Peptides 52 (2014) 44–48

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Plasma adrenomedullin levels are associated with long-term outcomes of acute ischemic stroke

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ARTICLE INFO

Article history:
Received 14 November 2013
Received in revised form
22 November 2013
Accepted 25 November 2013
Available online 12 December 2013

Keywords:
Ischemic stroke
Outcome
Adrenomedullin

ABSTRACT

Plasma adrenomedullin concentration has been found to be enhanced in ischemic stroke. Up to now, little is known about the association of plasma adrenomedullin concentration with clinical outcomes of ischemic stroke. This study recruited 138 patients with ischemic stroke and 138 healthy volunteers. Unfavorable outcome was defined as modified Rankin Scale score >2 at 3 months. Plasma adrenomedullin concentrations were determined by enzyme-linked immunosorbent assay. Plasma adrenomedullin concentrations were statistically significantly higher in patients than in healthy individuals (79.9 ± 27.3 pg/mL *vs.* 36.8 ± 10.4 pg/mL; $P < 0.001$). 3-Month mortality was 20.3% (28/138) and sixty-six patients (47.8%) had unfavorable outcome in 3 months. A logistic regression analysis identified plasma adrenomedullin concentration as an independent predictor of 3-month mortality (odds ratio, 1.211; 95% confidence interval, 1.101–1.582; $P = 0.004$) and unfavorable outcome (odds ratio, 1.193; 95% confidence interval, 1.082–1.447; $P = 0.006$). Receiver operating characteristic curve analysis showed that plasma adrenomedullin concentration predicted 3-month mortality (area under curve, 0.806; 95% confidence interval, 0.730–0.868) and unfavorable outcome (area under curve, 0.816; 95% confidence interval, 0.742–0.877) with the high predictive value. Its predictive performance was similar to that of National Institutes of Health Stroke Scale score ($P = 0.694$ or 0.206). Its combined use with National Institutes of Health Stroke Scale score did not improve the predictive value ($P = 0.236$ or 0.590). Thus, adrenomedullin may aid to predict long-term clinical outcomes of patients with ischemic stroke.

1. Introduction

Adrenomedullin (AM) is a 52-amino acid residue peptide which was isolated from human pheochromocytoma tissue by Kitamura and colleagues in 1993 [9]. It has numerous biological actions which are of potential importance to cardiovascular homeostasis, growth and development of cardiovascular tissues and bone, prevention of infection, and regulation of body fluid and electrolyte balance [16]. Circulating AM can be detected in human blood, and the plasma concentration of AM reportedly increases in patients with cardiovascular diseases [23], rheumatoid arthritis [5] and diabetes mellitus [17]. Furthermore, AM is also present in various human tissues, including cerebral cortex [7,10,20]. *In vivo and in vitro* studies have documented that AM causes the vasodilation of cerebral arteries [1,4,14,22] and that focal cerebral ischemia increases transcription of the AM gene in the brain [22]. Increased plasma concentrations of AM are associated with poor clinical condition in patients with subarachnoid hemorrhage [8]. Moreover, plasma AM concentrations in the patients with chronic ischemic stroke (IS) are also significantly higher than the levels in the healthy control subjects [6,21]. A recent study has showed that AM gene expression in peripheral blood leukocytes is associated with severity of IS [15]. These findings led us to investigate the ability of plasma AM concentration to predict the long-term disease outcomes in the patients with acute IS.

2. Patients and methods

2.1. Study population

Patients with IS who presented to The First People's Hospital of Hangzhou between May 2011 and May 2013 were prospectively identified. Only patients who were admitted for the treatment of first-ever IS confirmed by brain magnetic resonance imaging and diagnosed at the emergency room were included in this study. Patients were excluded if they had previous renal or hepatic insufficiency, malignancy, recent infection, surgery, or major trauma.

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0196-9781/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.peptides.2013.11.025

Healthy individuals without history of arterial hypertension, diabetes and neoplastic, cardiovascular, inflammatory, renal, lung or endocrine diseases were evaluated as controls if they presented to our hospital and had blood collected as part of medical examination on May 2013. The study was conducted in accordance with the guidelines approved by the Human Research Ethics Committee at our hospital. Written informed consent was obtained from the patients or their relatives.

2.2. Clinical assessment

Medical evaluation including demographic characteristics, vascular risk factors, stroke symptoms and signs, and blood biochemistry were all recorded upon admission. The initial stroke severity score was based on the National Institute of Health Stroke Scale (NIHSS). An unfavorable outcome was defined as a modified Rankin Scale score >2 at 3 months. For follow-up, structure telephone interviews were performed by 1 doctor, blinded to clinical information and AM levels.

2.3. Determination of AM in plasma

Peripheral venous blood samples were obtained from forearm veins at study entry in healthy controls and on admission in patients and were collected in sterile tubes containing ethylene-diamine-tetraacetic-acid. After centrifugation (1500 × *g* for 20 min), plasma samples were stored at −70 °C until assayed. Plasma AM levels were measured using a commercial enzyme immunoassay kit (R&D Systems, Heidelberg, Germany). All experiments were performed by an investigator blinded to the study group assignment. All measurements were performed in duplicate.

2.4. Statistical analysis

Analysis of the data was performed using the Statistical Package for the Social Sciences for Windows version 15.0 (SPSS, Chicago, IL). The normality of data distribution was assessed by the Kolmogorov–Smirnov test or Shapiro–Wilk test. Continuous variables were presented as mean ± standard deviation or median (interquartile range) as appropriate and differences between variables were compared using *t* test or Mann–Whitney *U* test. Categorical variables were recorded as frequency counts and differences in proportions were analyzed using the chi-square test or Fisher exact test as appropriate. Spearman's rank correlation coefficient was used to analyze two variables' association. The relations of AM to 3-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 were used to find the best cut off values of plasma AM levels capable for identifying 3-month mortality and unfavorable outcome. The area under curve (AUC) was calculated based on the ROC curves. A combined logistic-regression model was used to estimate the additive benefit of AM to NIHSS score. A $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Study population characteristics

A total of 138 IS patients and 138 healthy controls were enrolled. There were no significant differences observed in age and sex between the two groups (both $P > 0.05$). The baseline demographic data, cardiovascular risk factors, and stroke characteristics of patients in the study are described in Table 1. As shown in Fig. 1, plasma AM level was (79.9 ± 27.3) pg/mL in IS patients, and was statistically significantly higher than that in healthy control

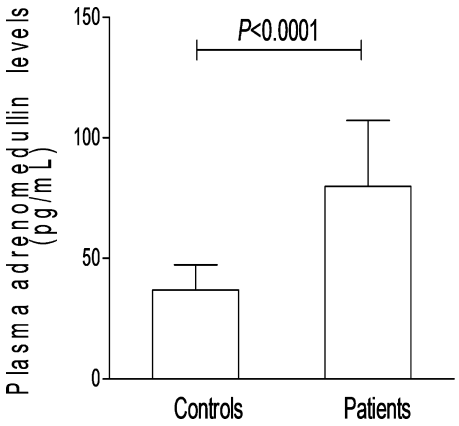

Fig. 1. Graph showing comparison of plasma adrenomedullin concentrations between healthy controls and patients with ischemic stroke. Data were presented as mean ± standard deviation. Comparison was completed using *t* test.

(36.8 ± 10.4 pg/mL; $P < 0.001$). As shown in Fig. 2, plasma AM levels were highly correlated with NIHSS scores ($r = 0.681$, $P < 0.001$).

3.2. Mortality prediction

3-Month mortality was 20.3% (28/138). Table 1 showed that non-survivals had elder age, higher body mass index, higher percentage of diabetes mellitus, coronary heart disease and atrial fibrillation, higher NIHSS score, and higher glucose, C-reactive protein and AM levels. A multivariate logistic-regression analysis showed that NIHSS score (OR, 1.296; 95% CI, 1.105–1.702; $P < 0.001$) and plasma AM level (OR, 1.211; 95% CI, 1.101–1.582; $P = 0.004$) were the independent predictors of 3-month mortality.

As shown in Fig. 3, a ROC curve analysis demonstrated that the plasma AM level of 86.4 pg/mL predicted 3-month mortality with AUC of 0.806 (95% CI, 0.730–0.868), sensitivity of 82.1% and specificity of 66.4%. The predictive performance of the AM concentration was thus similar to that of NIHSS scores (AUC, 0.827; 95% CI, 0.754–0.886) ($P = 0.694$). In a combined logistic-regression model, AM improved the AUC of NIHSS score to 0.855 (95% CI, 0.785–0.909) but the differences were not significant ($P = 0.236$).

3.3. Unfavorable outcome prediction

Sixty-six patients (47.8%) had unfavorable outcome in 3 months. Table 1 showed that the patients with unfavorable outcome had

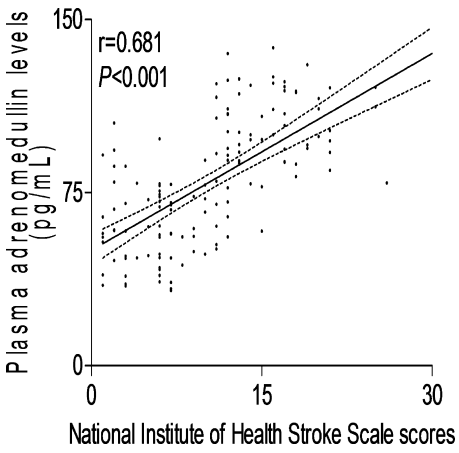

Fig. 2. Graph showing relationship between plasma adrenomedullin concentrations and National Institute of Health Stroke Scale scores using Spearman's rank correlation coefficient.