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Abstract

The intercellular adhesion molecule-1 (ICAM-1) expressed by endothelial cells is crucial in promoting adhesion and transmigration of circulating leukocytes across the blood-brain barrier (BBB). Migrated immunocompetent cells, in turn, release mediators that stimulate glial and endothelial cells to express ICAM-1 and release cytokines, possibly sustaining cerebral damage. Following activation, proteolytic cleavage of membrane-anchored ICAM-1 results in measurable levels of a soluble form, sICAM-1. The aims of this study were to investigate the changes of sICAM-1 levels in ventricular CSF and serum and to elucidate the influence of structural brain damage as estimated by computerized tomography (CT) as well as the extent of BBB dysfunction as calculated by the CSF/serum albumin ratio (QA) in patients with severe traumatic brain injury (TBI). All investigated parameters revealed two subgroups. Patients belonging to group A had sICAM-1 levels in CSF above normal range, presented marked cerebral damage and a disturbance of the BBB (range 0.6-24.7 ng/ml, n = 8). In contrast, patients belonging to group B had no elevation of sICAM-1 values in CSF (range 0.3-3.9 ng/ml, n = 5; p < 0.017) and showed minor cerebral damage with an intact BBB in most cases. In addition, overall analysis showed that sICAM-1 in CSF correlated with the extent of BBB damage as indicated by the QA (r = 0.76; p < 0.001). These results suggest that increased sICAM-1 levels in CSF might depict ongoing immunologic activation and that sICAM-1 correlates with the extent of tissue and BBB damage. The origin of soluble ICAM-1 in CSF and its pathophysiologic role after TBI remains to be clarified.
Soluble ICAM-1 in CSF Coincides with the Extent of Cerebral Damage in Patients with Severe Traumatic Brain Injury

ULRIKE E. PLEINES,1 JOHN F. STOVER,2 THOMAS KOSSMANN,2 OTMAR TRENTZ,2 and MARIA C. MORGANTI-KOSSMANN1

ABSTRACT

The intercellular adhesion molecule-1 (ICAM-1) expressed by endothelial cells is crucial in promoting adhesion and transmigration of circulating leukocytes across the blood-brain barrier (BBB). Migrated immunocompetent cells, in turn, release mediators that stimulate glial and endothelial cells to express ICAM-1 and release cytokines, possibly sustaining cerebral damage. Following activation, proteolytic cleavage of membrane-anchored ICAM-1 results in measurable levels of a soluble form, sICAM-1. The aims of this study were to investigate the changes of sICAM-1 levels in ventricular CSF and serum and to elucidate the influence of structural brain damage as estimated by computerized tomography (CT) as well as the extent of BBB dysfunction as calculated by the CSF/serum albumin ratio (QA) in patients with severe traumatic brain injury (TBI). All investigated parameters revealed two subgroups. Patients belonging to group A had sICAM-1 levels in CSF above normal range, presented marked cerebral damage and a disturbance of the BBB (range 0.6–24.7 ng/ml, n = 8). In contrast, patients belonging to group B had no elevation of sICAM-1 values in CSF (range 0.3–3.9 ng/ml, n = 5; p < 0.017) and showed minor cerebral damage with an intact BBB in most cases. In addition, overall analysis showed that sICAM-1 in CSF correlated with the extent of BBB damage as indicated by the QA (r = 0.76; p < 0.001). These results suggest that increased sICAM-1 levels in CSF might depict ongoing immunologic activation and that sICAM-1 correlates with the extent of tissue and BBB damage. The origin of soluble ICAM-1 in CSF and its pathophysiologic role after TBI remains to be clarified.

Key words: adhesion molecules; blood-brain barrier; sICAM-1; traumatic brain injury

INTRODUCTION

The intercellular adhesion molecule-1 (ICAM-1, CD54) is expressed on endothelial cells, astrocytes, microglia, and B- and T-lymphocytes and is up-regulated in response to various stimuli (Frohman et al., 1989; Satoh et al., 1991a; Sobel et al., 1990). ICAM-1 mediates leukocyte cell adhesion and antigen-specific T-cell activation by binding to β2-integrin molecules, such as lymphocyte function-associated molecule-1 (LFA-1, CD11a/18) and complement receptor type 3 (Mac-1, CD11b/18), expressed on leukocytes and macrophages (Smith et al., 1989; Diamond et al., 1990; Dustin and Springer, 1988; Rothlein et al., 1986). Proteolytic cleavage...
age of cell-bound ICAM-1 following functional interaction between leukocytes and ICAM-1 results in measurable levels of a circulating and soluble protein (sICAM-1) (Rothlein et al., 1991; Seth et al., 1991).

Under normal conditions, cerebral endothelial cells show very low constitutive adhesion molecule expression, and only a few leukocytes and macrophages are found within the brain because of the impermeability of the blood-brain barrier (BBB) to resting white blood cells (Weckerle, 1993). Transient adhesion, transendothelial and subendothelial migration of leukocytes are promoted by adhesion molecules and request the participation of signalling mediators such as platelet activating factor (PAF) or interleukin (IL)-8 released by neutrophils (Abelda et al., 1994; Carlos and Harlan, 1994; Rössler et al., 1992; Zimmermann et al., 1992). Leukocytes transmigrated into the brain release pro-inflammatory cytokines such as IL-1, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, which, in turn, up-regulate the expression of ICAM-1 on various cell types (Aloisi et al., 1992; Fabry et al., 1992; Frohman et al., 1989; Satoh et al., 1991b) and produce cytotoxic agents such as glutamate, oxygen radicals, and proteolytic enzymes (Zhuang et al., 1993). The release of pro-inflammatory cytokines (Kossmann et al., 1996, 1997; Morganti-Kossmann et al., 1997) and neurotoxins (e.g., glutamate) within the brain is thought to aggravate BBB damage, leading to vasogenic and cytotoxic brain edema formation (Greenwood, 1991; Weckerle, 1993), possibly resulting in a self-sustaining vicious circle (Cross et al., 1991; Staub et al., 1996).

Various experimental models of ischemia revealed a correlation between the amount of accumulated granulocytes, increased cortical water content, and elevated intracranial pressure (Biagas et al., 1992; Schoettle et al., 1990; Zhuang et al., 1993), reflecting the contribution of leukocytes to secondary brain damage. The administration of specific antibodies directed against ICAM-1 significantly reduced neutrophil accumulation, edema formation, infarction size, and neurologic damage after transient middle cerebral artery occlusion in rats (Bowes et al., 1993; Matsuo et al., 1994; Zhang et al., 1994). In ICAM-1 knockout mice, infarct volume and neurologic deficits were markedly reduced after focal cerebral ischemia, and survival was significantly prolonged in comparison with ICAM-1+/+ animals (Connolly et al., 1996). An increased expression of ICAM-1 within cerebral parenchyma may lead to release of the soluble form of ICAM-1 in CSF as a result of proteolytic cleavage, possibly reflecting ongoing posttraumatic immunomodulation.

The aims of this study were to investigate the alterations of sICAM-1 levels in CSF and serum in patients following severe traumatic brain injury (TBI) and to elucidate whether or not sICAM-1 correlates with the extent of brain damage and with the alterations of BBB function as calculated by the CSF/serum albumin ratio (Q_A).

MATERIALS AND METHODS

Patients

A total of 13 patients (range 16–67 years; mean 37.5 years; 3 females, 10 males) were included in this study. The patients were treated according to a standardized protocol at the Division of Trauma Surgery at the University Hospital Zürich, Switzerland (Stocker et al., 1995). All patients suffered from severe TBI and had a Glasgow coma score (GCS) ≤9 upon admission. Patients with thoracic, abdominal, pelvic, or spinal cord injuries were excluded. After clinical and computerized tomography (CT) evaluation, intraventricular catheters were implanted to monitor intracranial pressure (ICP) and to therapeutically drain CSF. Control CSF samples were taken from eight patients without TBI following either diagnostic lumbar puncture without neuropathology or ventriculoperitoneal shunt. The study protocol was approved by the University Hospital Medical Ethics Board. The patients were clinically evaluated according to the Glasgow outcome score (GOS) (Jennett and Bond, 1975), a numeric scale that describes the neurologic outcome of patients, assessed 3 and 6 months after TBI (GOS 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good recovery).

CSF and Serum Sampling

Drained CSF, collected on ice over 24 h, and arterial serum samples drawn once daily were centrifuged at 1000 rpm for 10 min at 4°C and frozen at −70°C until further analysis.

Analysis of Soluble ICAM-1

Soluble ICAM-1 was analyzed by sandwich enzyme-linked immunosorbent assay (ELISA) using a commercial kit (R&D Systems, Abingdon, UK). The standard curve was linear from 0 to 46 ng/ml, with a lower detection limit at 0.35 ng/ml. Absorbance was measured at 450 nm with a correction wavelength of 620 nm using a microplate reader (Dynatech Laboratories Inc., Alexandria, MD).

Evaluation of Brain Damage According to Computerized Tomography (CT)

CT scans were evaluated by an independent blinded investigator. The extent of cerebral damage was assessed

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by calculating the size of contusions and pericontusional edema formation, applying the mathematical formula for ellipsoid structures [volume = \(4/3\pi \times a \times b \times c (\text{cm}^3)\)] and by measuring the distance from the ventricular system in centimeters.

**Blood-Brain Barrier Damage**

The extent of BBB dysfunction was estimated by calculating the CSF/serum albumin ratio (\(Q_A\)) daily. The BBB was defined as intact with \(Q_A\) levels up to 0.007. The disturbance of the BBB permeability was rated mild, moderate, and severe, with \(Q_A\)-values ranging from 0.007–0.01, 0.01–0.02, and above 0.02, respectively (Reiber and Felgenhauer, 1987). CSF and serum albumin were measured by automatized laser photometry (BNA Automat, Behringwerke, Marburg a.L., Germany).

**Statistical Analysis**

Statistical analysis was performed using the Mann-Whitney U-test with a modified Bonferroni correction for repeated measurements and linear regression analysis. The upper normal limit of sICAM-1 was defined as mean plus three standard deviations of control values. Results are given as mean ± standard error of the mean (SEM). Differences were considered significant at \(p < 0.05\).

**RESULTS**

**Soluble ICAM-1 in CSF and Serum**

Soluble ICAM-1 was measured daily by ELISA in CSF and serum of 13 patients following TBI for a time period up to 19 days. Table 1 summarizes the epidemiological data as well as the means and ranges of sICAM-1 and \(Q_A\) for each individual.

This analysis revealed two subgroups of patients for sICAM-1 values in CSF. In order to compare the groups statistically, we used the mean of all sICAM-1 measurements of each patient for up to 19 days after trauma and calculated the average of the means for each group. The differences were analyzed by the nonparametric Mann-Whitney U-test for all parameters. Patients belonging to group A had significantly higher sICAM-1 values in CSF compared with those in group B (group A, range 0.6–24.7 ng/ml; average of the mean ± SEM 7.15 ± 0.83, \(n = 8\); group B, range 0.3–3.9 ng/ml, average of the mean 1.42 ± 0.23, \(n = 5\); \(p = 0.003\)). In group B, CSF sICAM-1 levels were comparable with control values (control CSF, range 0.27–1.97; mean 0.9 ± 0.2 ng/ml). With regard to the kinetics of sICAM-1, it appeared that CSF sICAM-1 levels increased within 24 h after trauma in group A, remained elevated during 10 days, and decreased gradually over time, while concentrations of sICAM-1 in group B remained within the normal range during the entire study period (Table 2). The kinetics of sICAM-1 in CSF and serum are shown for both patient groups in Fig. 1.

Serum sICAM-1 concentrations were nearly 100-fold higher than corresponding CSF values. Contrary to changes in CSF, serum levels were not significantly elevated until day 9 in both groups. Overall analysis showed no differences between groups A and B during the investigated time period after trauma (group A, range 121.2–822.9 ng/ml, average of the mean 414.6 ± 21.37; group B, range 118.2–890.2 ng/ml, average of the mean 354.3 ± 37.45, \(p = 0.24\)). However, the kinetics of sICAM-1 in serum showed an elevation in group A at

**Table 1. Epidemiological Data of 13 Traumatic Brain Injury Patients According to Groups A and B**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Group</th>
<th>sICAM CSF (ng/ml)</th>
<th>sICAM Serum (ng/ml)</th>
<th>Albumin Quotient ((Q_A))</th>
<th>GOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>67</td>
<td>A</td>
<td>5.0 ± 1.6</td>
<td>392.0 ± 38.1</td>
<td>0.0198 ± 0.011</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>48</td>
<td>A</td>
<td>8.3 ± 5.8</td>
<td>385.4 ± 175.2</td>
<td>0.0267 ± 0.021</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>55</td>
<td>A</td>
<td>7.2 ± 4.2</td>
<td>344.7 ± 125.6</td>
<td>0.0242 ± 0.016</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>26</td>
<td>A</td>
<td>10.9 ± 4.2</td>
<td>488.9 ± 89.3</td>
<td>0.0242 ± 0.005</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>31</td>
<td>A</td>
<td>9.3 ± 5.5</td>
<td>439.4 ± 68.4</td>
<td>0.0100 ± 0.018</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>31</td>
<td>A</td>
<td>3.6 ± 1.7</td>
<td>415.1 ± 29.7</td>
<td>0.0214 ± 0.007</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>53</td>
<td>A</td>
<td>6.4 ± 3.8</td>
<td>349.3 ± 156.3</td>
<td>0.0114 ± 0.012</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>59</td>
<td>A</td>
<td>6.6 ± 2.6</td>
<td>507.3 ± 202.9</td>
<td>0.0127 ± 0.005</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>19</td>
<td>B</td>
<td>1.2 ± 0.5</td>
<td>394.9 ± 30.6</td>
<td>0.0036 ± 0.001</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>23</td>
<td>B</td>
<td>2.3 ± 0.9</td>
<td>299.8 ± 66.2</td>
<td>0.0041 ± 0.004</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>41</td>
<td>B</td>
<td>1.2 ± 0.3</td>
<td>495.4 ± 233.2</td>
<td>0.0032 ± 0.0012</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>m</td>
<td>16</td>
<td>B</td>
<td>0.9 ± 0.3</td>
<td>250.3 ± 46.9</td>
<td>0.0018 ± 0.0003</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>f</td>
<td>18</td>
<td>B</td>
<td>1.6 ± 0.7</td>
<td>360.0 ± 57.9</td>
<td>0.0034 ± 0.0014</td>
<td>5</td>
</tr>
</tbody>
</table>

Geometric means ± SD of soluble ICAM-1 (ng/ml) in CSF and serum, albumin quotient (\(Q_A\)), and the Glasgow outcome scale (GOS) are given.
changes in serum, a CSF/serum ratio for sICAM-1 (QsICAM-1) was assessed as previously shown for patients with neurologic diseases (Rieckmann et al., 1993). This calculation showed significantly higher QsICAM-1 values in group A compared with group B (QsICAM-1: group A, range 0.0031–0.097, average of the mean 0.019 ± 0.002; group B, range 0.0009–0.013, average of the mean 0.0045 ± 0.001; p = 0.004). In addition, the fluctuations of sICAM-1 in CSF occurred independently from those in serum in all patients (data not shown).

**BBB Damage**

Significantly elevated CSF sICAM-1 levels in group A coincided with a more disturbed BBB as estimated by QA compared with patients (group B) with low CSF sICAM-1 values (group A, QA range 0.002–0.088, average of the mean 0.017 ± 0.002; group B, range 0.0014–0.019, average of the mean 0.003 ± 0.0004; p = 0.0034). Patients in group A showed a severe BBB damage during the first posttraumatic days, changing over the following days to a moderately disturbed BBB and nearly normalizing within the third week. In group B, the QA-

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**Table 2. Kinetics of sICAM-1**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 9</th>
<th>Day 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>9.8 ± 3.6</td>
<td>9.5 ± 1.6</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>1.1 ± 0.2</td>
<td>1.9 ± 0.5</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum</td>
<td>286.9 ± 27.3</td>
<td>514.4 ± 58.7</td>
<td>509.0 ± 107.0</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum</td>
<td>298.0 ± 42.5</td>
<td>476.5 ± 141.5</td>
<td>343.9 ± 25.1</td>
</tr>
</tbody>
</table>

Levels of sICAM-1 in CSF decreased over time in group A, whereas sICAM-1 values in group B remained unchanged. In serum, sICAM-1 values showed an elevation in group A at day 9 persisting up to the end of the study period, whereas in group B, there was only a transient elevation between days 9 and 13, followed by a rapid decrease to normal ranges.

In order to further determine whether higher sICAM-1 levels in CSF may depend on intrathecal release or on

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**FIG. 1.** Levels of soluble intercellular adhesion molecule-1 (sICAM-1) in cerebrospinal fluid (CSF) and serum following traumatic brain injury (TBI). Changes of sICAM-1 in CSF and serum of patients suffering from severe TBI are presented as group A (● = high sICAM-1 levels) and group B (△ = low sICAM-1 levels). Results are given as geometric mean ± SEM. In group B, the size of the symbol is larger than the SEM at most time points. The number of samples (n) daily available for analysis for each patient group is given at the bottom of the figure. The gray area represents the normal range of sICAM-1 levels in both fluids and was calculated as mean ± 3SD of control samples.
values remained normal or mildly elevated during the entire study period (data not shown).

In order to analyze the dependency of sICAM-1 levels in CSF on the dysfunction of the BBB, linear regression analysis of sICAM-1 in CSF and QA values of all patients was performed (Fig. 2). This analysis showed a correlation between the levels of sICAM-1 in CSF and the QA \( r = 0.76, p < 0.001 \). However, some patients had sICAM-1 values in CSF above the normal range, although the BBB was only mildly to moderately disturbed (Fig. 2).

**Extent of Cerebral Damage as Estimated by CT**

Cranial CT scans were evaluated upon admission and on days 1, 5, and 14 after injury. Patients with higher CSF sICAM-1 levels (group A) showed larger structural lesions, represented as contusions, with a gradual progression of perifocal edema and a smaller distance to the ventricular system. To the contrary, patients with low CSF sICAM-1 values (group B) showed small contusions, and the perifocal edema did not expand toward the ventricular system in any patient (Fig. 3).

**Levels of sICAM-1 and the Glasgow Outcome Scale (GOS)**

The GOS was determined for all patients 3 and 6 months after traumas. Patients in group A recovered to different extents, having GOS values between 1 and 5 [GOS 1 \( n = 1 \), GOS 3, \( n = 3 \), GOS 4 \( n = 3 \), GOS 5 \( n = 1 \)]. Interestingly, all patients belonging to group B showed a good recovery with only minor neurologic deficits (GOS = 5, \( n = 5 \), Table 1).

**Influence of Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP)**

No significant differences were observed in the two groups in regard to the ICP (group A, maximum ICP range 6–69 mm Hg, average of the mean 20.2 ± 1.3 mm Hg; group B, maximum ICP range 11–43 mm Hg, average of the mean 20.5 ± 1.1 mm Hg, \( p = 0.88 \)) and CPP (group A, range 73.5–115.8 mm Hg, average of the mean 72.5 ± 2.2; group B, range 66–107.2 mm Hg, average of the mean 68.9 ± 2.3, \( p = 0.39 \)).

**DISCUSSION**

The release of sICAM-1 was investigated in CSF and serum samples of patients with severe TBI for up to 19 days after trauma. Analysis of the data revealed that increase of sICAM-1 values in CSF is associated with the presence of cerebral contusions as well as with an unfavorable outcome. In addition, a significant correlation between the levels of sICAM-1 in CSF and the disturbance
FIG. 3. Soluble intercellular adhesion molecule-1 (sICAM-1) levels are associated with computed tomography (CT) scan pattern. CT scans at days 0, 1, 5, and 14 were analyzed with respect to (A) size of cerebral contusion (cm³), (B) pericontusional edema, and (C) distance from the ventricular system, and grouped according to the levels of sICAM-1 in cerebrospinal fluid (CSF), as described in Materials and Methods. Patients with high sICAM-1 values in CSF (group A) show larger contusion sizes decreasing over time, and a progressive perifocal edema with only a small distance to the ventricular system. Patients with low CSF sICAM-1 values (group B) show small contusion volumes, unchanged perifocal edema, and a large distance to the ventricular system.
SOLUBLE ICAM-1 IN CSF AFTER TRAUMATIC BRAIN INJURY

of the BBB was also shown. However, it is not clear from this study whether increased the sICAM-1 found in CSF originates from plasma via translocation through the BBB or is derived from intracerebral production.

Increased sICAM-1 values in CSF may result from enhanced posttraumatic expression of ICAM-1 on activated cells combined with proteolytic cleavage of the membrane-bound form (Rothlein et al., 1991; Seth et al., 1994; Budnik et al., 1996; Rieckmann et al., 1995a) or from a sustained cleavage of constitutively expressed membrane-bound ICAM-1. Apart from enzymatic cleavage, the soluble form of ICAM-1 is also believed to be produced anew, since two distinct mRNAs, one for membrane-bound ICAM-1 and one for soluble ICAM-1, have been demonstrated (Simmons et al., 1988; Staunton et al., 1989; Wakatsuki et al., 1995). sICAM-1 in CSF may originate from cerebral endothelial cells and astrocytes, since these cell-types were shown to express (ICAM-1 in vitro (Frohman et al., 1989; Satoh et al., 1991a; Rieckmann et al., 1995a) and in vivo (Cannella et al., 1995; Sharief et al., 1993; Sobel et al., 1990; Shibayama et al., 1996; Isaksson et al., 1997).

Since serum levels of sICAM-1 are up to 100-fold higher than those in CSF, a damaged BBB is required for passive translocation and penetration of these molecules into the central nervous system (CNS). The simultaneous and significant increase of QA values and elevated sICAM-1 levels of patients belonging to group A underline the importance of diffusion processes through the BBB, as already discussed for inflammatory neurologic diseases (Jander et al., 1993; Sharief et al., 1993; Rieckmann et al., 1993). However, variations in serum sICAM-1-levels did not correspond to changes in CSF. Comparable levels of serum sICAM-1 were found in both patient groups, whereas CSF sICAM-1 values were up to 10 times higher in group A than in group B, thus resulting in a higher QsICAM-1 in group A as well. The QsICAM-1 values found in group A were comparable with levels reported in patients with inflammatory diseases of the CNS (Rieckmann et al., 1993). It remains to be clarified whether sICAM-1 in CSF is elevated because of intrathecal production or because of increased leakage across the BBB.

Apart from traumatically induced damage of cerebral endothelial cells with subsequent passive translocation of serum sICAM-1, it is believed that trauma-related shearing of endothelial cells in itself induces enhanced expression of ICAM-1 (Nagel et al., 1994). Supportive of this hypothesis is the finding that a few patients included in this study showed elevated sICAM-1 values with nearly normal BBB function (Fig. 2), suggesting possible intrathecal release of sICAM-1. A slight dysfunction of the BBB may not be sufficient for a passive leakage of sICAM-1 from the periphery into CSF, since the molecular weight of sICAM-1 is greater than that of albumin (80–120 kD and 60 kD, respectively). Independently
from its origin, sICAM-1 present in the CNS may affect the function of the BBB, inducing the release of cytokines and neurotoxic factors by activated leukocytes (Sharief et al., 1993; Weckerle et al., 1993). The exact origin of sICAM-1 in CSF, however, remains to be elucidated.

Although the $Q_A$ may only give a reference for the true BBB, it was used, since we hypothesize that the increased albumin concentration in CSF derives from the contused tissue and reaches theventricular system as previously described (Duvdevani et al., 1995; Önal et al., 1997). The course of $Q_A$ levels in the CSF of patients with TBI reflects the sICAM-1 pattern, showing an elevation during the first days, followed by a significant decrease by the end of the second week (data not shown). The rise of sICAM-1 and albumin in CSF is likely influenced by the underlying BBB damage, while clearance of these molecules represents a more complex phenomenon. For albumin, animal studies investigating the restoration profile of contusion and ischemic injury revealed albumin to persist within the extracellular space at the damaged area for up to 10 days prior to removal (Baldwin et al., 1996; Kuroiwa et al., 1985). Apart from glial and/or neuronal uptake (Tengvar and Ollson, 1982; Liu and Sturner, 1988; Hoshino et al., 1996), a reverse vesicular transport from the extracellular space to blood via transendothelial passage may also occur (Vorbrodt et al., 1987). Removal of extravasated proteins is thought to mainly result from pressure-driven bulk flow into the adjacent ventricular system (Rosenberg et al., 1980; Ohata et al., 1990) and the subarachnoid space (Ohata et al., 1992). Similar mechanisms for sICAM-1 clearance might be anticipated but require further investigation.

The levels of sICAM-1 in CSF correlated with the extent of brain damage and the clinical outcome. Higher sICAM-1 levels in CSF were found in patients with perifocal damage, progressing over time and reaching theventricular system, compared with those with smaller lesions and stable perifocal edema.

Interestingly, patients with smaller structural lesions and lower sICAM-1 levels in the CSF had a good outcome, as determined by the GOS of 5, whereas patients with moderate or unfavorable outcome had elevated sICAM-1 levels and larger brain lesions combined with progressive edema. Although sICAM-1 may reflect the degree of tissue damage and the resulting immunologic response, it cannot be considered a prognostic marker, since the remaining half of the patients with high sICAM-1 still had a moderate to good outcome. The lack of differences for ICP and CPP recorded every hour in the two different groups is most likely due to therapeutic influences, since ICP was lowered by CSF drainage and CPP was kept above 70 mm Hg, according to the treatment protocol (Stocker et al., 1995). Analysis of sICAM-1 only once a day, as performed in the present study, cannot accurately reveal possible fluctuations within 24 h.

While the function of membrane-bound ICAM-1 in attracting and binding circulating immunocompetent cells has been identified, the physiologic role of the soluble form has not been fully understood. The circulating and soluble form of ICAM-1 is believed to play a pivotal role in the local regulation of adhesion and de-adhesion of leukocytes binding to endothelial cells (Rieckmann et al., 1995b). Furthermore, sICAM-1 could possibly bind to circulating leukocytes within the next proximity or at a distance from the actual site of tissue damage and consequently antagonize the ICAM-1 interaction to its ligand LFA-1, expressed on leukocytes (Meyer et al., 1995). Thus, sICAM-1 may possibly attenuate the extent of attraction, binding, and activation of leukocytes therefore preventing excessive migration of these cells and tissue damage (Gearing et al., 1992; Rothlein et al., 1991).

Irrespective of its potential immunologic function, analysis of sICAM-1 in CSF may facilitate early diagnosis of inflammatory and immunologic response within traumatized brain parenchyma, since ICAM-1 is considered an early marker of immune activation and response (Diamond et al., 1990; Seth et al., 1991).

To date, possible therapeutic interventions in patients with TBI are directed against resident membrane-bound ICAM-1 in order to minimize secondary brain damage. In animal models of ischemic brain injury, antibodies directed against ICAM-1 reduced neurologic deficits (Bowes et al., 1993; Matsuo et al., 1994; Zhang et al., 1994). In humans, methylxanthine derivatives such as pentoxifylline have been shown to successfully modulate the immune system by attenuating the release of pro-inflammatory cytokines and reducing the expression of membrane-bound adhesion molecules (Mandi et al., 1995; Rieckmann et al., 1996). However, further detailed investigation is required to test the clinical application of these drugs in patients suffering from severe TBI.

In conclusion, sICAM-1 may reflect an ongoing inflammatory response within the CNS and may depend on the magnitude of damaged cerebral tissue in patients with TBI. However, the cellular origin of sICAM-1 in CSF as well as the mechanism regulating intrathecal elevation of sICAM-1 following TBI (cleavage, anew synthesis) remain to be elucidated.

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