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Prognostic value of leptin: 6-Month outcome in patients with intracerebral hemorrhage☆

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ABSTRACT

Leptin has recently been discussed as a novel biomarker for the clinical outcome of critical illness. This study aims to investigate the prognostic value of leptin with regard to long-term clinical outcomes in patients with intracerebral hemorrhage. In 50 healthy controls and 92 patients with acute spontaneous basal ganglia hemorrhage presenting to the emergency department of a large primary care hospital, we measured plasma leptin levels using an enzyme-linked immunosorbent assay in a blinded fashion. Plasma leptin levels on admission were considerably higher in patients than healthy controls. A significant correlation emerged between plasma leptin level and National Institutes of Health Stroke Scale score. A multivariate analysis identified plasma leptin level as an independent predictor for 6-month clinical outcomes including 6-month mortality and unfavorable outcome (Modified Rankin Scale score > 2). Using receiver operating characteristic curves, we calculated areas under the curve for 6-month clinical outcomes. The predictive performance of leptin was similar to, but did not obviously improve that of National Institutes of Health Stroke Scale scores. Thus, leptin may help in the prediction of 6-month mortality and unfavorable outcome after intracerebral hemorrhage.

1. Introduction

Leptin, the 16,000 Da protein product of the obesity gene (ob), is principally derived from white adipose tissue, and not only acts on the central nervous system to reduce appetite and increase energy expenditure, but also plays crucial roles in regulating inflammation and immune [1,4,8,9,13–15]. Present investigations on animals have found that brain cortex leptin mRNA expression and serum leptin level are up-regulated in mouse with ischemic brain injury and in rat with traumatic brain injury [2,6,18]. Moreover, leptin levels in peripheral blood are highly associated with cerebral hemorrhagic or ischemic stroke [16,17], and independently predict in-hospital and 1-week mortality of patients with intracerebral hemorrhage (ICH) and 6-month clinical outcome of pediatric traumatic brain injury [7,11,19]. This follow-up study further evaluated leptin as a marker to predict long-term functional outcome and mortality at 6 months after admission in acute ICH patients.

2. Materials and methods

2.1. Study population

This prospective study was conducted during the period of January 2010–March 2012 by the Department of Neurosurgery, Traditional Chinese Medical Hospital of Zhejiang Province. The consecutive patients with acute spontaneous basal ganglia hemorrhage were evaluated within 6 h from symptoms onset at the emergency room. Exclusion criteria included existing previous neurological disease, head trauma, use of antiplatelet or anticoagulant medication, presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, and chronic heart or lung disease, with the exceptions of diabetes mellitus and hypertension. The patients who underwent a surgical procedure and had missing of follow-up or unavailable leptin measurements were also excluded. Healthy individuals were evaluated as controls if they presented to our hospital and had blood collected as part of medical examination on March 2012. The study was conducted in accordance with the guidelines approved by the Human Research Ethics Committee at Traditional Chinese Medical Hospital of Zhejiang Province. Written informed consent was obtained from the study subjects or their relatives.

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2.2. Clinical and radiological assessment

The level of neurological status on admission was assessed by National Institutes of Health Stroke Scale (NIHSS) scores. Early neurological deterioration was defined as the increase of ≥4 points in the NIHSS score at 24 h from symptoms onset. At 6 months after ICH, the patients that scored >2 on the modified Rankin Scale were considered as having an unfavorable outcome.

All computerized tomography scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. Patients underwent an initial CT scan on admission and a follow-up CT scan at 24 h from symptoms onset. Hematoma volume was measured according to the previously reported formula $A \times B \times C \times 0.5$ [10]. Hematoma growth was defined as an increase of >33% in the volume of intraparenchymal hemorrhage as measure by CT compared with the initial scan [5].

2.3. Immunoassay methods

The informed consents were obtained from study population or family members in all cases before the blood were collected. Venous blood in the healthy individuals or the ICH patients was drawn at study entry or on admission. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at 3000*g* for 30 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. The concentration of leptin in plasma was analyzed by enzyme-linked immunosorbent assay using commercial kits (R&D Systems, Minneapolis, MN, USA) in accordance with the manufactures' instructions. The person carrying out the assays was completely blinded to the clinical information.

2.4. Statistical analysis

Statistical analysis was done using the SPSS 12.0 statistical package (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. Significance for intergroup differences was assessed by chi-square test or Fisher exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Receiver operating characteristics (ROC) curves were configured to establish the cut-off points of leptin with the optimal sensitivity and specificity predicting 6-month clinical outcomes. Finally, 2 logistic regression analyses were performed to determine the factors that could be considered as independent predictors of 6-month clinical outcomes, using the forward stepwise method. Variables showing a $P < 0.1$ in univariate analysis were included in the multivariate model. In a combined logistic-regression model, we estimated the additive benefit of leptin to NIHSS score. A *P* value < 0.05 was considered significant.

3. Results

3.1. Study population's characteristics

Finally, 92 ICH patients and 50 healthy controls were enrolled in this study. The intergroup differences in age, gender and body mass index were not statistically significant (all $P > 0.05$). The demographic, clinical and laboratory data of patients were provided in Table 1. The admission leptin levels were significantly increased in all patients (19.1 ± 7.7 ng/mL) compared with healthy control individuals (7.9 ± 3.3 ng/mL, $P < 0.001$). A significant correlation emerged between plasma leptin level and NIHSS score ($r = 0.561$, $P < 0.001$) as well as between plasma leptin level and plasma C-reactive protein level ($r = 0.542$, $P < 0.001$).

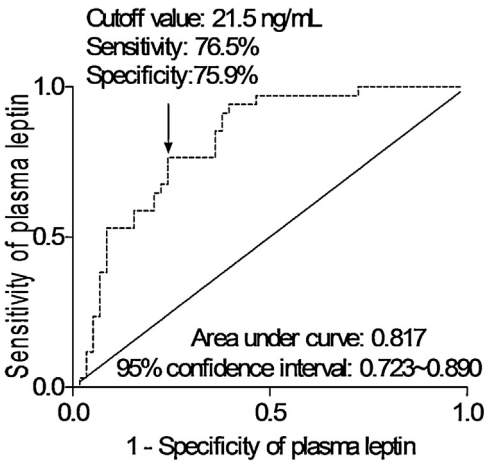

Fig. 1. Graph showing receiver operating characteristic curve analysis of plasma leptin level for 6-month mortality.

3.2. Impact of leptin on 6-month mortality

Thirty-four patients (37.0%) died from ICH at 6 months. Higher baseline plasma leptin level was associated with 6-month mortality, as well as other variables shown in Table 1. A multivariate analyses selected NIHSS score (odds ratio (OR), 1.221; 95% confidence interval (CI), 1.129–1.804; $P < 0.001$) and baseline plasma leptin level (OR, 1.216; 95% CI, 1.124–2.501; $P < 0.001$) as the independent predictors for 6-month mortality. A ROC curve showed that the plasma leptin level predicted 6-month mortality of patients with high area under curve (AUC) (Fig. 1). The predictive value of the leptin concentration was thus similar to that of NIHSS score (AUC, 0.850; 95% CI, 0.761–0.916) ($P = 0.586$). In a combined logistic-regression model, leptin improved the AUC of NIHSS score to 0.880 (95% CI, 0.796–0.939) but the difference was not significant ($P = 0.228$).

3.3. Impact of leptin on 6-month unfavorable outcome

Fifty-one patients (55.4%) suffered from unfavorable outcome at 6 months. Higher baseline plasma leptin level was associated with 6-month unfavorable outcome, as well as other variables shown in Table 1. A multivariate analyses selected NIHSS score (OR, 1.304; 95% CI, 1.142–1.917; $P < 0.001$) and baseline plasma leptin level (OR, 1.284; 95% CI, 1.141–2.760; $P < 0.001$) as the independent predictors for 6-month unfavorable outcome. A ROC curve showed that the plasma leptin level predicted 6-month unfavorable outcome of patients with high AUC (Fig. 2). The predictive value of the leptin concentration was thus similar to that of NIHSS score (AUC, 0.882; 95% CI, 0.798–0.940) ($P = 0.329$). In a combined logistic-regression model, leptin improved the AUC of NIHSS score to 0.920 (95% CI, 0.845–0.966) but the difference was not significant ($P = 0.067$).

4. Discussion

Recent two studies have demonstrated that leptin levels in peripheral blood independently predict in-hospital and 1-week mortality of the patients with ICH [7,19]. To the best of our knowledge, this study is among few studies that analyzed the association of plasma leptin level with long-term clinical outcomes in ICH. This study demonstrated that the plasma leptin levels on admission is considerably increased and markedly predicts 6-month