Prognostic Value of Early S100 Calcium Binding Protein B and Neuron-Specific Enolase in Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage: A Pilot Study

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■ BACKGROUND: **This prospective study was undertaken to investigate the value of early S100 calcium binding protein B (S100B) and neuron-specific enolase (NSE) in prognosticating outcome in patients with poor-grade aneurysmal subarachnoid hemorrhage and to develop a statistical model and cutoff values for clinical practice.**

■ METHODS: **Between 2012 and 2014, patients with poor-grade subarachnoid hemorrhage (Hunt and Hess grade 3–5) who were admitted within 24 hours after hemorrhage were prospectively enrolled. Serum NSE and S100B levels were assayed once daily during the first 3 days after hemorrhage. Patient characteristics, Glasgow Coma Scale score, Hunt and Hess grade, and Fisher grade at admission were recorded. Glasgow Outcome Scale (GOS) score was obtained at 6 months and dichotomized as poor (score 1–3) or good (score 4–5). Logistic regression and receiver operating characteristic curve were used to assess the value of S100B and NSE in predicting outcome, and cutoff values were calculated using conditional interference trees.**

■ RESULTS: **The study included 52 patients. Hunt and Hess grade was 3 in 23 patients, 4 in 15 patients, and 5 in 14 patients. S100B range was 0.07–5.62 μg/L (mean 0.87 μg/L ± 1.06). NSE range was 5.7–94.2 μg/L (mean 16.1 μg/L ± 10.5). At 6-month follow-up, 23 patients (44.2%) had a poor outcome, and 29 patients (55.8%) had a good outcome. Both S100B at day 1 ($P = 0.004$; cutoff 0.202 μg/L) and NSE at day 1 ($P = 0.047$; cutoff 9.4 μg/L) predicted good outcome with a specificity of 100%. The specificity of mean S100B in detecting patients with poor outcome reached 100% ($P = 0.003$) when combined with mean NSE levels.**

■ CONCLUSIONS: **S100B and NSE measured during the first 3 days after hemorrhage showed, separately and combined, a significant predictive value in prognosticating clinical outcome in patients with poor-grade subarachnoid hemorrhage. A multicenter study with a large patient cohort is necessary to validate the above-mentioned cutoff values for clinical practice.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) resulting from aneurysm rupture is a life-threatening disease with a large economic burden.[1] It has an incidence of 9 cases per 100,000 patient-years[2] and occurs most commonly in patients 40–60 years old.[3] Standard measures to prognosticate the severity of initial brain injury and anticipate the clinical outcome include the neurologic

Key words
- Intracranial aneurysm
- NSE
- S100
- Subarachnoid hemorrhage

Abbreviations and Acronyms
AUC: Area under the curve
CT: Computed tomography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
H&H: Hunt and Hess
NSE: Neuron-specific enolase
ROC: Receiver operating characteristic
S100B: S100 calcium binding protein B
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurological Surgeons

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examination and neuroimaging studies. Glasgow Coma Scale (GCS) score and Hunt and Hess (H&H) grade are clinical scores that have been long established in neurologic practice and are useful in predicting outcome. However, clinical evaluation of patients with poor-grade SAH is often subject to interobserver variability and becomes more difficult in patients given sedatives and analgesics. Biochemical markers, such as neuron-specific enolase (NSE) and S100 calcium binding protein B (S100B), are not investigator dependent, have been widely investigated and assumed to support the clinical evaluation of the primary brain injury, and are used clinical practice in the context of traumatic brain injury.[4-9]

NSE is a glycolytic enzyme that can be found in the neuronal cytoplasm, is specific for brain injury, and has no extracranial sources,[10,11] whereas S100B is not limited to the central nervous system and has been found in skeletal muscle, skin, and fat. Therefore, an elevation of S100B after trauma can also be attributed to extracranial injuries.[11] The mechanism of brain injury and the resulting delayed cerebral ischemia is different in patients with SAH, and the tissue damage occurs primarily within the central nervous system, which is why a distinct investigation of S100B and NSE among patients with SAH is necessary.

Higher values of S100B and, to a lesser degree, higher values of NSE in patients with SAH were found to be associated with a poor outcome.[12-14] However, a prognostic model to apply theses biomarkers in clinical practice, especially in the subgroup of patients in whom clinical evaluation is limited, has not been established yet. We conducted this pilot study prospectively to investigate the value of early S100B and NSE in prognosticating outcome in patients with poor-grade SAH and to determine cutoff values and a statistical model for outcome prediction that might help physicians in clinical decision making.

MATERIALS AND METHODS

Patients

In accordance with local and institutional laws and data protection regulations, approval by the local ethics committee (Ethik-Komission Der Ärztekammer Hamburg) was obtained for this study. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Between November 2012 and November 2014, all patients with SAH who were admitted to our hospital were screened for this study, and patients who met the inclusion criteria were prospectively enrolled after informed consent was obtained. Patients with newly diagnosed aneurysmal SAH, graded $\geq$3 on the H&H scale with bleeding occurring $\leq$24 hours before the admission were included. Intended number to include was 50. Patients who were admitted with recurrent bleeding and patients <18 years old were excluded.

Treatment of SAH

All patients underwent computed tomography (CT) angiography or conventional cerebral angiography, if required, and were assigned either to surgical or endovascular treatment by a board of attending neurosurgical and neuroradiologic consultants. An external ventricular drain was inserted on proof of hydrocephalus on the initial CT scans, followed by the actual aneurysm treatment of choice. After treatment, all patients were transferred to the intensive care unit, and anesthesia was reduced if possible with the focus on extubation and clinical evaluation. To prevent vasospasm, normovolemia and a mean blood pressure >90 mm Hg were maintained. In addition, all patients received nimodipine for at least 2 weeks, intravenous nimodipine during the first 7 days after hemorrhage followed by oral nimodipine if the patient was able to swallow; otherwise, intravenous nimodipine was continued.[15] Daily transcranial Doppler examinations were performed to assess vasospasm. If flow rates increased by >50 cm/second within 24 hours or a threshold of mean 200 cm/second was exceeded, conventional angiography was performed. If vasospasm was confirmed during angiography, intra-arterial nimodipine was administered. CT scans were performed based on patient clinical presentation or at least once before discharge to rule out posthemorrhagic hydrocephalus. After completing treatment in the intensive care unit, patients were referred to a rehabilitation program specializing in neurologic disorders. Patients had follow-up evaluation 6 months after discharge.

Clinical Parameters

Patient age, sex, initial GCS score evaluated either by the emergency physician before admission to the treating hospital or at admission, H&H grade, and blood distribution by Fisher grade were recorded. In addition, cardiovascular comorbidities, diabetes, and nicotine or ethanol abuse in the patient history were identified. Evidence of cerebral vasospasm and/or infarction was recorded and included in the statistical analysis.

Outcome was obtained using the Glasgow Outcome Scale (GOS) score[16] ranging from 1 to 5 with ascending grade of recovery at the time of discharge and at 6-month follow-up. Clinical assessment was performed by a physician blinded to the NSE and S100B assays. For statistical evaluation, outcome was calculated for individual GOS values as well as dichotomized as poor with a GOS score of 1–3 points and good with a GOS score of 4–5 points.

NSE and S100B Assays

Blood samples were taken on days 1, 2, and 3 after admission once daily. After centrifugation, the serum samples were kept at −20°C until analysis. Serum samples were analyzed by the LIAISON Analyzer (DiaSorin Deutschland GmbH, Dietzenbach, Germany) using the S100B and NSE chemiluminescence assays according to manufacturer instructions.

Statistical Analyses

Logistic regression and receiver operating characteristic (ROC) curve were used to assess the specificity and sensitivity of S100B and NSE levels (for each day and overall maximum and mean) in the prediction of clinical outcome. ROC curves were also used to compare S100B and NSE with other predictive scores (H&H grade, GCS score, and Fisher grade). Conditional interference trees were calculated to identify significant cutoff values for outcome prediction at 6-month follow-up for NSE and S100B and in combination with Fisher grade, H&H grade, and GCS score as possible covariates.