Plasma S100B Level After Acute Spontaneous Intracerebral Hemorrhage

Pilar Delgado, MD; Jose Alvarez Sabin, MD, PhD; Esteban Santamarina, MD; Carlos A. Molina, MD, PhD; Manuel Quintana; Anna Rosell, PhD; Joan Montaner, MD, PhD

Background and Purpose—We sought to determine plasma S100B level after acute (<24 hours) spontaneous intracerebral hemorrhage (ICH) and to study its relation with neurological outcome.

Methods—We determined S100B concentration on plasma samples from 78 ICH patients on admission. Clinical (Glasgow Coma Scale and National Institutes of Health Stroke Scale [NIHSS] scores) and radiological information (ICH and perihematomal edema volumes) were collected at baseline and follow-up visits. Early neurological deterioration, defined as the increase of ≥4 points in the NIHSS score at 48 hours, and unfavorable outcome (modified Rankin Scale >2) at 3 months were also recorded.

Results—The median S100B level was higher than our laboratory reference values for healthy controls (103.6 versus 48.5 pg/mL; \( P < 0.0001 \)) and a positive correlation was observed between S100B level and baseline ICH volume \(( r = 0.45; P < 0.0001 )\). The median S100B level was higher in patients who deteriorated early (256.8 versus 89.7 pg/mL; \( P = 0.001 \)) and also in patients with an unfavorable outcome (136 versus 75.9 pg/mL; \( P = 0.003 \)). Multivariate analysis showed baseline ICH volume as the best predictor for both early neurological deterioration (odds ratio 15; 95% CI, 2.9 to 76.3) and unfavorable outcome at 3 months (odds ratio 17; 95% CI, 2.0 to 142).

Conclusion—Increased S100B level is found after acute spontaneous ICH, in association with a worse early and late evolution, and closely related to initial hematoma volume. (Stroke. 2006;37:2837-2839.)

Key Words: biomarkers ■ intracerebral hemorrhages ■ S100B ■ stroke

S100B is a Ca\(^{2+}\)-binding protein found in the central nervous system, mainly in glial cells. This protein increases in biological fluids of patients with brain injury of different causes, being a consolidated marker of brain damage.\(^1\)\(^2\) In ischemic stroke, high S100B level has been associated with infarct size, with outcome and with the neurovascular status on admission.\(^3\)\(^4\) Moreover, it could be a surrogate marker of successful thrombolysis in tissue plasminogen activator–treated patients.\(^5\)

Although the use of brain-specific proteins for monitoring cellular reaction during brain pathology is winning an ever-increasing importance, information about the role of proteins indicating destruction of glial tissue, as S100B, in spontaneous intracerebral hemorrhage (ICH) is lacking. Therefore, we aimed to investigate plasma level of S100B in a group of patients with ICH and its relation to neurological outcome.

Methods

Study Population

Our target group consisted of consecutive patients with spontaneous supratentorial ICH evaluated in the emergency room within the first 24 hours from stroke onset. Between January 2003 and March 2004, a total of 100 ICH patients were initially evaluated. Exclusion criteria were the presence of a vascular malformation, impaired coagulation, anticoagulant therapy, head trauma, hemorrhagic infarction or tumoral bleedings. The patients who underwent a surgical procedure were also excluded. Finally, 78 patients were included after informed consent was obtained from them or their relatives. The Ethics Committee approved all aspects of the study protocol.

Clinical and Radiological Assessment

The median time from symptom onset to hospital admission was 5.7 (2.4 to 8.8) hours. On arrival to the emergency department, a detailed history of vascular risk factors, concomitant medication, blood pressure, body temperature and blood samples were taken, before the baseline CT scan was performed. Glasgow Coma Scale and National Institutes of Health Stroke Scale (NIHSS) scores were recorded to assess the level of consciousness and neurological status on admission and at follow-up visits (24 hours, 48 hours, 7 days and 3 months). Early neurological deterioration (END) was defined as the increase of ≥4 points in the NIHSS score at 48 hours and modified Rankin Scale (mRS) score at 3 months were used to evaluate functional outcome. Patients that scored >2 on the mRS were considered as having an unfavorable outcome.

A second CT scan was repeated at third day. All CT scans were performed according to the Neuroradiology Department protocol. Investigators who read them were blinded to clinical information. ICH volume was measured according to the previously reported...
formulas $A \times B \times C \times D \times E$ and perihematoma edema (PE) volume was also measured by subtracting hyperdense volume from the total lesion area. The presence of hematoma or PE enlargement between baseline and follow-up CT scans was also recorded. ICH location was categorized as deep or lobar and the presence of intraventricular (IVE) or subarachnoidal extension of hematoma was also assessed at baseline and follow-up CT scans.

**Immunooassay Methods**

For S100B measurements, EDTA tubes were used to collect peripheral blood and plasma was immediately obtained by centrifugation and stored at $-80^\circ$C until analysis was done. S100B determination was done using an enzyme-linked immunosorbent assay—ELISA—according to the manufacturer’s instructions (Biosite Inc). Blood samples were always drawn before baseline CT scan.

**Statistical Analysis**

Statistical analysis was done using the SPSS 12.0 statistical package. Significance for intergroup differences was assessed by Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. To study correlations between continuous variables, Spearman correlation coefficients were used. Receiver operating characteristics curves were configured to establish the cut-off points of S100B with the optimal sensitivity and specificity predicting END and unfavorable outcome. Finally, 2 logistic regression analyses were performed to determine the factors that could be considered as independent predictors of neurological deterioration and unfavorable outcome, using the forward stepwise method by the likelihood ratio test. Variables showing a $P<0.1$ in univariate analysis were included in the multivariate model. A $P$ value $<0.05$ was considered significant.

**Results**

**Clinical and Laboratory Findings**

Demographic, clinical and radiological data from baseline CT scans are provided in the Table. END occurred in 12 patients and 61% had an unfavorable outcome (mRS $>2$) at 3 months. Sixteen patients died (20.5%) from all sample. The median S100B level was higher than our laboratory reference value for healthy controls (103.6 [54.6 to 194.9] versus 48.5 [22.7 to 76.7] pg/mL; $P<0.001$) and a significant correlation emerged between S100B level and leukocyte count ($r=0.3$; $P=0.015$) and between S100B and glucose level ($r=0.28$; $P=0.026$).

**Radiological Features Related to S100B Level**

There was a positive correlation between baseline ICH volume and the S100B level ($r=0.45$; $P<0.0001$; Figure) and also between PE volumes and the S100B levels ($r=0.27$; $P=0.033$). Those patients who presented IVE and subarachnoidal extension had higher S100B level than those who did not (186.9 [87.5 to 457.4] versus 91.8 [37.3 to 135.9] pg/mL; $P=0.002$ and 1203.1 [316.2 to 1602.6] versus 96.8 [38.1 to 155.7] pg/mL; $P<0.001$, respectively). The patients who presented IVE had larger hematomas than those who did not (43.7 [23.0 to 63.8] versus 8.9 [3.7 to 23.5] cc; $P<0.001$). Finally, the median S100B level was higher in lobar as compared with deeply located ICH (225.0 [90.9 to 423.9] versus 97.5 [43.3 to 138.7] pg/mL; $P=0.001$). The median S100B level at baseline was not related to further ICH or PE enlargement.

**Neurological Outcome and S100B Level**

Patients with higher S100B level presented more often with END, which was also associated with lobar location and higher baseline ICH volume. A baseline S100B level $>118$ pg/mL predicted END with 0.92 sensitivity and 0.70 specificity.

Moreover, higher S100B level was also associated with unfavorable outcome at 3 months, as well as other variables shown in the Table. A baseline S100B level $>97$ pg/mL predicted unfavorable outcome with 0.74 sensitivity and 0.70 specificity. However, the multivariate analyses selected ICH volume as the only independent predictor for both END

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### Baseline Clinical, Laboratory and Radiological Characteristics and Factors Associated With Unfavorable Outcome

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=78)</th>
<th>Yes (n=48)</th>
<th>No (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75 (63–80)</td>
<td>75 (62–80)</td>
<td>74 (63–80)</td>
<td>0.76</td>
</tr>
<tr>
<td>Gender, male</td>
<td>53 (68%)</td>
<td>33 (68%)</td>
<td>20 (67%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Location, lobar</td>
<td>20 (26%)</td>
<td>15 (31%)</td>
<td>5 (17%)</td>
<td>0.12</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>11 (6–16)</td>
<td>14 (7–17)</td>
<td>7 (4–9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS</td>
<td>15 (14–15)</td>
<td>15 (14–15)</td>
<td>15 (14–15)</td>
<td>0.19</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>176±29</td>
<td>178±27</td>
<td>175±32</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95±21</td>
<td>94±24</td>
<td>97±19</td>
<td>0.62</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>9.8±3.3</td>
<td>10.4±3.5</td>
<td>8.5±3.0</td>
<td>0.035</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>7.2±2.2</td>
<td>7.7±2.3</td>
<td>6.6±2.2</td>
<td>0.039</td>
</tr>
<tr>
<td>S100B pg/mL</td>
<td>103 (54–194)</td>
<td>136 (88–297)</td>
<td>75 (0–138)</td>
<td>0.003</td>
</tr>
<tr>
<td>ICH volume, mL</td>
<td>17 (4–38)</td>
<td>29 (9–46)</td>
<td>4 (1–10)</td>
<td>0.001</td>
</tr>
<tr>
<td>PE volume, mL</td>
<td>4 (0.9–15)</td>
<td>10 (1–25)</td>
<td>0.94 (0–5)</td>
<td>0.004</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (6%)</td>
<td>4 (8.3%)</td>
<td>1 (3.3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>IVE</td>
<td>20 (25%)</td>
<td>17 (35%)</td>
<td>3 (10%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Data are expressed as n (%), medians (interquartile range) and means±SD as appropriate.

SAE indicates subarachnoidal extension; BP, blood pressure; GCS, Glasgow Coma Scale.
Discussion

This study found increased S100B plasma level after acute (<24 hours) spontaneous ICH in association with worse early and late clinical evolution. It is well known that S100B is increased in other central nervous system diseases such as ischemic stroke, anoxic encephalopathy or trauma patients. S100B is considered a relevant diagnostic tool in perinatal context, particularly by its ability to predict intraventricular hemorrhage in preterm and asphyxiated full-term infants, when other clinical or radiological assessments are still silent. Moreover, S100B level has been reported to increase overtime after middle cerebral artery ischemic infarction. In this context, early increases can predict a malignant course of infarction in proximal middle cerebral artery occlusion, and late increases (48 to 72 hours after stroke onset) provide the best prediction for unfavorable long-term outcome. To our knowledge, this is the first time that S100B plasma level has been investigated soon after spontaneous ICH in adults. In our study, the extent of hematoma strongly correlated with S100B level and, although both ICH volume and S100B were associated with early and late clinical evolution, ICH volume was the strongest predictor of outcome in our population. It remains to be investigated whether S100B alone might add some information in small to medium hematomas. We found S100B level related to other biological markers of stress reaction and to other radiological features related to larger hematomas. Overall, our data suggest that S100B level in this early period might reflect the initial hemorrhagic insult (as demonstrated by the close relation between S100B and ICH volume). Our findings might have some potential clinical applications, such as the use of S100B level as a surrogate marker in future trials testing hemostatic agents or neuroprotective drugs.

Whether serial S100B measurements may add more accurate prognostic information in patients with ICH and the optimal time points for such measurements needs to be further investigated.

Disclosures

None.

References

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