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Plasma levels of adrenomedullin in patients with traumatic brain injury: Potential contribution to prognosis

Tie-Jiang Chen*, Qing-Yang Fu, Wu-Quan Wu

Department of Emergency Surgery, Yiwu Central Hospital, 699 Jiangdong Road, Yiwu 322000, Zhejiang Province, China

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ABSTRACT

High plasma levels of adrenomedullin have been associated with stroke severity and clinical outcomes. This study aimed to analyze plasma levels of adrenomedullin in traumatic brain injury and their association with prognosis. One hundred and forty-eight acute severe traumatic brain injury and 148 sex- and age-matched healthy controls were recruited in this study. Plasma adrenomedullin concentration was measured by enzyme-linked immunosorbent assay. Unfavorable outcome was defined as Glasgow Outcome Scale score of 1–3. Compared to controls, the patients had significantly higher plasma concentrations of adrenomedullin, which were also highly associated negatively with Glasgow Coma Scale score. Plasma adrenomedullin level was proved to be an independent predictor for 6-month mortality and unfavorable outcome of patients in a multivariate analysis. A receiver operating characteristic curve was configured to show that a baseline plasma adrenomedullin level predicted 6-month mortality and unfavorable outcome of patients with high area under curve. The predictive performance of the plasma adrenomedullin concentration was also similar to that of Glasgow Coma Scale score for the prediction of 6-month mortality and unfavorable outcome of patients. In a combined logistic-regression model, adrenomedullin improved the area under curve of Glasgow Coma Scale score for the prediction of 6-month mortality and unfavorable outcome of patients, but the differences did not appear to be statistically significant. Thus, high plasma levels of adrenomedullin are associated with head trauma severity, and may independently predict long-term clinical outcomes of traumatic brain injury.

Introduction

Traumatic Brain Injury (TBI) is known to represent a major public health concern potentially resulting in death or neurological impairment [6,17]. The pathophysiological mechanisms implicated in the cellular and molecular change following TBI remains unclear [1]. Reliable biomarkers for early prediction of prognosis and functional recovery are very few [13]. Adrenomedullin (AM) is a vasoactive peptide first isolated from pheochromocytoma [12]. Its gene expression is promoted by various stimuli, including inflammation, hypoxia, oxidative stress, mechanical stress and activation of the renin–angiotensin and sympathetic nervous systems [22]. AM possesses neuroprotection in experimental brain disease models including ischemic stroke [28] and traumatic brain injury [2], as well as cardioprotection in human myocardial infarction [11]. Blood levels of AM have been associated with prognosis of plenty of diseases including myocardial infarction, heart failure and pulmonary hypertension [7]. AM has also been reported to be present in neurons and glia in the central nervous system [8]. Recently, circulating AM has been demonstrated to be of prognostic importance in ischemic or hemorrhagic stroke [27,29]. The present study aimed to further investigate the ability of plasma AM to predict long-term clinical outcomes in a group of patients with acute severe TBI.

Materials and methods

Study population

This study included severe isolated head trauma patients with postresuscitation Glasgow Coma Scale (GCS) score of 8 or less from Yiwu Central Hospital between April 2010 and April 2013. Non-selection criteria involved 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

* Corresponding author. Tel.: +86 0579 85209666.
E-mail address: hzhzzhoufeng@163.com (T.-J. Chen).

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volunteers were recruited as control group. At study entrance, all participants or their legal representatives gave their informed consent, and study protocol was approved by the Ethics Committee of Yiwu Central Hospital before implementation.

Clinical and radiological assessment

Information regarding the following variables: postresuscitation GCS score, systolic blood pressure, blood oxygen saturation, blood glucose and papillary reactivity was obtained at admission. Head trauma severity was assessed using initial postresuscitation GCS score. Shock was defined as systolic blood pressure less than 90 mmHg [10]. Hypoxia was defined as blood oxygen saturation less than 85% [10]. Hyperglycemia was defined as blood glucose more than 11.1 mmol/L [16]. Hypoglycemia was defined as blood glucose less than 2.2 mmol/L [26]. Neurology deterioration was defined as occurring in patients who manifested clinically identified episodes of one or more of the following: (1) a spontaneous decrease in GCS motor scores of 2 points or more from the previous examination; (2) a further loss of papillary reactivity; (3) development of papillary asymmetry greater than 1 mm; or (4) deterioration in neurological status sufficient to warrant immediate medical or surgical intervention [10].

All computerized tomography (CT) scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. Abnormal cisterns, midline shift >5 mm and subarachnoid hemorrhage were recorded on initial CT scan. CT classification was performed using Traumatic Coma Data Bank criteria on initial postresuscitation CT scan according to the method of Marshall et al. [19].

Participants were followed up until death or completion of 6 months after head trauma. The functional outcome was defined by Glasgow outcome scale (GOS) score. GOS was defined as follows: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery [9]. Unfavorable outcome was defined as GOS of 1–3. For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information and AM levels.

Determination of plasma AM levels

The informed consents were obtained from all participants or their legal representatives before the blood were collected. Venous blood was drawn at study entry in the control group and on admission in the patients. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at $1500 \times g$ for 20 min at 4 °C to collect plasma. Plasma was stored at −70°C until assayed. Plasma AM concentration was analyzed by enzyme-linked immunosorbent assay using commercial kits (R&D Systems, Heidelberg, Germany) in accordance with the manufactures' instructions. The blood samples were run in duplicate. Researchers running enzyme-linked immunosorbent assays were blinded to all patient details.

Statistical analysis

Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). All values are expressed as mean ± standard deviation or counts (percentage) unless otherwise specified. Comparisons were made by using (1) Chi-square test or Fisher exact test for categorical data, (2) Student *t* test for continuous distributed variables. The association of plasma AM levels with GCS scores was analyzed using Spearman correlation coefficient. The relations of AM to 6-month mortality and unfavorable outcome were assessed in a logistic-regression model with odds ratio (OR) and 95% confidence interval (CI). The receiver operating characteristic (ROC) curves was used to determine the best threshold of AM values to predict 6-month clinical outcomes with calculated area under curve (AUC). In a combined logistic-regression model, the additive benefit of AM to GCS score was estimated. A *P* value of <0.05 was considered significant for all test.

Table 1
The demographic data, clinical and biochemical characteristics of 148 patients.

Characteristics	
Sex (male/female)	98/50
Age (y)	43.6 ± 17.6
GCS score on admission	5.4 ± 1.8
Shock on admission	29 (19.6%)
Hyperglycemia on admission	36 (24.3%)
Hypoglycemia on admission	8 (5.4%)
Hypoxia on admission	15 (10.1%)
Pupils unreactive on admission	75 (50.7%)
CT classification 5 or 6	76 (51.4%)
Abnormal cisterns on initial CT scan	72 (48.7%)
Midline shift > 5 mm on initial CT scan	74 (50.0%)
Presence of traumatic SAH on initial CT scan	78 (52.7%)
Neurological deterioration	30 (20.3%)
Mechanical ventilation	125 (84.5%)
Intracranial surgery in 1st 24 h	70 (47.3%)
Admission time (h)	2.1 ± 1.2
Plasma-sampling time (h)	3.0 ± 1.3
Systolic arterial pressure (mmHg)	119.5 ± 32.6
Diastolic arterial pressure (mmHg)	72.4 ± 20.9
Mean arterial pressure (mmHg)	88.1 ± 23.9
Heart rate (beats/min)	86.9 ± 21.9
Body temperature (°C)	36.6 ± 0.8
Respiratory rate (respirations/min)	18.8 ± 3.9
Blood oxygen saturation (%)	91.2 ± 5.9
Blood white blood cell count ($\times 10^9$/L)	7.7 ± 2.8
Blood hemoglobin level (g/L)	124.5 ± 24.2
Blood platelet count ($\times 10^9$/L)	169.3 ± 40.1
Blood glucose level (mmol/L)	11.5 ± 3.6
Blood sodium level (mmol/L)	142.5 ± 8.6
Blood potassium level (mmol/L)	4.4 ± 0.7
Prothrombin time (s)	14.7 ± 2.4
Thrombin time (s)	18.3 ± 2.7
Partial thromboplastin time (s)	38.9 ± 6.4
Plasma C-reactive protein level (mg/L)	11.0 ± 3.4
Plasma fibrinogen level (g/L)	4.3 ± 1.9
Plasma D-dimer level (mg/L)	2.8 ± 1.3
Plasma adrenomedullin level (pg/mL)	114.2 ± 44.1

Numerical variables were presented as mean ± standard deviation. Categorical variables were expressed as counts (percentage). GCS, Glasgow Coma Scale; CT, computerized tomography; SAH, subarachnoid hemorrhage.

Results

Study population characteristics

This study finally assessed one hundred and forty-eight severe isolated head trauma patients and 148 sex- and age-matched healthy controls. Table 1 summarized the demographic data, clinical and biochemical characteristics of patients at baseline. Compared to controls, the patients had significantly higher plasma concentrations of AM (114.2 ± 44.1 pg/mL vs. 46.6 ± 16.0 pg/mL, $P < 0.0001$). Fig. 1 showed that plasma concentrations of AM were also highly associated negatively with GCS scores ($r = -0.568$, $P < 0.0001$).

Functional outcome prediction

Sixty-six patients (44.6%) had unfavorable outcome at 6 months after head trauma. In Table 2, a univariate analysis found that plasma AM levels were markedly higher in patients with unfavorable outcome than favorable outcome. When configured was