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Blood levels of adrenomedullin on admission predict outcomes after acute intracerebral hemorrhage

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ABSTRACT

Increased plasma adrenomedullin level has been associated with critical illness. This study aimed to investigate the correlations of plasma adrenomedullin concentration with 3-month clinical outcomes and early neurological deterioration of patients with acute intracerebral hemorrhage. One hundred fourteen patients and 112 healthy controls were recruited. Relationships of plasma adrenomedullin concentrations with early neurological deterioration, 3-month mortality and unfavorable outcome (modified Rankin Scale score >2) were evaluated. Plasma adrenomedullin concentrations were increased in patients than in healthy individuals and were highly associated with National Institutes of Health Stroke Scale scores. A multivariate analysis selected plasma adrenomedullin concentration as an independent predictor for 3-month clinical outcomes and early neurological deterioration. A receiver operating characteristic curve analysis showed plasma adrenomedullin concentration predicted 3-month clinical outcomes and early neurological deterioration with high area under curves. The predictive value of adrenomedullin was similar to that of National Institutes of Health Stroke Scale score. In a combined logistic-regression model, adrenomedullin did not improve the predictive value of National Institutes of Health Stroke Scale score. Thus, elevated plasma adrenomedullin concentration is highly associated with 3-month clinical outcomes and early neurological deterioration of patients with acute intracerebral hemorrhage.

1. Introduction

Adrenomedullin, a 52-amino acid residue peptide, is a vasodilator peptide and was first isolated from human pheochromocytoma tissue by Kitamura and colleagues in 1993 [9]. It is later found to be widely distributed throughout mammalian tissues, including the brain [5,10,20,26]. Adrenomedullin has shown neuroprotection in experimental brain disease models including ischemic stroke [23] and traumatic brain injury [1], as well as cardioprotection in human myocardial infarction [7]. Plasma adrenomedullin level increases with the World Health Organization stages of hypertension, and correlates with blood pressure and the severity of target organ damage [6]. Plasma adrenomedullin increases with the severity of heart failure [24] and renal impairment [6]. Adrenomedullin is also implicated in septic, hemorrhagic or cardiogenic shock, pulmonary hypertension and diabetes [22]. In the patients with subarachnoid hemorrhage, the increased adrenomedullin levels in the peripheral blood are highly associated with poor clinical condition [8]. Recent data have identified that elevation of adrenomedullin gene expression in peripheral blood leukocytes is associated with severity of ischemic stroke [14] and high plasma adrenomedullin level also has been an independent factor of long-term clinical outcomes in ischemic stroke [25]. These results suggest adrenomedullin may represent a potential biomarker of neurological outcome in intracerebral hemorrhage. Thus, the present study aimed to investigate the ability of plasma adrenomedullin to predict the early neurological deterioration and long-term disease outcome in the patients with acute intracerebral hemorrhage.

2. Patients and methods

2.1. Study population

The study was performed at Quzhou people's Hospital between January 2010 and October 2012. Patients with spontaneous basal ganglia hemorrhage were enrolled in the study. Exclusion criteria were previous stroke, severe head trauma, use of antiplatelet or anticoagulant medication, presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, and chronic

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heart or lung disease. Those patients, who underwent surgical hematoma evacuation, had unavailable adrenomedullin measurements or had missing of follow-up, were also excluded. Subjects were evaluated as controls if they presented to our hospital and had blood collected as parts of medical examination on October 2012. The study protocol and informed consent approach were approved by the Ethics Committee of Quzhou people's Hospital before implementation. The study individuals or their relatives provided written informed consent to participate in this trial.

2.2. Clinical and radiological assessment

On arrival at the emergency department, a detailed history of vascular risk factors, concomitant medication, National Institutes of Health Stroke Scale (NIHSS) score, body temperature, heart rate, respiratory rate, and blood pressure were taken. Early neurological deterioration was defined as an increase of ≥4 points in the NIHSS score or death at 24 h from symptoms onset [19].

All computed tomographic (CT) scans were performed according to the Neuroradiology Department protocol. The investigators who read them were blinded to clinical information. Hematoma volume was calculated according to the formula $A \times B \times C \times 0.5$, where A and B represent the largest perpendicular diameters through the hyperdense area on CT scan, and C represents the thickness of hematoma [11]. Hematoma growth was defined as hematoma enlargement >33% at 24 h [2]. The presence of intraventricular extension of hematoma was also recorded on initial CT scan.

2.3. End point

Participants were followed up until death or completion of 3 months after stroke. The end points were unfavorable outcome and death after 3 months. The functional outcome was defined by modified Rankin Scale (mRS) score. The unfavorable outcome was defined as a mRS score >2. For follow-up, we used structure telephone interviews performed by 1 doctor, blinded to clinical information and adrenomedullin levels.

2.4. Immunoassay methods

Venous blood of healthy controls was drawn at study entry, and venous blood of patients was drawn on admission. The blood samples were immediately placed into sterile ethylenediaminetetraacetic acid test tubes and centrifuged ($3000 \times g$, 30 min, 4 °C) to collect plasma. Plasma was stored at −70 °C until assayed. Plasma adrenomedullin concentrations were determined by enzyme-linked immunosorbent assay (ELISA), using a human adrenomedullin ELISA Kit (R&D Systems, Heidelberg, Germany) according to the manufacturer's protocol. The blood samples were run in duplicate. Researchers running ELISAs were blinded to all subjects' details.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0 (MedCalc Software, Mariakerke, Belgium). The normality of data distribution was assessed by the Kolmogorovor–Smirnov test or Shapiro–Wilk test. The categorical variables are presented as percentages, and the continuous variables are presented as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Comparisons were made by using (1) chi-square test or Fisher exact test for categorical data, (2) unpaired Student *t* test for continuous normally distributed variables, and (3) the Mann–Whitney *U*-test for continuous non-normally distributed variables. The association of plasma adrenomedullin levels with NIHSS scores was analyzed using spearman correlation coefficient. The relations of adrenomedullin to 3-month clinical outcomes and early neurological deterioration were assessed in a logistic-regression model with odds ratio (OR) and 95% confidence interval (CI). The receiver operating characteristic (ROC) curves were used to determine the best threshold for on admission values of adrenomedullin to predict 3-month clinical outcomes and early neurological deterioration. The area under curve (AUC) was calculated based on the ROC curves. AUC ranges from 0.5 to 1.0. An AUC closer to 1 indicates a higher predictive power. In a combined logistic-regression model, we estimated the additive benefit of adrenomedullin to NIHSS score. A *P* value of <0.05 was considered significant for all test.

3. Results

3.1. Study population characteristics

During the study period, a total of 130 consecutive patients were initially evaluated. Of these, 16 were excluded for the following reasons: 4 cases had previous stroke; 1 cases, previous severe head trauma; 4 cases, presence of other prior systemic diseases; 5 cases, surgical hematoma evacuation; 2 cases, unavailable adrenomedullin measurement; 2 cases, missing of follow up. Finally, 114 were included in the analysis. A control group consisted of 112 individuals. The main characteristics of the patients and controls are summarized in Table 1. The intergroup differences of patients and controls in the age, sex, hypertension and diabetes mellitus were not statistically significant (both $P > 0.05$).

Table 1
The characteristics of study population.

Characteristics	Patients	Controls	*P* value
Number	114	112	
Gender (male/female)	69/45	65/47	0.703
Age (y)	65.7 ± 10.5	63.2 ± 9.1	0.412
Hypertension	96 (84.2%)	85 (75.9%)	0.117
Diabetes mellitus	32 (28.1%)	26 (23.2%)	0.403
NIHSS score	14 (10)	–	–
Hematoma volume (mL)	30.0 (30.0)	–	–
Presence of intraventricular hemorrhage	45 (39.5%)	–	–
Hemorrhage growth	20 (17.5%)	–	–
END	23 (20.2%)	–	–
Admission time (h)	4.6 (5.0)	–	–
Plasma-sampling time (h)	5.4 (5.0)	–	–
Systolic arterial pressure (mmHg)	171.2 ± 21.7	142.3 ± 16.4	<0.001
Diastolic arterial pressure (mmHg)	96.5 ± 9.7	84.9 ± 7.2	<0.001
Blood glucose level (mmol/L)	10.0 (6.1)	5.4 (3.2)	<0.001
Plasma C-reactive protein level (mg/L)	6.5 (4.6)	3.1 (2.3)	<0.001
Plasma D-dimer level (mg/L)	2.4 (1.5)	0.4 (0.1)	<0.001
Blood white blood cell count ($\times 10^9$/L)	7.3 (4.9)	7.1 (2.2)	0.124
Blood hemoglobin level (g/L)	119.3 ± 21.0	122.5 ± 22.3	0.482
Blood platelet count ($\times 10^9$/L)	166.9 ± 52.5	171.1 ± 65.2	0.267
Prothrombin time (s)	12.0 ± 1.7	12.6 ± 1.8	0.791
Thrombin time (s)	16.4 ± 2.7	15.9 ± 2.4	0.451
Partial thromboplastin time (s)	34.1 ± 5.1	32.8 ± 4.9	0.590
Plasma fibrinogen level (g/L)	3.8 ± 1.7	3.6 ± 1.5	0.721
Plasma adrenomedullin level (pg/mL)	96.7 ± 38.1	35.5 ± 11.2	<0.001

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 exact test for categorical variables, and by Student t or Mann–Whitney *U* test for continuous variables. NIHSS, National Institutes of Health Stroke Scale; END, early neurological deterioration.