control CT scan. Increased midline shift, hemispheric swelling, or progressive loss of the diameter of the basilar cisterns was defined as progressive after effects.

Data Analysis

The Sigma Stat® 3.0 software package (SPSS® Inc., Chicago, USA) was used for all statistical analysis. Statistical significance between groups was determined by the Mann-Whitney U-test. Statistical relation between ICP- and S-100B levels as well as Q_{alb} and S100-B levels was assessed by linear regression analysis. A p-value <0.001 was considered as statistically significant. Data are given in mean ± SEM.

Results

Patient Collective and Clinical Data

In total, 23 patients with severe traumatic brain injuries were enrolled (15 males, 8 females; mean age 44 ± 7years). The major reasons for TBI were traffic accidents or fall from greater heights. There was no evidence of complications, such as intracranial haemorrhage or infection following the insertion of the intraventricular catheter.

Three groups of patients were observed. In group I (n = 8) patients with a mean ICP ≤15mmHg were enrolled, group II (n = 8) and group III (n = 7) enrolled patients with ICP values >15mmHg and therefore treated with mannitol infusions. Group II-patients developed no PIH; in contrast to group III-patients all developing PIH. 4 patients of group III received osteoclastic craniotomy 40 ± 14h after TBI. 19 patients made uneventful recoveries, 2 patients died on day 5 and 6. Another 2 patients died on day 8 due to untreatable brain edema and/or brain stem herniation. All of them were group III-patients. These mortalities occurred all during ICU hospitalization. The groups did not differ significantly with respect to prognostic factors on admission such as gender, age or CT classification according to Marshall (Marshall LF et al. 1991).

For the control group CSF- and serum- samples were obtained from 10 healthy volunteers (5 males, 5 females; age: 40 ± 11years) receiving spinal anaesthesia for an elective orthopaedic surgery of the lower extremity.

S100-B in Cerebrospinal Fluid (CSF)

In the control collective cerebrospinal S100-B, obtained via lumbar puncture, accounted for 0.2 ± 0.03pg/ml (n = 10). Since S100-B concentration shows a decrease between ventricular and lumbar CSF with a ratio of 3.5:1 (Reiber 2001), the calculated ventricular S100-B concentration in control patients accounted for 0.8 ± 0.1pg/ml.

In group I (n = 8, ICP ≤15mmHg) CSF S100-B levels were significantly increased on admission (169 ± 12pg/ml) and remained significantly increased until 72h (13 ± 5pg/ml) after TBI in comparison to the control group. Group II-patients presented with S 100-B levels of 839 ± 71pg/ml on admission. The S100-B level of group II remained significantly elevated in comparison to group I until the end of the observation period (160 ± 43pg/ml). CSF S100-B levels in group III accounted for 760 ± 77pg/ml on admission. However, 24h after TBI values increased again in contrast to group I and II and with a significant higher value of 597 ± 50pg/ml, reaching an anew peak at 48h (710 ± 32pg/ml). 72h after TBI levels in group III accounted for 531 ± 32pg/ml, therefore presenting a slight decrease. CSF S100-B levels of group III therefore were significantly higher in comparison to group II during 24 to 72h after TBI (for data see Fig. 1).

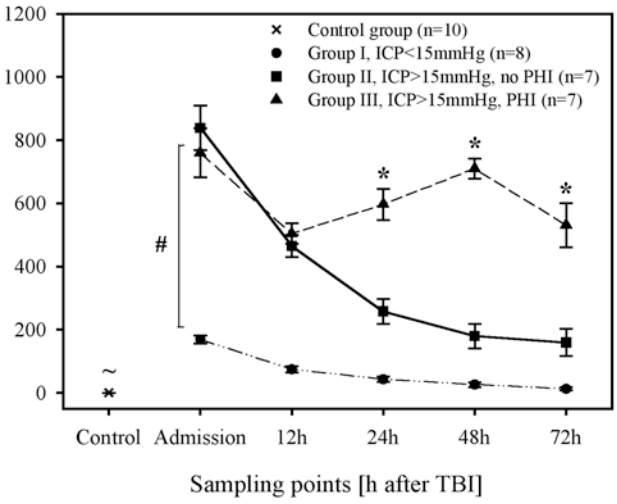

Fig. 1. Graph showing serial changes in cerebrospinal fluid concentrations (CSF) of S100-B in negative controls (squares, n = 10), followed by group I (circle, n = 8) and group II (triangle, n = 7) on admission, 12h, 24h, 48h and 72h, given in pg/ml. Data in mean ± SEM, * versus group I, both patient groups are significantly elevated as compared to negative controls, p<0.001.

S100-B in Serum

In the control collective serum S100-B accounted for 0.1 ± 0.01pg/ml (n = 10). In group I (n = 8, ICP ≤15mmHg) serum S100-B levels were significantly elevated on admission (1.5 ± 0.2pg/ml) and remained significantly increased until 72h (0.4 ± 0.1pg/ml) after TBI in comparison to the controls. In group II (n = 8, ICP>15mmHg, no PIH) the serum level accounted for 5.4 ± 1.0pg/ml on admission and remained significantly elevated in comparison to group I until the end of the observation period (1.4 ± 0.2pg/ml). Serum S100-B levels in group III accounted for 5.7 ± 1.1pg/ml on admission. However, 48h after TBI values increased again in contrast to group I and II and were therefore significantly higher with a value of 3.8 ± 0.7pg/ml, reaching a top value after 72h (4.7 ± 0.6pg/ml). The dynamics of serum S100-B are depicted in Fig. 2.

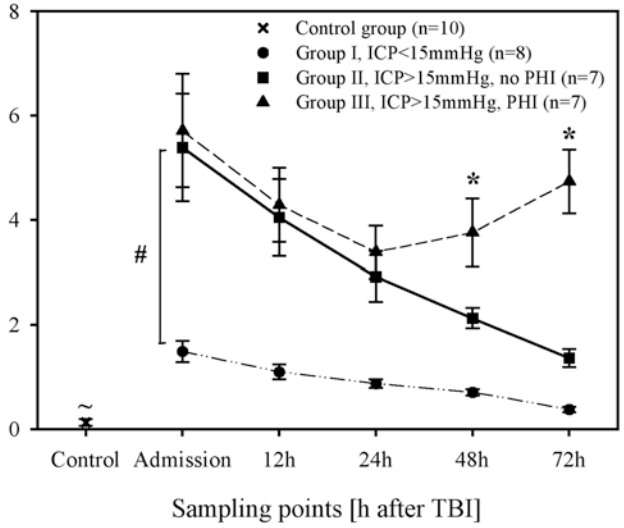

Fig. 2. Graph showing serial changes in serum of S100-B in negative controls (squares, n = 10), followed by group I (circle, n = 8) and group II (triangle, n = 7) on admission, 12h, 24h, 48h and 72h, given in pg/ml. Data in mean ± SEM, *versus group I, both patient groups are significantly elevated as compared to negative controls, $p<0.001$.

Correlation of Intracranial Pressure (ICP) to CSF S100-B

On admission, ICP in group I was 14 ± 1mmHg and decreased continually down to 9 ± 1mmHg at 72h after TBI. None of the patients had an increased ICP during the entire study period. Group II-patients had significantly higher ICP on admission (38 ± 2mmHg) and significantly elevated values in comparison to group I until 72h after trauma (17 ± 2mmHg). For group I and II a positive correlation ($r^2 = 0.925$, $p<0.001$) was found between CSF S100-B and ICP at each sampling point (data not shown).

However, the 2 patients of group II, who died on day 5 and 6, revealed an anew increase of ICP up to 17 and 30 mmHg as well as S100-B concentration up to 242.2 pg/ml and 355.7pg/ml after a continuous decrease of ICP as well as of S100-B values during the first 48h.

Correlation of Blood Brain Barrier (BBB) Dysfunction (Q_{alb}) to CSF S100-B

The CSF/serum albumin ratio (Q_{alb}) was 0.010 ± 0.001 in group I and 0.026 ± 0.003 in group II on admission. During the observation period, Q_{alb} of group I remained within ranges of a mild to moderate dysfunction whereas in group II an initially severely disturbed BBB improved continuously to a moderate to mild dysfunction at 72h after trauma (0.013 ± 0.003). A positive correlation ($r^2 = 0.793$, $p < 0.001$) was found between CSF S100-B and Q_{alb} for each sampling point.

Discussion

The presented clinical study was conducted to evaluate the correlation of CSF protein S100-B levels and post-traumatic BBB-dysfunction. In all enrolled TBI patients significantly elevated CSF S100-B concentrations were found, decreasing gradually over the first 72h after trauma. Patients exhibiting an ICP >15mmHg, revealed nearly 5fold higher S100-B levels in comparison to patients with an ICP ≤15mmHg. S100-B levels strongly correlated to ICP values in all patients. Concerning the function of the BBB a correlation between CSF S100-B and Q_{alb} as parameter for the function of the BBB was demonstrated.

S100 protein is an acidic, calcium-binding protein found in the brain as homodimer or heterodimer with a molecular weight of 22kDa. S100-B, the beta-dimer is present in high concentrations in glial cells and Schwann cells (Otto et al. 2000). Serum S100-B is metabolized in the kidney and excreted in the urine with an elimination time of 30min (Ghanem et al. 2001). Elevated S-100B concentrations in serum and cerebrospinal fluid (CSF) have been reported in patients with severe TBI, and are likely to reflect the degree of brain injury (Kogel et al. 2004; Hayakata et al. 2004). Biberthaler et al. also clearly demonstrated the clinical relevance of S100-B serum assessment for the identification of high-risk patients after minor head trauma (MHT) (Biberthaler et al. 2002; Biberthaler et al. 2004).

In our study, S100-B in CSF was significantly elevated in TBI patients, exhibiting an ICP>15mmHg compared to patients with an ICP ≤15mmHg and the control group. Our data are in accordance with the data presented by Hayakata. In 23 patients with severe TBI, the mean peak CSF S100-B concentration was 630 ± 173 pg/ml after TBI (Hayakata et al. 2004) presenting an increase during the first 6h after TBI and gradually decreasing thereafter. Since we did not assess S100-B 6 hours after TBI, we cannot assure this increase as described by Hayakata. However, in comparing the presented study with Hayakata's results a discrete difference of S100-B concentration in control patients was found (actual study: 0.8 ± 0.09 pg/ml / Hayakata: 3.3 ± 1.3 pg/ml).

Pleines et al. also examined S100-B levels of healthy controls describing a level of 1.4 ± 0.2 pg/ml (Pleines et al. 2001). Our results are more in accordance to our presented values, however, also these differences are small.

Ucar et al. reported an average CSF S100-B concentration of 62 ± 21.8 pg/ml in his collective of 32 TBI patients with unfavourable outcome (Ucar et al. 2004). However, his data are also in line with our work, as corresponding to the significantly lower S100-B values, in Ucar's group also the average ICP was significantly lower. In this context the present study showed clearly that CSF S100-B concentration significantly correlates with the ICP, determined at the time CSF samples were taken. Group II-patients with high-ICP therefore presented a CSF S100-B concentration of 819 ± 78 pg/ml. These results confirm the theory of Hayakata, who also found leads for a significant correlation between ICP and S100-B (Hayakata et al. 2004). Moreover, Raabe et al. reported a significant correlation between the serum S100-B and contusion volume determined from CT scans (Raabe et al. 1998). However, as it is not ethically feasible to perform CT scans every 12h according to our protocol, we cannot clarify to what degree the increase in CSF S100-B reflects the

extent of ongoing brain damage at each sampling point.

Although, we did not find statistical significant differences between patients with unfavourable and favourable outcome, group I- patients had a primary tendency to higher GOS in comparison to group II. Secondly the group II-patients who died shortly after the observation period, revealed an anew increase of S100-B concentrations in CSF. In this context, Hayakata clearly demonstrated, that the CSF S100-B concentration was significantly higher in patients with an unfavourable outcome than in patients with a favourable one (Hayakata et al. 2004). Also Ucar et al. reported that the CSF S100-B concentration was significantly higher in patients with an unfavourable outcome (Ucar et al. 2004). A possible reason for not being able to confirm the relationship between CSF S100-B-concentrations and clinical outcome might be the small number of enrolled patients within the subgroups.

However, due to its increased release into CSF and serum after cell degradation in CNS, S100-B is off high diagnostic relevance (Sindic et al. 1982; Otto et al. 1997). Reiber clearly demonstrated that the brain derived fraction in CSF for S100-B protein exceeds 99% due to an empirical CSF/serum ratio of 18:1 (Reiber 2001). Moreover, he showed that in patients with blood brain barrier dysfunctions due to a restricting stenosis or tumor CSF S100-B concentration is invariant to increasing Q_{alb}. However, the release mechanism after an insult such as traumatic brain trauma is not yet clarified. Several authors have reported that S100-B is released by cell damage and is also actively secreted into the extracellular space by glial activation (Pleines et al. 2001; Rothermundt et al. 2003). Raabe suggested that it subsequently might directly enter the serum via a damaged BBB or might enter the CSF and then is absorbed into the blood via the CSF circulation (Raabe et al. 2003). As we clearly could indicate, high CSF S100-B levels correlate directly to Q_{alb}, a relevant parameter of the function of the BBB. This result is accordant to the data from Marchi et al., who indicated, that S100-B might be an early marker of BBB openings, that may even precede neuronal damage (Marchi et al. 2003).

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