Cerebrospinal Fluid Creatine Kinase–BB Isoenzyme Activity and Outcome After Subarachnoid Hemorrhage

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Background: The brain is rich in creatine kinase–BB isoenzyme activity (CK-BB), which is not normally present in cerebrospinal fluid (CSF). Results of previous studies have shown that CK-BB can be detected in the CSF of patients with aneurysmal subarachnoid hemorrhage (SAH), but whether CK-BB levels correlate with patients' neurologic outcomes is unknown.

Objective: To evaluate the relationship between CSF CK-BB level and outcome after SAH.

Design: Prospective observational cohort.

Setting: University-affiliated tertiary care center.

Patients: Convenience sample of 30 patients seen for cerebral aneurysm clipping.

Interventions: We sampled and assayed CSF for CK isoenzymes a median of 3 days after SAH in 27 patients, and at the time of unruptured aneurysm clipping in 3 patients.

Main Outcome Measures: Without knowledge of CK results, we assigned the Glasgow Outcome Scale score early (≈1 week) and late (≈2 months) after surgery.

Results: Higher CSF CK-BB levels were associated with higher Hunt and Hess grades at hospital admission (Spearman rank correlation, $r = 0.69$; $P < .001$), lower Glasgow Coma Scale scores at hospital admission ($r = -0.72$; $P < .001$), and worse early outcomes on the Glasgow Outcome Scale ($r = -0.64$; $P < .001$). For patients with a favorable early outcome (Glasgow Outcome Scale score, 3-5), all CK-BB levels were less than 40 U/L. With a cutoff value of 40 U/L, CK-BB had a sensitivity of 70% and a specificity of 100% for predicting unfavorable early outcome (Glasgow Outcome Scale score, 1-2). Having a CK-BB level greater than 40 U/L increased the chance of an unfavorable early outcome, from 33% (previous probability) to 100%, whereas a CK-BB level of 40 U/L or less decreased it to 13%. Similar findings were obtained when considering late outcomes.

Conclusion: The level of CSF CK-BB may help predict neurologic outcome after SAH.

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PATIENTS AND METHODS

In a prospective study, we attempted to collect CSF samples from all adults seen at Harborview Medical Center, Seattle, Wash, for cerebral aneurysm clipping during a 23-week period. Patients were identified within 24 hours of hospital admission. Clinical data included demographic information, dates of ictus and hospital admission, Hunt and Hess grade and Glasgow Coma Scale (GCS) score at hospital admission after resuscitation, and hospital course. Aneurysm location was determined by biplane contrast angiography or contrast infusion computed tomography. We prospectively assigned the ordinal Glasgow Outcome Scale (GOS) score to all patients. A single investigator (W.M.C.) determined early and late GOS scores. Early outcome was the GOS score approximately 1 week after aneurysm clipping. After hospital discharge, all patients were followed up through at least 1 outpatient hospital visit or death, whichever came first. Late outcome was the GOS score approximately 2 months after aneurysm clipping and was based on outpatient medical records at the time of follow-up. The study defined following commands and having comprehensible speech as favorable outcomes (GOS score, 3-5), and being vegetative or dead as unfavorable outcomes (GOS score, 1-2).

Samples of CSF were collected from lumbar drains or ventriculostomies. Patients routinely underwent external lumbar drainage after induction of general endotracheal anesthesia for aneurysm clipping, while some underwent external ventriculostomy if they had preoperative hydrocephalus. These external drainage systems were in place throughout the aneurysm clipping surgery to afford brain relaxation, as needed. A CSF sample was collected from lumbar drains immediately before surgery or from ventriculostomies not later than immediately before surgery. The date, time, and site of sampling were recorded. Samples were spun, and the supernatant was frozen at -80°C.

All CK isoenzyme determinations were done without knowledge of any clinical information in the Enzymology Laboratory at the University of Washington, Seattle, using published methods. Briefly, CSF samples were thawed and initially treated with 1 mg of dithiothreitol per 1 mL of CSF to reactivate reversibly oxidized CK. After electrophoresis, CK isoenzyme activity was quantitated with a fluorosence method using CK reagents (Cardiotorac; Corning Medical and Scientific, Palo Alto, Calif) and a fluorometer/densitometer (model 790; Corning Medical and Scientific). Isoenzyme electrophoresis was not performed for samples with a total CK activity level of less than 10 U/L, in which case the CK-BB level was assumed to equal the total CK activity level. The CSF CK results were not available to the clinicians or recorded in patients’ medical records to avoid affecting clinicians’ behavior, and were available to the investigators determining outcome only after early and late outcomes were decided.

We hypothesized that CSF CK-BB level would reflect preoperative brain damage associated with SAH and thus, would correlate with outcome. We used nonparametric statistics for the analyses, including the Wilcoxon rank sum test and Spearman rank correlation (the closer the absolute value of the Spearman rank correlation coefficient [|ρ|] is to 1.0, the stronger the correlation). Statistical significance was defined as P<.05 (2-tailed). This study was approved by the University of Washington Human Subjects Review Committee.

Patients were not included in this study because, despite our best efforts at coordinating CSF sample collection and laboratory processing, we were unable to obtain CSF electrophoresis results for these patients. The median age of the 30 patients was 52.5 years (range, 23-83 years), and 22 (73%) were women. Arterial locations of the unruptured aneurysms and those suspected to have bled included anterior communicating (n = 9, 30%), middle cerebral (n = 5, 17%), posterior communicating (n = 5, 17%), basilar (n = 4, 13%), and posterior inferior cerebellar (n = 2, 7%). Other aneurysm locations included the ophthalmic, superior cerebellar, anterior choroidal, posterior cerebral, and internal carotid arteries. Two of 27 patients with SAH died in the hospital before the ruptured aneurysm could be clipped, both of whom had CSF samples collected from ventriculostomies. The other patients underwent surgery a median of 2 days (range, 1-21 days) after SAH and a median of 1 day (range, 0-6 days) after admission. Early outcome was significantly related to age, Hunt and Hess grade, and GCS score at hospital admission after resuscitation (Table). Early outcome was not significantly related to sex, aneurysm location, or time interval to operation (data not shown). However, the number of patients involved in this preliminary investigation was small.

The CSF samples came from lumbar drains in 16 patients and from ventriculostomies in 14 patients. For 27 patients with ruptured aneurysms, CSF was sampled a median of 3 days (range, 1-21 days) after SAH. For 3 patients with unruptured aneurysms, CSF was sampled immediately before surgery via lumbar drains. The CSF CK-BB level was measured earlier than the higher risk period for vasospasm. Samples from ventriculostomies tended to be obtained the first day after SAH (median, 2 days), and samples from lumbar drains were obtained a median of 2.5 days after SAH; this difference was not significant (P = .98). Time from ictus until CSF sampling was extreme in 1 patient, whose CK-BB level, sampled 21 days after SAH, was 10 U/L and GOS score was 3.

At early outcome determination, a median of 7 days after CSF sampling and a median of 9 days after SAH, CSF CK-BB levels were significantly higher for those who had unfavorable vs favorable outcomes (Table and Figure 1). The strongest rank correlation with GOS score at early outcome was for GCS score (ρ = 0.82), followed by Hunt and Hess grade (ρ = 0.74) and CSF CK-BB (ρ = 0.64) (P<.001 for all) (Table). Given that all these factors were strongly associated with outcome, CSF CK-BB level was correlated with GCS score (ρ = 0.72) and Hunt and Hess grade (ρ = 0.69) (P<.001 for both); CSF CK-BB level was not significantly correlated with age (ρ = 0.30; P = .10). Elevated CSF CK-BB levels were not related to the presence of vasospasm, as measured by transcranial Doppler or angiography at any time after SAH (P = .80). For patients with an unfavorable early outcome, the mean CSF CK-BB value was 420 U/L (median, 321.5 U/L; range, 3-1108 U/L); 75% of their CK-BB values were greater than 18 U/L. For pa-
tients with a favorable early outcome, the mean CSF CK-BB value was 7 U/L (median, 4.5 U/L; range, 1-40 U/L); 75% of their CK-BB values were less than 7.8 U/L.

The sensitivity, specificity, and predictive values for early outcomes were computed for a CSF CK-BB cutoff value of 40 U/L (Figure 2), which ensured a specificity and positive predictive value of 100% for predicting an unfavorable outcome. Maximizing the specificity resulted in a sensitivity of only 70% for predicting an unfavorable outcome and a negative predictive value of 87%. This cutoff value was chosen because, for patients with favorable outcomes at either follow-up, all CK-BB levels were 40 U/L or less. Having a CK-BB level greater than 40 U/L increased the chance of an unfavorable early outcome, from 33% (previous probability) to 100%, whereas a CK-BB value of 40 U/L or less decreased the chance of an unfavorable outcome, from 33% to 13%.

For comparison, receiver operator characteristic curves for CSF CK-BB level, Hunt and Hess grade, and GCS score are presented in Figure 3. Each point on the curve represents the sensitivity (true positives) and 1-specificity (false positives) for a particular cutoff value. The values needed to ensure a specificity of 100%, ie, no false positives, were greater than 40 for CSF CK-BB level, greater than 4 for Hunt and Hess grade, and less than 5 for GCS score. Hunt and Hess grade and GCS score performed in a similar fashion, with a 10% sensitivity at these cutoff values. If the desire is to avoid false positives—the erroneous conclusion that a patient will do poorly based on the test result—then the CSF CK-BB performs

### Early Neurologic Outcome for 30 Patients Seen for Aneurysmal Clipping*

<table>
<thead>
<tr>
<th>Predictors†</th>
<th>Favorable Outcomes</th>
<th>Unfavorable Outcomes</th>
<th>Total (N = 30)</th>
<th>Statistic (P)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 7)</td>
<td>2 (n = 3)</td>
<td>3 (n = 6)</td>
<td>4 (n = 9)</td>
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<tr>
<td><strong>Age, y</strong></td>
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<tr>
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<td>63.0</td>
<td>53.5</td>
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<tr>
<td>Median</td>
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<tr>
<td><strong>GCS score</strong></td>
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<td></td>
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<tr>
<td>Median</td>
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<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
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<td><strong>CSF CK-BB level, U/L</strong></td>
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<td>1-40</td>
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<tr>
<td>Median</td>
<td>321.5</td>
<td>4.5</td>
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</table>

*H&H indicates Hunt and Hess; GCS, Glasgow Coma Scale; and CSF CK-BB, cerebrospinal fluid creatine kinase–BB isoenzyme activity.
†Unruptured aneurysms are defined as H&H grade 0; all H&H grades and GCS scores are at admission after resuscitation.
‡Spearman rank correlation coefficients (ρ) were used when considering 5 outcome categories. The Wilcoxon rank sum test was used when considering 2 outcome categories.

**Figure 1.** Cerebrospinal fluid creatine kinase–BB isoenzyme activity (CSF CK-BB), as related to early neurologic outcome. Unfavorable outcome is defined as dead or vegetative (10 of 30 patients).

**Figure 2.** A 2 × 2 table showing prognostic performance of cerebrospinal fluid creatine kinase—BB isoenzyme activity (CSF CK-BB) for predicting early outcome using a cutoff value of 40 U/L. Unfavorable outcome is defined as dead or vegetative. Confidence intervals (95% CIs) are based on a binomial distribution.
better than the other measures, with a 70% sensitivity at the cutoff value.

Levels of CSF CK-BB were higher for the 14 patients sampled from ventriculostomy (mean, 263.4 U/L; median, 16.0 U/L; range, 2-1108 U/L) than for the 16 patients sampled from lumbar drain (mean, 40.8 U/L; median, 4.5 U/L; range, 1-532 U/L) (P = .03) (Figure 1). Although samples from ventriculostomies tended to be obtained the first day after SAH (median, 2 days) and those from lumbar drains were obtained a median of 2.5 days after SAH, this difference was not significant (P = .98). Regardless, CSF CK-BB levels were significantly higher in patients with an unfavorable vs a favorable early outcome, whether the CSF came from a ventriculostomy (14 patients) (P = .02) or a lumbar drain (16 patients) (P = .04).

Because only 2 patients changed their outcomes between early and late follow-up, results for late outcome are similar to those for early outcome. Two patients with CK levels less than 40 U/L in the favorable outcome group at early follow-up were in the unfavorable outcome group at late follow-up, a median of 57 days after SAH. Both of these patients developed nosocomial pneumonia, 1 rebled before surgery, and 1 developed symptomatic moderate vasospasm after surgery. These events occurred after CSF sampling. No patient with an unfavorable outcome at early follow-up improved to a favorable one at late follow-up. All patients with an unfavorable late outcome except 1 were dead; only 1 remained vegetative.

Level of CSF CK-BB significantly correlated with GOS score at late outcome (ρ = −0.59; P = .001). For patients with an unfavorable late outcome, mean CSF CK-BB value was 351 U/L (median, 142.5 U/L; range, 1-1108 U/L), 79% of their CK-BB values were greater than 6 U/L. For patients with a favorable late outcome, mean CSF CK-BB value was 7 U/L (median, 4.5 U/L; range, 1-40 U/L). This difference was significant (P = .007). At late follow-up, a cutoff CK-BB value of 40 U/L retained a 100% specificity and positive predictive value for an unfavorable outcome, whereas the sensitivity decreased to 58% with a negative predictive value of 78%. For patients who always had an unfavorable outcome (never had a GOS score of 3-5 at any time during outcome measurement), mean CSF CK-BB value was 420 U/L (median, 322 U/L; range, 3-1108 U/L). For patients who ever had a favorable outcome, mean CSF CK-BB value was 7 U/L (median, 4.5 U/L; range, 1-40 U/L). This difference was again significant (P < .001).

Using the cutoff value of 40 U/L, 3 patients had false-negative results, namely, an unfavorable outcome, despite a low CSF CK-BB level (see Figure 1 and patients with 3, 5, and 22 U/L). These patients were sampled 1, 2, and 7 days after SAH. We attempted to find a plausible intervening insult after the CSF CK-BB level determination to explain the 3 false-negative values. Their initial GCS scores were 8, 10, and 11, and all were Hunt and Hess grade 3. One 81-year-old patient rebled and died before surgery. The second patient had a left middle cerebral infarction postoperatively. The third patient had a large (> 20 mL) intraparenchymal hematoma and died with intracranial pressure problems.

In this prospective study, a high CSF CK-BB value strongly related to an unfavorable outcome after SAH. Whether considering the outcome early (= 1 week) or late (= 2 months) after surgery, all patients who were vegetative or died had CSF CK-BB levels greater than 40 U/L. Thus, this cutoff value ensured a specificity and positive predictive value of 100% for an unfavorable outcome. Having a CSF CK-BB value of 40 U/L or less was no guarantee of a favorable outcome. Three patients had false-negative results with low values and unfavorable early outcomes, but all had complications of their SAH after CSF sampling that could have explained their unfavorable outcomes. Correlations with early outcome, as assessed with the GOS, were of similar strength, and all were highly statistically significant (P < .001) for Hunt and Hess grade (ρ = −0.74), GCS (ρ = 0.82), and CSF CK-BB (ρ = −0.64). Whether the CSF CK-BB value provides independent prognostic information beyond these clinical scales was not addressed in this study, but would not be unexpected.

The strength of this study rests in its specific hypothesis, prospective design, and masking of investigators and clinicians to the results of the test. The enzyme assay is well established and has been shown to correlate with neurologic outcome after cardiac arrest and head trauma, both at this institution and in the settings of experimental canine stroke and acute cerebrovascular accidents. That some patients were sampled from ventriculostomies and some from lumbar drains is a potential problem. Patients whose CSF was sampled from ventriculostomies had CK-BB values that were higher than those whose CSF was sampled from lumbar drains. Also, patients requiring ventriculostomies were sicker than those who did not and were at greater risk for unfavorable outcomes. Perhaps the need for a ventriculostomy is more predictive of an unfavorable outcome than is CSF CK-BB level, and ventriculostomies themselves cause elevated enzyme activity in the CSF. Against such an argument is the finding that, when analyses are restricted to the 14 patients whose samples were collected from ven-
triculostomies, CSF CK-BB level is still strongly related to outcome ($P = .02$), despite the small numbers.

The major weakness of this study is that it enrolled only a small number of patients from a convenience sample and from a single institution. Additional studies are needed to clarify the optimal time and site of CSF sampling, to define the best CSF CK-BB cutoff value, and to confirm whether CSF CK-BB level adds to other prognostic information such as GCS score, Hunt and Hess grade, or results of neuroimaging. The timing of sampling is important because CSF CK-BB was measured earlier than the higher risk period for vasospasm. Only after additional studies are done will the prognostic utility of CSF CK-BB after SAH and its safety be defined. Until such time, we advise against using CSF CK-BB values to help make decisions about a patient's suitability for aneurysm clipping, or about limiting the degree of medical support.

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