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S100b and BNP predict functional neurological outcome after intracerebral hemorrhage

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Abstract

Objective—To determine the predictive value of S100b and brain natriuretic peptide (BNP) to accurately and quickly determine discharge prognosis after primary supratentorial intracerebral hemorrhage (ICH).

Methods—After IRB approval and informed consent, blood samples were obtained and analyzed from 28 adult patients consecutively admitted to the neuroscience intensive care unit with computed tomography-proven supratentorial ICH from June 2003 and December 2004 within the first 24 h after symptom onset for S100b and BNP. Functional outcomes on discharge were dichotomized to favorable (mRS<3) or unfavorable.

Results—BNP (a neurohormone) and S100b (a marker of glial activation) were found to be independently highly predictive of functional neurological outcome at the time of discharge as measured by modified Rankin Score (BNP: $p<0.01$, $r=0.46$; S100b: $p<0.01$, $r=0.42$) and Barthel Index (BNP: $p<0.01$, $r=0.54$; S100b: $p<0.01$, $r=0.50$). Although inclusion of either biomarker produced additive value when included with traditional clinical prognostic variables, such as the ICH Score (Barthel index: $p<0.01$, $r=0.66$; mRS: $p<0.01$, $r=0.96$), little predictive power is added with inclusion of both biomarkers in a regression model for neurological outcome.

Conclusions—Serum S100b and BNP levels in the first 24 h after injury accurately predict neurological function at discharge after supratentorial ICH.

Keywords

intracerebral hemorrhage; prognosis; s100 proteins; brain natriuretic peptide; intensive care; neurological outcome

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Introduction

Primary supratentorial intracerebral hemorrhage (ICH) is a relatively common and devastating disease with little improvement in functional neurological outcome over the last decade despite advances in medical technology. (Broderick et al., 2007) While acute diagnosis is relatively straightforward since the advent of computed tomography (CT) scanning, the ultimate prognosis remains difficult to predict early in the disease course, especially in light of the decision of many families to ‘withdraw care’ on patients deemed unlikely to have favorable long-term functional outcome by their physicians. This uncertainty has resulted in a wide spectrum of patient outcomes, from complete rehabilitation to persistent vegetative state, underscoring the need for adjunctive prognostic tools to guide initial management decisions in the setting of acute ICH.

Traditionally, in the acute setting, prognosis following ICH has been guided by several variables, including age, hematoma location, size, and ventricular extension. (Garibi et al., 2002, Juvela, 1995) However, these traditional prognostic variables remain imperfect, and often are not adequate to provide a realistic assessment of likely outcome in an individual patient. Although direct neuronal injury from mass effect of the hematoma plays an important role in determining outcome, advances in the critical care arena have resulted in some patients surviving this initial insult only to deteriorate due secondary injury from cerebral edema. Consequently, it is increasingly recognized that, neuroinflammation plays an important role in mediating this cerebral edema, secondary neuronal injury, and ultimately, functional outcome. (James et al., 2007). Thus, it is feasible that biochemical markers of neuronal injury and inflammation might provide adjunctive prognostic information, as well as a surrogate measure of neuropathophysiology to assess the effect of potential therapeutic interventions.

The role of biomarkers have been previously described in other mechanisms of acute brain injury, including ischemic stroke, (Lynch et al., 2004, Nakagawa et al., 2005) traumatic brain injury, (Sviri et al., 2006) and subarachnoid hemorrhage (McGirt et al., 2004, Stranjalis et al., 2007). In particular, markers reflective of astrocytic activation, such as S100B, have a relatively large body of evidence demonstrating elevation after acute ischemic stroke (Lynch et al., 2004, Mizukoshi et al., 2005, Reynolds et al., 2003) and subarachnoid hemorrhage. (Lynch et al., 2005) Moreover, S100B has shown some promise as a surrogate marker for therapeutic intervention in ischemic stroke, (Elting et al., 2002) and a predictor of hemorrhagic conversion and outcome. (Foerch et al., 2006, Foerch et al., 2007, Jonsson et al., 2001, Kokocinska et al., 2007) Furthermore, a recent examination of S100b levels after subarachnoid hemorrhage revealed a correlation with long-term functional outcome but also disclosed the complex nature of the clinical use of serological markers, in that their utility for prognosis can be limited in clinically relevant timeframes. (Sanchez-Pena et al., 2008) Additionally, S100b is one of a small number of serological proteins previously demonstrated to correlate with functional outcome after ICH. (Delgado et al., 2006)

Brain natriuretic peptide (BNP), though not previously evaluated specifically after ICH, has been historically assessed in the setting of heart failure (Valli et al., 1999) and recent data has demonstrated elevated BNP levels after acute brain injuries, such as ischemic stroke, (Koenig et al., 2007, Nakagawa et al., 2005) traumatic brain injury, (Sviri et al., 2006) and subarachnoid hemorrhage. (Fukui et al., 2004, McGirt et al., 2004) To date, the relevance of BNP in the setting of ICH acute is poorly understood. However, there is emerging preclinical evidence to suggest that BNP may play an adaptive role in recovery from acute brain injury, possibly through augmentation of cerebral blood flow. (2008)

In the current study, we evaluate the hypothesis that these two biomarkers, S100b and BNP, both shown previously to provide diagnostic and prognostic significance in other mechanisms

of acute brain injury, would provide greater benefit for prognosis after supratentorial primary ICH than traditional clinical and radiographic criteria, or either biomarker alone.

Methods

Patients

After approval from the Duke University Medical Center Institutional Review Board was received, patients were enrolled after written, informed consent was obtained from study participants or their legal designates. The primary end point in this study was functional neurological outcome at time of hospital discharge as assessed by the Barthel Index (BI) and modified Rankin Score (mRS). Supratentorial ICH was confirmed by computed tomography (CT) imaging prior to enrollment. Exclusion criteria included age less than 18 years, confirmed pregnancy, known or suspected brain tumor, known or suspected CNS vascular malformation, presence of subarachnoid blood, massive head trauma, time of presentation greater than 24 h after symptom onset, or multiple organ dysfunction at the time of admission.

Blood samples were taken from 28 consecutive patients admitted to the Neuroscience Intensive Care Unit (NICU) between January 1, 2000 and December 31, 2003, with CT-proven supratentorial ICH during multiple timeframes from symptom onset (0-6 h, 6-12 h, and 12-24 h). The highest serum value recorded in the first 24 h after symptom onset was used for the analysis and comparisons. Symptom onset was defined as last known time of baseline neurological function. Upon entry into the study, demographics were recorded, and Glasgow Coma Score (GCS), NIH Stroke Scale (NIHSS) and ICH Score (Hemphill et al., 2001) were tabulated. Briefly, the ICH Score is a 6-point scale validated to stratify risk after primary ICH in humans and consists of initial GCS, hematoma volume and location, presence of intraventricular blood, and age. During the first 36 hours after admission, CT scans were obtained and evaluated for hemorrhage volume (cm³), midline shift (MLS, mm), and presence of intraventricular hemorrhage (IVH); additionally the latency from ictus to the study scan was recorded. Upon discharge from the hospital, mRS, BI, hospital length of stay (LOS), and NICU LOS were recorded by a single observer blinded to biomarker data.

Immunoassay Procedure

Blood drawn from each patient was centrifuged (10 000g), and the resulting supernatant was immediately frozen at 70°C until analysis was completed. Measurements of biochemical markers involved in the inflammatory cascade were performed by Biosite, Inc. (San Diego, CA). All immunoassays were forward immunometric (sandwich) assays performed in 384-well microtiter plates using a Tecan Genesis RSP 200/8 Workstation (Tecan US, Durham, NC). Each plasma sample was assayed in duplicate. The biotinylated antibody was added to neutravidin-coated 384-well black plates (Pierce Chemical Co., Rockford, IL) and incubated at room temperature for 1 h. The plate was washed, and then plasma samples (10 µL) were aliquoted into the wells. After incubation for 1.25 h, the plate was washed again, and the alkaline phosphatase-conjugated antibody was added. After an additional incubation for 1.25 h, the plate was washed a third time, and AtttoPhos® substrate (JBL Scientific, San Luis Obispo, CA) was added to measure the amount of alkaline phosphatase-conjugated antibody bound in each well. The plates were read by a fluorometer with an excitation wavelength of 430 nm and an emission wavelength of 570 nm. Each well was read six times at 114-s intervals, and a rate of fluorescence generation was calculated. Calibrators were prepared gravimetrically in pooled plasma from healthy donors. One tube in each set of calibrators included neutralizing antibody for correction of endogenous antigen present in the plasma pool. Calibration curves were eight points run in duplicate in columns 1 and 2 and repeated in columns 23 and 24 of the assay plate. The calibration curve was calculated using a fourparameter logistic fit. (Reynolds et al., 2003)

Imaging

All patients enrolled into the study were diagnosed with CT-proven supratentorial ICH prior to blood sampling. Because re-bleeding and initial cerebral edema formation occur within the first 24 h after ictus, the imaging scan used for the study protocol was the next subsequent scan that occurred within 36 h after admission. A blinded neuroradiologist assessed CT scans in the following manner: On the CT slice with the largest area of ICH, the largest diameter (A) of the hematoma was measured in centimeters. The dimension of the hemorrhage perpendicular to the largest diameter represented the second diameter (B) in centimeters. The height of the hematoma was calculated by multiplying the number of slices involved by the slice thickness, providing the third diameter (C). The three diameters were multiplied and then divided by two ($A \times B \times C / 2$) to obtain the volume of ICH in cubic centimeters. (Kothari et al., 1996) For the purpose of determination of (C) diameter, the first and last slices where hematoma is first and last noted were not counted. Additionally, intraventricular hemorrhage (IVH) was defined as an intraventricular hyperdense image not attributable to calcification or the choroid plexus. MLS of the septum pellucidum was measured by a neuroradiologist blinded to biomarker data and corrected for magnification using the scale provided on each CT image. MLS was calculated as the distance from the center of the anterior horns of the lateral ventricles on the CT slice containing the third ventricle to a perpendicular line connecting the anterior and posterior insertions of the falx cerebri. A MLS of >2 mm was considered significant.

Statistical Methodology

Continuous variables are described by mean and standard deviation, and categorical variables with percentages. Association between biomarkers and radiographic outcomes (hematoma volume and midline shift), analyzed as continuous variables, were investigated with linear regression. Association between biomarkers and patient outcomes were investigated with linear regression analysis for the Barthel Index, which was analyzed as a continuous variable, and logistic regression analysis for modified Rankin Score, which was analyzed as a dichotomous outcome (favorable vs. unfavorable outcome). After investigating univariate associations, biomarkers were investigated together, and in combination with ICH score, to determine the increase in model predictive ability when additional variables are included. Multivariate model assumptions were tested. Additive effects were assessed with two-way interactions between covariates. Goodness of fit was assessed for logistic regression models with Hosmer-Lemeshow test. Collinearity among predictors was assessed with tolerance and variance inflation tests. All analyses were performed with SAS version 9.3 or JMP 7.0.1.

Results

Baseline characteristics for subjects enrolled are shown in Table 1. BNP values are significantly correlated with ICH score ($r^2 = 0.42$, $p = 0.02$) and MLS ($r^2 = 0.42$, $p = 0.0002$) but not ICH volume ($r^2 = 0.14$, $p = 0.49$), LOS ($r^2 = 0.02$) or initial GCS ($r^2 = 0.21$). S100b values are significantly correlated with ICH score ($r^2 = 0.39$, $p = 0.04$), MLS ($r^2 = 0.54$, $p < 0.0001$), and ICH volume ($r^2 = 0.48$, $p = 0.01$) but did not correlate with LOS ($r^2 = 0.01$) or initial GCS ($r^2 = 0.32$).

Univariate linear and logistic regression analysis demonstrated that BNP values are significantly associated with outcome, as measured by BI ($p < 0.0001$; slope 0.11, 95% CI 0.69-0.15) and dichotomized mRS ($p = 0.04$; odds ratio 1.023, 95% CI 1.002-1.044); similarly, S100b values are predictive of outcome (BI, $p < 0.0001$, slope 0.16, 95% CI 0.09-0.22; mRS, $p = 0.02$, odds ratio 1.02, 95% CI 1.003-1.039).

To investigate the additional predictive ability that these biomarkers have beyond the ICH score, we included them with the ICH score in multivariable models predicting BI and

dichotomized mRS score. In a multivariable linear regression model predicting BI, ICH score alone accounts for 44% of the variability in BI, as measured by the r^2 value. After including S100 and BNP in the model, the adjusted r^2 value increases to 0.66. Multivariable linear regression model for BI containing all three predictors is shown in Table 2. In a multivariable logistic regression model predicting favorable mRS outcome (Table 3), ICH score has a very high c-index, indicating good predictive ability (c-index = 0.86, 95% confidence limits 0.69-1.01); after the addition of S100 and BNP, the c-index increases to 0.96 (95% confidence limits 0.89-1.02). Although the comparison of the area under the ROC curves indicates that these are not statistically different in this small sample ($p=0.13$), a trend is evident in the data. Furthermore, when hemorrhage volume, the more traditional measure for functional outcome and an essential component of the ICH Score, is evaluated in this model, an r^2 value for the Barthel index is determined to be 0.19, which is lower than for either biomarker alone or in combination, and a c-index for mRS is 0.87, which is similar to the ICH Score, BNP level and S100 level. Due to the high correlation between S100 and BNP ($r = 0.79$), a model constructed utilizing both biomarkers provides marginally increased predictive ability over using only one. These models are summarized in Table 4. However, when taken together the use of S100 and BNP levels suggest improved predictive value for neurological outcome at hospital discharge over traditional prognostic tools and when used in conjunction with these clinical scales improve the prognostic power than when either is used in isolation.

Discussion

Biological markers have been demonstrated to correlate with outcomes in a number of different acute brain injury mechanisms, including traumatic brain injury, (Biberthaler et al., 2002) ischemic stroke, (Reynolds et al., 2003) and subarachnoid hemorrhage. (Stranjalis et al., 2007) Furthermore, it appears that after acute brain injury a panel of biomarkers may add potential benefit in terms of diagnostic precision and prognostic accuracy over any one biomarker alone. (Laskowitz et al., 2005) Thus, a biomarker-based test may have utility in providing additional prognostic information when used in conjunction with traditional radiographic and clinical variables to guide early management decisions, as in global ischemia after cardiac arrest, (Ekmektzoglou et al., 2007, Sodeck et al., 2007) and as a surrogate endpoint in early clinical trials, such as in ischemic infarction (Pettigrew et al., 2006) and SAH. (Lynch et al., 2005) To this end, our data demonstrate that both S100b and BNP are highly correlative with functional neurological outcome following primary supratentorial ICH at the time of hospital discharge and add additional predictive value over traditional prognostic scoring systems.

The calcium binding protein, S100b, belongs to a family of microglial proteins found as dimers of two different subunits (alpha and beta) with types alpha—beta and beta—beta described as S100b protein. When acute structural damage occurs to microglia and Schwann cells, S100b is released into the cerebrospinal fluid and, with disruption of the blood-brain barrier, into the blood. (Abraha et al., 1997) Therefore, not only is serum S100b reflective of glial injury but may also be indicative of blood—brain barrier dysfunction. (Kanner et al., 2003) Furthermore, it is not affected by hemolysis and remains stable for several hours allowing for delayed but reliable serological analysis after acquisition. Finally, its short half-life makes measurements readily applicable to current pathophysiological state and vital to determination of intervention in acute care settings. (Buttner et al., 1997)

Brain natriuretic peptide (BNP) is a neurohormone produced as a pro-hormone (pro-BNP) comprised of 108 amino acids. (Valli et al., 1999) BNP is then enzymatically cleaved into physiologically active BNP and the amino-terminal portion of the pro-hormone after being released primarily from the cardiac ventricles in response to increased wall tension. (Mukoyama et al., 1991) Serum BNP is typically elevated in patients with heart failure

(Mukoyama et al., 1990), but BNP levels have been found to rise early and rapidly after acute brain injury. (Nakagawa et al., 2005) By means of its natriuretic and diuretic properties, this neurohormone produces a myriad of biological effects, such as vasodilatation, (Laragh, 1985) changes in electrolyte and fluid balances, (Epstein et al., 1987) and inhibition of the sympathetic nervous system. (Floras, 1990) Although there is a paucity of data regarding BNP levels after ICH, recent reports demonstrate elevations after subarachnoid hemorrhage (SAH), (Fukui et al., 2004, McGirt et al., 2004, Yarlagadda et al., 2006) traumatic brain injury, (Sviri et al., 2006) and ischemic stroke. (Koenig et al., 2007, Nakagawa et al., 2005) Although preliminary data suggests that BNP elevations may be associated with an increase in cerebral blood flow after acute brain injury, it remains unclear whether this is an adaptive response related to increasing cerebral blood flow (Akdemir et al., 1997, Iida et al., 2001, Nogami et al., 2001) or a deleterious effect resulting in increased ischemia, (Sviri et al., 2000, Sviri et al., 2003).

In patients suffering from ICH, few published data exist examining the prognostic role of serological markers. Relationships have been drawn between certain serum biomarkers in differentiating ischemic from hemorrhagic stroke (Allard et al., 2004, Laskowitz et al., 2005) as well as prediction of early hematoma expansion, such as matrix metalloproteinases. (Abilleira et al., 2003) However, the use of serological markers to determine functional outcome after ICH is currently limited to IL-11 (Fang et al., 2005) and S100b. Weglewski et al. (Weglewski et al., 2005) demonstrated the time course over which S100b elevates and then declines to baseline following ICH. Furthermore, both early deterioration and long-term functional outcomes (3 months) were found to correlate with S100b levels on admission after ICH. However, Delgado et al. (Delgado et al., 2006) did not find that S100b provided a superior level of prediction when compared to initial ICH volume by CT, though utilization of mRS as their neurological endpoint may be less specific than BI. It is clear that discovery of a serological marker(s) predictive of functional neurological outcome after ICH with high sensitivity and specificity is highly desirable.

Our data suggest that two biomarkers, S100b and BNP, are highly correlative with functional neurological outcome after ICH and that when either is used in conjunction with more traditional prognostic scoring systems, such as the ICH Score, (Hemphill et al., 2001) there is an incremental increase in ability to predict prognosis. It appears that, mechanistically, these biomarkers may be related to enhanced inflammation, as demonstrated by their correlation with MLS, an accepted surrogate for cerebral edema. (James et al., 2009) Interestingly, the lack of correlation of S100b and BNP in our dataset with more traditional predictive variables, such as GCS and hematoma volume, may suggest that these serological proteins may be more reflective of a secondary inflammatory effect, rather than the initial injury due to mass effect. It is important to note, however, that our data do not demonstrate an improvement in predictive power by using both markers concordantly. In addition to determining the exact time course of elevation and underlying pathophysiological mechanisms represented by these markers, further studies should also address the possibility of utilizing biomarkers in differentiating the exact causes of ICH (primary, amyloid angiopathy, etc.).

There are several limitations of our data that should be addressed. First, this is a small pilot study and should not be used to dictate current clinical care strategies. We believe we have identified two useful and important biological markers that add to existing knowledge regarding prognosis after ICH; however, clinical utility needs to be borne out by further study. Next, outcome measures were assessed at discharge rather than in the post-rehabilitation period, allowing for the possibility of some patients initially dichotomized into unfavorable status to ultimately obtain higher functional condition after several months of rehabilitation. We believe this is less likely as both biomarkers correlated strongly with traditional prognostic tools, such as the ICH Score. Also, the use of the highest biomarker level within the first 24 h

after ictus, rather than at a fixed time point, may have further biased the results, i.e. if less impaired patients with theoretically better prognoses missed the peak biomarkers level due to discharge or, inversely, mortally injured patients died prior to peak levels. We feel that either circumstance is unlikely as there was a positive correlation with poor neurological outcome (including death) and protein level, and no patients died or were discharged within the first 24 h after entry to the study. Third, some of the patients that died in this study underwent withdrawal of care, which is fundamentally different than death in the setting of maximum therapeutic intervention. However, as ICH volume and GCS both correlate with each other and with outcome in our dataset, we believe it is likely that our results would be borne out in a long-term study to evaluate more definitive outcome measures. Finally, our values were followed only over first 24 h after hemorrhage, and it is possible that there may be a second peak of serum values as inflammation increases during hemoglobin breakdown, which typically occurs several days after hemorrhage.

Although this study was not designed to examine the utility of repeated measurements, ultimately the utility of biological markers may finally rest in their ability to be followed over time, which is far easier than performing serial imaging studies. Despite the diagnostic and prognostic value of CT imaging for hemorrhage volume in the acute setting, there remains a significant degree of indecision regarding end of life decisions in the first 24 to 48 h after ICH. However, it appears that S100b and BNP elevation in the first 24 h after injury may augment existing technologies to assist in these difficult decisions.

Conclusions

S100b and BNP are highly correlated with functional neurological outcome at hospital discharge after supratentorial primary ICH. Furthermore, these biomarkers add prognostic information over traditional ICH scores that incorporate clinical and radiographic features. Further study for exact time course of serological changes and their prognostic value for long-term functional and neurocognitive examination are indicated.

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Table 1

Characteristics of patients admitted after supratentorial ICH. (SD — standard deviation, ICH — intracerebral hemorrhage, IVH — intraventricular hemorrhage; ICH Volume — intracerebral hemorrhage lesional volume by computer tomography, CT — computed tomography, MLS — midline shift, GCS — Glasgow Coma Score, NIHSS — NIH Stroke Scale, mRS — modified Rankin Score, BI — Barthel Index, LOS — length of stay, BNP — brain natriuretic peptide, S100b — S100 calcium binding protein b)

Age	Mean (SD)
Gender (% male)	50.0
Race (% Caucasian)	57.12
ICH Volume (cm ³)	30.65 (31.30)
Presence of IVH (%)	42.86
Latency to CT	9.32 (3.88)
MLS (mm)	5.04 (4.61)
GCS	10.46 (4.43)
NIHSS	15.19 (12.19)
ICH Score	1.57 (1.23)
mRS	3.39 (1.55)
BI	50.71 (37.11)
Hospital LOS	16.36 (28.40)
Peak BNP in 1 st 24 hours	236.41 (245.62)
Latency to highest serum BNP value	12.32 (15.81)
Peak S100b in 1 st 24 hours	203.63 (163.96)
Latency to highest serum S100b value	8.03 (12.7)

Table 2

Multivariable predictors of Barthel Index (BNP — brain natriuretic peptide, S100b — S100 calcium binding protein b, ICH — intracerebral hemorrhage)

	Slope	95% Confidence limits	P value
BNP	0.06	0.006-0.12	0.03
S100b	0.04	0.05-0.13	0.34
ICH score	11.95	4.01-19.89	0.005

Adjusted R-square value=0.66

Table 3

Multivariable predictors of favorable modified Rankin Score (BNP — brain natriuretic peptide, S100b — S100 calcium binding protein b, ICH Score— Intracerebral Hemorrhage Score)

	Odds ratio	95% Confidence limits	P value
BNP	1.016	0.98-1.05	0.32
S100b	1.017	0.99-1.05	0.24
ICH score	3.93	0.80-19.26	0.09

C-index=0.96

Measures of model predictive ability for biomarkers for functional neurological outcome in patients after supratentorial ICH. (BNP - brain natriuretic peptide, S100b — S100 calcium binding protein b, ICH Score - Intracerebral Hemorrhage Score, ICH Volume — Intracerebral hemorrhage lesional volume by computer tomography)

Table 4

Outcome	Predictor					
	BNP	S100b	BNP + S100b	ICH score	ICH Volume	BNP + S100b + ICH score
Barthel Index (adjusted r^2 value)*	0.54	0.50	0.58	0.44	0.19	0.66
Stratified mRS (c-index) #	0.87	0.89	0.91	0.86	0.87	0.96

* r^2 value represents the proportion of variability in the outcome measure accounted for by predictors in the model.

c-index value is a measure of the predictive ability of the model; 1.0 represents perfect