Serum S100B Predicts a Malignant Course of Infarction in Patients With Acute Middle Cerebral Artery Occlusion

Christian Foerch, MD; Bettina Otto, MD; Oliver C. Singer, MD; Tobias Neumann-Haefelin, MD; Bernard Yan, MD; Joachim Berkefeld, MD; Helmut Steinmetz, MD; Matthias Sitzer, MD

Background and Purpose—Early predictors of infarct volume may improve therapeutic decisions in patients with acute cerebral ischemia. We investigated whether measurements of serum astroglial protein S100B can predict a malignant course of infarction in acute middle cerebral artery (MCA) occlusion.

Methods—We included 51 patients (24 women, mean age 69.1±12.4 years) admitted within 6 hours after stroke symptom onset caused by proximal MCA occlusion, as shown by magnetic resonance angiography (n=39), intra-arterial angiography (n=4), or transcranial duplex sonography (n=8). Blood samples were drawn at hospital admission and 8, 12, 16, 20, and 24 hours after symptom onset. Serum S100B concentrations were determined using a fully automated immunoluminometric assay. A malignant course of infarction was defined as the occurrence of clinical signs of cerebral herniation within the first 7 days of treatment or the clinical decision to perform decompressive hemicraniectomy caused by critical space-occupying swelling as detected by repeated neuroimaging.

Results—Sixteen patients developed malignant infarction (31%). Beginning with the 12-hour value, mean S100B serum concentrations were significantly higher in patients with a malignant course compared with those without (12 hours 1.23±1.24 versus 0.29±0.45 μg/L; 16 hours 1.80±1.65 versus 0.38±0.53 μg/L; 20 hours 1.90±1.53 versus 0.44±0.48 μg/L; and 24 hours 2.41±1.59 versus 0.57±0.66 μg/L; all P<0.001). A 12-hour S100B value >0.35 μg/L predicted malignant infarction with 0.75 sensitivity and 0.80 specificity. A 24-hour value >1.03 μg/L provided 0.94 sensitivity and 0.83 specificity.

Conclusions—The serum marker S100B can predict a malignant course of infarction in proximal MCA occlusion. This finding may improve the identification and monitoring of patients at particularly high risk for herniation. (Stroke. 2004; 35:2160-2164.)

Key Words: biological markers ■ brain edema ■ cerebral infarction ■ middle cerebral artery

Large infarcts caused by acute proximal middle cerebral artery (MCA) occlusion are often accompanied by space-occupying edema and subsequent cerebral herniation with high mortality (“malignant” MCA infarction).1 Nonsurgical antiedematous treatment such as controlled hyperventilation, intravenous osmotherapy, mild to moderate hypothermia, or deep barbiturate coma have limited effects and do not reliably prevent fatal transtentorial herniation in this condition.1,2 Therefore, decompressive hemicraniectomy (DHC) has received increasing attention.3–5 However, the critical questions regarding DHC remain: whom to treat and when to treat. Attempts to establish reliable diagnostic tools to identify patients at particular risk of malignant MCA infarction have included determinations of diffusion- and perfusion-weighted MRI parameters,6,7 of a critical lesion volume on computed tomography (CT),8,9 of cerebral blood flow by means of single-photon emission CT,10 or of metabolic measures using positron emission tomography (PET) and microdialysis.11 Clearly, most of these procedures are relatively time consuming and not always feasible. In acute ischemic stroke, the astroglial protein S100B is released into peripheral blood, reaching maximum serum concentrations between day 2 and day 4, correlating with infarct size.12,13 The aim of the present study was to test whether serum S100B can be used to predict malignant MCA infarction within the first 24 hours after symptom onset.

Materials and Methods

Study Population

Between February 2002 and October 2003, a total of 423 consecutive patients who were admitted to our hospital within 6 hours after onset of acute focal neurological symptoms were screened for the presence of proximal MCA occlusion (ie, MCA main stem or carotid-T-occlusion). Depending on the clinical setting, the screening was performed by means of magnetic resonance angiography, intra-arterial angiography (IA) or transcranial duplex sonography (TCD). From a total of 67 patients diagnosed having proximal MCA occlusion and not always feasible. In acute ischemic stroke, the astroglial protein S100B is released into peripheral blood, reaching maximum serum concentrations between day 2 and day 4, correlating with infarct size.12,13 The aim of the present study was to test whether serum S100B can be used to predict malignant MCA infarction within the first 24 hours after symptom onset.

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Table 1. Baseline Characteristics and Clinical Variables Separated for Malignant and Nonmalignant Course of MCA Infarction of 51 Patients Included in the Present Analysis

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Malignant</th>
<th>Nonmalignant</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean±SD)</td>
<td>70.8±9.3</td>
<td>68.4±13.7</td>
<td>0.503</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>7 (44)</td>
<td>17 (49)</td>
<td>0.494</td>
</tr>
<tr>
<td>Left MCA territory, n (%)</td>
<td>6 (38)</td>
<td>18 (51)</td>
<td>0.268</td>
</tr>
<tr>
<td>MCA+ACA territory, n (%)</td>
<td>7 (44)</td>
<td>2 (6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Time to hospital admission (hours)</td>
<td>2.5±1.5</td>
<td>1.7±1.0</td>
<td>0.030</td>
</tr>
<tr>
<td>NIHSS at admission (mean±SD)</td>
<td>18±4</td>
<td>15±6</td>
<td>0.126</td>
</tr>
<tr>
<td>Infarct volume (mL)</td>
<td>293.2±89.0</td>
<td>106.5±101.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Vascular risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>14 (88)</td>
<td>26 (74)</td>
<td>0.248</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (50)</td>
<td>10 (29)</td>
<td>0.122</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0 (0)</td>
<td>12 (34)</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke etiology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>3 (19)</td>
<td>4 (11)</td>
<td>0.381</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>8 (50)</td>
<td>25 (71)</td>
<td>0.122</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>5 (31)</td>
<td>6 (17)</td>
<td>0.218</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis (IV)</td>
<td>4 (25)</td>
<td>11 (31)</td>
<td>0.453</td>
</tr>
<tr>
<td>Thrombolysis (IA)</td>
<td>6 (37)</td>
<td>16 (46)</td>
<td>0.406</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>15 (94)</td>
<td>17 (49)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Mann–Whitney U test or χ² test was used for statistical comparison between the two groups. *Adjustment according to the modified Bonferroni correction was performed (*indicates significant findings, P<0.003). IA indicates intra-arterial; IV, intravenous.

occlusion, patients with evidence of concomitant intracerebral hemorrhage (n=2), bilateral infarcts (n=3), concomitant ischemia in the posterior circulation (n=1), history of previous stroke (n=3), or other central nervous system diseases (n=3) were excluded. Additionally, 4 patients declined study participation. The remaining 51 patients (24 women, mean age±SD 69.1±12.4 years) were included in the present investigation. Within this group, proximal MCA occlusion was diagnosed by means of magnetic resonance angiography in 39 patients, IA in 4, and TCD in 8. The study was approved by the local ethics committee. Informed consent for study participation was obtained from patients or their next of kin.

At hospital admission, a standardized neurological examination was performed. The National Institutes of Health Stroke Scale (NIHSS) was used to assess clinical impairment. Mean NIHSS was 16.2±5.3 ranging from 2 to 26. Fifteen patients received intravenous thrombolytic therapy (0.9 mg/kg recombinant tissue plasminogen activator), and 22 patients received intra-arterial thrombolytic therapy (1.0 to 1.5×10⁹ IU urokinase). The remaining 14 patients could not be treated by thrombolysis because of the following exclusion criteria: age >85 years (n=2), abdominal tumor (n=1), oral anticoagulation (n=2), exceeding the 6-hour time window after completion of initial diagnostics (n=1), recent surgical intervention (n=1), minor neurological deficit (NIHSS <4; n=1), and absence of a perfusion/diffusion mismatch on MRI within the 3-to 6-hour time window (n=6). Baseline characteristics of the study population, including vascular risk factors, stroke etiology, and clinical variables are shown in Table 1.

Blood Sampling and S100B Measurements

Venous blood samples (2 mL) were collected at hospital admission, and at 8, 12, 16, 20, and 24 hours after stroke symptom onset. Blood samples were immediately centrifuged (2703g; 5 minutes), and serum was separated and stored at −25°C. Measurement of S100B serum concentrations was performed using a commercially available monoclonal 2-site immunoluminometric assay on a fully automated LIA-mat system (Byk-Sangtec Diagnostica), which measured the β-subunit of protein S100 as defined by 3 monoclonal antibodies. The detection limit of this test was 0.02 µg/L. Intra-assay and interassay variability varied between 2.8% to 6.4% and 2.2% to 10.7%, respectively.

Malignant Infarction Definition

Malignant MCA infarction was defined as the occurrence of 1 of the following: (1) loss of brain stem reflexes and death within the first 7 days after symptom onset; (2) transient or persistent clinical signs of cerebral herniation (anisocoria) within the first 7 days after symptom onset plus basal intracranial mass effect on corresponding CT scan; or (3) a decision to perform DHC because of space-occupying swelling of the infarction with imminent herniation as judged by the treating neurologist and neurosurgeon (see below). According to our institutional guidelines, DHC is always considered if a patient experiences (1) a large (total or more than two thirds of MCA territory) MCA infarction with or without additional ischemia in the ipsilateral anterior cerebral artery (ACA) territory and signs of clinical deterioration (decreasing level of consciousness, anisocoria), or (2) a large MCA infarction with or without additional ipsilateral ACA infarction and progressive brain swelling with compression of ipsilateral lateral ventricle, midline shift, or compression of the basal cisterns on follow-up CT scanning. Patients >75 years of age, with severe comorbidity, with reduced life expectancy, or with dementia are not considered for DHC.

Infarct Volumetry

Infarct volumetry was based on MRI (fluid-attenuated inversion recovery; n=19) or CT (n=31) scans performed on average 4.5±1.4 days after symptom onset. One patient showed loss of brain stem reflexes within 24 hours after stroke onset, and a second brain scan...
could not be obtained. For infarct volumetry on MRI scans, we used commercially available software (MRVision; MRVision Inc), and for CT scans, we used public domain software from the National Institutes of Health. In patients with DHC, the most recent scan obtained before DHC was used for volumetry. Measurements of lesion volume were performed independently by 2 observers, 1 of whom was blinded to all other data. Interobserver agreement was determined, and accuracy measures for predicting malignant infarction were derived from cross-tabulations. The χ² statistic was used to indicate significant findings. CIs for accuracy measures were calculated according to the Wilson method. Furthermore, cut points for an optimized sensitivity or specificity >0.95 were calculated, respectively. Because several consecutive statistical tests were performed, α-adjustment according to the modified Bonferroni procedure was applied at each step of analysis.

**Statistical Analysis**

Statistical analyses were performed using the SPSS 10.0 software package (SPSS Inc). For statistical comparison of S100B values between the malignant and the nonmalignant group, we used Mann–Whitney U test. Using receiver-operating characteristic (ROC) curve analysis, cut points for the corresponding S100B values were determined, and accuracy measures for predicting malignant infarction were derived from cross-tabulations. The χ² statistic was used to indicate significant findings. CIs for accuracy measures were calculated according to the Wilson method. Furthermore, cut points for an optimized sensitivity or specificity >0.95 were calculated, respectively. Because several consecutive statistical tests were performed, α-adjustment according to the modified Bonferroni procedure was applied at each step of analysis.

**Results**

Sixteen of 51 patients developed malignant MCA infarction (31%). Among them, 8 patients developed complete loss of brain stem reflexes and died within the first 7 days, 2 showed transient or persistent clinical signs of herniation and corresponding mass effect on brain imaging, and in 6, patients DHC was performed. These conditions occurred between 12 and 24 hours in 2 patients, between 24 and 48 hours in 4, between 48 and 72 hours in 7, between 72 and 96 hours in 2, and in 1 patient beyond 96 hours.

The mean S100B serum concentration at hospital admission was 0.26±0.62 µg/L (median 0.14 µg/L). Starting with the 12-hour value, S100B serum concentrations were significantly higher in the malignant group compared with patients with nonmalignant infarction (12 hours 1.23±1.24 versus 0.29±0.45 µg/L; 16 hours 1.80±1.65 versus 0.38±0.53 µg/L; 20 hours 1.90±1.53 versus 0.44±0.48 µg/L; and 24 hours 2.41±1.59 versus 0.57±0.66 µg/L; all P<0.001; Figure 1a). After excluding patients treated with DHC, S100B values remained significantly elevated in the malignant group for the 12-, 16-, 20-, and 24-hour values (all P<0.003; Figure 1b).

Using ROC curve analysis, we calculated cut-point values providing optimal sensitivity and specificity for prediction of malignant infarction. A 12-hour S100B value >0.35 µg/L predicted a subsequent malignant course of infarction with a sensitivity of 0.75 (95% CI, 0.51 to 0.90) and a specificity of 0.80 (95% CI, 0.64 to 0.90). A 24-hour value >1.03 µg/L provided a sensitivity of 0.94 (95% CI, 0.72 to 0.99) and a specificity of 0.83 (95% CI, 0.67 to 0.92; Table 2). In addition, we tested whether combining measures may further optimize sensitivity and specificity in our sample. In this approach, taking at least 1 of 4 S100B measures (12, 16, 20, and 24 hours after stroke onset) above cut point increased sensitivity to 1.00. In contrast, taking all 4 measures above cut point did not optimize specificity (Table 2). In addition to S100B values taken at fixed time points after symptom onset, we approximated a cut-point curve between 12 and 24 hours after stroke onset. Furthermore, cut-point curves were also

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**TABLE 2. Accuracy Measures for Prediction of Malignant Course of Infarction**

<table>
<thead>
<tr>
<th>S100B Measure</th>
<th>SENS (CI)</th>
<th>SPEC (CI)</th>
<th>PPV (CI)</th>
<th>NPV (CI)</th>
<th>OA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hours (CP=0.35 µg/L)</td>
<td>0.75 (0.51–0.90)</td>
<td>0.80 (0.64–0.90)</td>
<td>0.63 (0.41–0.81)</td>
<td>0.88 (0.72–0.95)</td>
<td>0.78</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>16 hours (CP=0.36 µg/L)</td>
<td>0.88 (0.64–0.97)</td>
<td>0.74 (0.58–0.86)</td>
<td>0.61 (0.41–0.78)</td>
<td>0.93 (0.77–0.98)</td>
<td>0.78</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>20 hours (CP=0.48 µg/L)</td>
<td>0.94 (0.72–0.99)</td>
<td>0.77 (0.61–0.88)</td>
<td>0.65 (0.45–0.81)</td>
<td>0.96 (0.82–0.99)</td>
<td>0.82</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>24 hours (CP=1.03 µg/L)</td>
<td>0.94 (0.72–0.99)</td>
<td>0.83 (0.67–0.92)</td>
<td>0.71 (0.50–0.86)</td>
<td>0.97 (0.83–0.99)</td>
<td>0.86</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>At least 1 measure&gt;CP</td>
<td>1.00 (0.81–1.00)</td>
<td>0.69 (0.52–0.81)</td>
<td>0.59 (0.41–0.76)</td>
<td>1.00 (0.86–1.00)</td>
<td>0.78</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>All measures&gt;CP</td>
<td>0.69 (0.44–0.86)</td>
<td>0.83 (0.67–0.92)</td>
<td>0.65 (0.41–0.83)</td>
<td>0.85 (0.70–0.94)</td>
<td>0.78</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CP indicates cut point; SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; OA, overall accuracy. α-adjustment according to the modified Bonferroni correction was performed (χ² test; *indicates significant findings, P<0.008).
Mean final infarct volume in the malignant group was 293.2±89.0 mL, and in the nonmalignant group, 106.5±101.5 mL (P<0.001; Mann–Whitney U test). From 12 hours after symptom onset, significant correlations between S100B measures and final infarct volume could be obtained. The significance of this correlation increased over time (12 hours R=0.525; 16 hours R=0.539; 20 hours R=0.681; 24 hours R=0.723; all P<0.001). Additionally, an infarct volume >177 mL (cut point derived from ROC analysis) predicted a malignant course of infarction with a sensitivity of 0.88 (95% CI, 0.64 to 0.97), a specificity of 0.77 (95% CI, 0.61 to 0.88), a positive predictive value of 0.64 (95% CI, 0.43 to 0.80), and a negative predictive value of 0.93 (95% CI, 0.78 to 0.98), respectively. The overall accuracy was 0.82 (P<0.001).

Discussion

The main result of the present study is that a single measurement of the S100B serum concentration obtained within 12 to 24 hours after symptom onset can predict a malignant course of infarction in patients with proximal MCA occlusion with a high degree of diagnostic accuracy.

It is well known from previous studies that serum S100B values increase in ischemic stroke, reaching maximum levels 2 to 4 days after onset.12,13 Furthermore, infarct size was shown to be a major determinant of both the initial slope of the S100B kinetic and the absolute S100B peak value.14,15 Our findings fit well within this context (Figure 1). We found low S100B concentrations at hospital admission and 8 hours after symptom onset. Starting with the 12-hour S100B value, patients who later developed malignant infarction showed significantly higher S100B values compared with those with a nonmalignant course. This difference further increased within the following hours and was greatest for the 24-hour value (Figure 1), most probably because of the much greater infarct size in the malignant group (Table 1).

For the 20- and 24-hour S100B measurements, only 1 of 16 patients with malignant infarction revealed values below the calculated cut points. This “false-negative” patient experienced clinical signs of delayed transient herniation (anisocoria from day 5 to day 8) and significant midline shift on corresponding brain scan, and he survived. In contrast to this high sensitivity of S100B, specificity was lower. Twenty-four hours after stroke, 6 of 35 patients with nonmalignant infarctions were misclassified as having a malignant course of infarction. This “false-positive” group consisted of patients with large MCA territory infarctions, with a mean lesion volume of 204.4 mL (range 85.6 to 272.0 mL) but without clinical signs of herniation.

We also calculated whether repeated S100B determinations may increase overall accuracy. If at least 1 of 4 S100B values taken between 12 and 24 hours ranged above the cut point, sensitivity appeared to increase to 1.0, but specificity decreased to 0.69. If all 12- to 24-hour S100B values were above the calculated cut point, specificity was not further improved, but sensitivity decreased (Table 2). Thus, repeated measurements did not seem to provide a higher diagnostic accuracy compared with a single value because of overlapping CIs.

To estimate S100B cut points at variable time points within the 12- to 24-hour time window, we extrapolated cut-point curves for optimized overall accuracy, optimized sensitivity (>0.95), and optimized specificity (>0.95; Figure 2). This may be helpful under various clinical circumstances. For example, optimum sensitivity may be desired in routine clinical practice to identify all patients who are at risk of developing a potentially life-threatening stroke to streamline further diagnostic and therapeutic management. On the other hand, optimum specificity may be required in interventional studies to identify patients with a very high probability of a malignant infarction.

Pathophysiologically, release of S100B into serum in acute ischemic stroke most likely reflects astroglial cell death followed by a leakage of this protein through an impaired blood–brain barrier. This explains the strong correlation between serum S100B and infarct volume in our data set and previously.12,14,15 Additionally, lesion size on diffusion-weighted MRIs (eg, likely to represent irreversible cell death) has also been found to be predictive for a malignant course of infarction.6,7 This suggests that a critical infarct volume is crucial for development of cerebral herniation, further supported by the present finding that an infarct volume of >177 mL provides a 0.88 sensitivity and 0.77 specificity, too. In contrast, patients with a nonmalignant course of infarction may have better collateral blood supply, resulting in smaller infarcts with a flattened S100B kinetic.

A shortcoming of the present study may be the small sample size and the inclusion of a subgroup of 6 patients in whom the diagnosis of malignant infarction was not based on clinical grounds but on the decision to perform prophylactic DHC according to institutional criteria detailed above. It remains unclear whether these patients would have developed a malignant clinical course. To address this issue, we have...
also calculated the diagnostic accuracy of S100B separately for the group of 10 patients who fulfilled the clinical criteria of malignant infarction. As shown in Figure 1, this exclusion of the DHC subgroup from the malignant group did not change our results. Additionally, the validity of the given cut points should be reconfirmed in a separate sample.

In summary, this study showed that a single S100B serum measurement performed 12 to 24 hours after symptom onset can predict the development of malignant infarction in patients with proximal MCA occlusion. Compared with previous efforts invested to predict a malignant course of infarction, including MRI parameters, microdialysis, and PET, a serum test is easy to deploy. It should be noted that S100B testing is presently not introduced into routine stroke care. By means of a standard analyzing system as used in the present study, the determination will take $\approx 30$ minutes and is available 24 hours. In the future, it is well conceivable that S100B will be also available as a bedside test. Therefore, S100B has the potential to become a valuable marker in guiding clinical and therapeutic decisions for this particularly life-threatening subtype of stroke.

References

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