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Comparison of the performances of copeptin and multiple biomarkers in long-term prognosis of severe traumatic brain injury

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ABSTRACT

Enhanced blood levels of copeptin correlate with poor clinical outcomes after acute critical illness. This study aimed to compare the prognostic performances of plasma concentrations of copeptin and other biomarkers like myelin basic protein, glial fibrillary astrocyte protein, S100B, neuron-specific enolase, phosphorylated axonal neurofilament subunit H, Tau and ubiquitin carboxyl-terminal hydrolase L1 in severe traumatic brain injury. We recruited 102 healthy controls and 102 acute patients with severe traumatic brain injury. Plasma concentrations of these biomarkers were determined using enzyme-linked immunosorbent assay. Their prognostic predictive performances of 6-month mortality and unfavorable outcome (Glasgow Outcome Scale score of 1–3) were compared. Plasma concentrations of these biomarkers were statistically significantly higher in all patients than in healthy controls, in non-survivors than in survivors and in patients with unfavorable outcome than with favorable outcome. Areas under receiver operating characteristic curves of plasma concentrations of these biomarkers were similar to those of Glasgow Coma Scale score for prognostic prediction. Except plasma copeptin concentration, other biomarkers concentrations in plasma did not statistically significantly improve prognostic predictive value of Glasgow Coma Scale score. Copeptin levels may be a useful tool to predict long-term clinical outcomes after severe traumatic brain injury and have a potential to assist clinicians.

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Introduction

Severe traumatic brain injury (STBI) is a frequent pathology and is associated with high morbidity and mortality [20]. Many found prognostic cell-type-specific proteins for STBI exist including myelin basic protein (MBP), glial fibrillary astrocyte protein (GFAP), the calcium-binding protein S100B, neuron-specific enolase (NSE), phosphorylated axonal neurofilament subunit H (pNF-H), tau protein and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) [2,12,14–17,21]. Vasopressin, also known as arginine vasopressin, is an antidiuretic hormone formed in the hypothalamus and secreted from the posterior pituitary gland [1]. Copeptin, a surrogate marker for arginine vasopressin, is associated with poor clinical outcomes in patients with acute brain injury such as STBI [5,11,13,23]. However, to our best knowledge, there is a paucity of available data in the literature on the comparisons between copeptin and other biomarkers including NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 for prediction of long-term clinical outcome in patients with STBI. We measured in this study the plasma concentrations of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 in acute STBI with a comparison analysis for their prediction of 6-month mortality and poor functional outcome.

Materials and methods

Study population

A prospective observatory study over period of 3 years from January 2010 to January 2013 at the Hangzhou First People's Hospital, Hangzhou, China was conducted. This study included the patients with isolated head trauma and postresuscitation Glasgow

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Coma Scale (GCS) score of 8 or less, and excluded the patients with less than 18 years of age, admission time >6 h, previous head trauma, neurological disease including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication, diabetes mellitus, hypertension or presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease. Healthy age- and sex-matched volunteers were recruited as control group. Written consent to participate in the study was obtained from study population or their relatives. This protocol was approved by the Ethics Committee of the Hangzhou First People's Hospital before implementation.

Clinical and radiological assessment

Head trauma severity was assessed using initial postresuscitation GCS score. Abnormal cisterns, midline shift >5 mm and traumatic subarachnoid hemorrhage were recorded on initial computerized tomography (CT) scan. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information.

Immunoassay methods

Venous blood was drawn for patients on admission and for healthy controls at study entry. The blood samples were immediately placed into sterile EDTA test tubes coated with ice and centrifuged at 3000 × *g* for 30 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. The plasma concentrations of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 were analyzed by enzyme-linked immunosorbent assay using commercial kits (Phoenix Pharmaceuticals, Belmont, CA) in accordance with the manufactures' instructions. The person carrying out the assays was completely blinded to the clinical information.

End point

Participants were followed up until death or completion of 6 months after head trauma. Clinical outcome included 6-month mortality and 6-month functional outcome. The functional outcome was defined by Glasgow Coma Scale (GOS) score. The scale has five categories: 1-death, 2-persistent vegetative state, 3-severe disability (conscious but disabled), 4-moderate disability (disabled but independent) and 5-good recovery (normal life even though there may be minor neurological and psychological deficits) [9]. GOS Scores were dichotomized in favorable and unfavorable outcomes (GOS of 4–5 vs. GOS of 1–3). For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information and these biomarkers levels.

Table 1
The change of plasma biomarkers levels in non-survivors compared with survivors.

Variables	Non-survivors	Survivors	*P* value
Copeptin (pg/mL)	5255.4 ± 1271.8	3466.4 ± 1080.3	<0.001
NSE (ng/mL)	22.5 ± 4.7	16.6 ± 5.3	<0.001
S100B (pg/mL)	638.9 ± 161.0	453.7 ± 106.7	<0.001
MBP (μg/mL)	21.2 ± 7.7	14.5 ± 3.4	<0.001
GFAP (pg/mL)	15.5 ± 4.5	10.0 ± 3.7	<0.001
Tau (pg/mL)	359.7 ± 85.0	251.9 ± 111.6	<0.001
pNF-H (pg/mL)	1037.9 ± 146.4	821.7 ± 190.6	<0.001
UCH-L1 (pg/mL)	4098.2 ± 1550.4	2468.2 ± 1279.1	<0.001

Intergroup comparisons were analyzed using t test. NSE indicates neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1.

Statistical analysis

Statistical analysis was done using the SPSS 19.0 statistical package (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The categorical variables are presented as counts (percentage), and the continuous variables are presented as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Statistical significance for intergroup differences was assessed by chi-square or Fisher's exact test for categorical variables, and by Student's *t*, Mann–Whitney *U* tests for continuous variables. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 levels that optimally predicted the 6-month mortality and unfavorable outcome with calculated area under curve (AUC). A combined logistic-regression model was configured to estimate the additive benefit of copeptin, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 to GCS score. A *P* value <0.05 was considered significant.

Results

Study population's characteristics

One hundred and two patients were enrolled, including 68 men and 34 women. The mean age was 40.5 ± 15.3 years (range, 18–78 years). The median initial postresuscitation GCS score was 5 (range, 3–8). 52 patients (51.0%) suffered from pupils unreactive on admission; 48 patients (47.1%), abnormal cisterns on initial CT scan; 54 patients (52.9%), midline shift >5 mm on initial CT scan; 56 patients (54.9%), presence of traumatic subarachnoid hemorrhage on initial CT scan. The mean admission time was 2.6 ± 1.3 h (range, 0.5–6 h). The mean plasma-sampling time was 3.5 ± 1.8 h (range, 1.0–10.0). In addition, 102 age- and gender-matched healthy individuals were recruited as controls.

Table 2
Comparisons of AUCs for prediction of 6-month mortality after severe traumatic brain injury.

Variables	AUC	95% CI	Criterion	Sensitivity	Specificity	*P* value
GCS score	0.880	0.800–0.936	<4	93.1%	68.5%	Ref.
Copeptin	0.864	0.782–0.924	>4169.5 pg/mL	86.2%	75.3%	0.755
NSE	0.803	0.713–0.876	>17.6 ng/mL	93.1%	61.6%	0.166
S100B	0.839	0.753–0.905	>484.1 pg/mL	82.8%	71.2%	0.476
MBP	0.805	0.715–0.877	>16.9 μg/mL	69.0%	80.8%	0.176
GFAP	0.819	0.730–0.888	>12.3 pg/mL	72.4%	71.2%	0.260
Tau	0.808	0.718–0.879	>303.2 pg/mL	79.3%	79.3%	0.212
pNF-H	0.815	0.726–0.885	>940.4 pg/mL	75.9%	74.0%	0.202
UCH-L1	0.809	0.720–0.880	>2039.9 pg/mL	69.0%	83.6%	0.213

Comparisons of AUCs for prediction of 6-month mortality after severe traumatic brain injury were based on receiver operating characteristic curves and analyzed using *z* test. GCS indicates Glasgow Coma Scale; AUC, area under curve; CI, confidence interval; NSE, neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; Ref., reference.

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