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Plasma leptin level predicts hematoma growth and early neurological deterioration after acute intracerebral hemorrhage

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ABSTRACT

Higher plasma leptin levels have been associated with poor clinical outcomes after intracerebral hemorrhage. Nevertheless, their links with hematoma growth and early neurological deterioration are unknown. Therefore, we aimed to investigate the relationship between plasma leptin levels, hematoma growth, and early neurological deterioration in patients with acute intracerebral hemorrhage. We prospectively studied 102 consecutive patients with acute spontaneous basal ganglia hemorrhage presenting within 6 h from symptoms onset. Significant hematoma growth was defined as hematoma enlargement >33% at 24 h. Early neurological deterioration was defined as an increase of ≥4 points in National Institute of Health Stroke Scale score at 24 h from symptoms onset. We measured plasma leptin levels on admission using an enzyme-linked immunosorbent assay in a blinded fashion. In multivariate logistic regression analysis, plasma leptin level emerged as the independent predictor of hematoma growth (odds ratio, 1.182; 95% confidence interval, 1.061–2.598; $P = 0.008$) and early neurological deterioration (odds ratio, 1.193; 95% confidence interval, 1.075–2.873; $P = 0.004$). Using receiver operating characteristic curves, we calculated areas under the curve for hematoma growth (area under curve, 0.844; 95% confidence interval, 0.759–0.908) and early neurological deterioration (area under curve, 0.857; 95% confidence interval, 0.774–0.918). The predictive performance of leptin was similar to, but did not obviously improve that of hematoma volume. Thus, leptin may help in the prediction of hematoma growth and early neurological deterioration after intracerebral hemorrhage.

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1. Introduction

Intracerebral hemorrhage (ICH) is associated with poor clinical outcomes [8]. Hematoma growth (HG) has been shown to be an independent determinant of death and disability after ICH [6,7]. 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 [4,5,12,14–16]. 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 [1,3,21]. Moreover, enhanced leptin levels have been previously demonstrated to be associated with a higher risk of ICH [17,18]. Although higher leptin levels have been shown to increase risk of poor outcome and death after ICH in several studies [9,13,22,23], the link between leptin levels, HG, and clinical deterioration in patients with acute ICH remains largely unknown. The aim of the present study was to investigate the relationship between leptin levels and HG in patients with acute ICH and their impact on early neurological deterioration (END).

2. Materials and methods

2.1. Study population

We prospectively evaluated consecutive patients with acute spontaneous basal ganglia hemorrhage admitted to our emergency room within 6 h from symptoms onset between April 2010 and October 2012. We excluded those patients who were under anticoagulant treatment, those with a Glasgow Coma Scale (GCS) score <9, those without a follow-up computerized tomography (CT) scan, those who died <24 h, and those who underwent a surgical procedure. A control group consisted of 102 healthy subjects. The study was conducted in accordance with the guidelines approved by the Human Research Ethics Committee at The First People's Hospital of Hangzhou, Nanjing Medical University. Written informed consent was obtained from study populations or family members.

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2.2. Clinical and radiological assessment

On admission, body temperature, systolic and diastolic blood pressure, GCS score, and National Institute of Health Stroke Scale (NIHSS) score were obtained from all patients. GCS score, NIHSS score, and ICH volume at baseline were used as markers of ICH severity. END was defined as the increase of ≥4 points in the NIHSS score at 24 h from symptoms onset. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. All patients underwent 2 cranial CT scans: an initial CT scan on admission (<6 h), and at 24 h from symptoms onset (follow-up CT scan). Hematoma volume was measured according to the previously reported formula $A \times B \times C \times 0.5$ [11]. HG was defined as an increase of >33% in the volume of intraparenchymal hemorrhage as measure by CT compared with the initial scan [2].

2.3. Immunoassay methods

Venous blood of patients was drawn on admission, and those of control group were drawn at study entry. 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 10.0 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 exact test for categorical variables, and by Student's *t*, Mann–Whitney *U* test or one-way analysis of variance for continuous variables. Least significant difference method was used for the post hoc test. The association of leptin with other variables was assessed by Spearman correlation coefficients. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma leptin level that optimally predicted the END and HG with calculated area under curve (AUC). Multivariable logistic regression analyses were performed to determine factors that could be considered as independent predictors of the END and HG, adjusted by confounding variables according to the results of the univariate analysis. Variables showing $P < 0.1$ in univariate analysis were included in the multivariate model. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). In a combined logistic-regression model, we estimated the additive benefit of leptin to hematoma volume. A *P* value <0.05 was considered significant.

3. Results

3.1. Study population's characteristics

Finally, 102 patients and 102 healthy controls were enrolled in this study. The intergroup differences in age, sex 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. 32 patients (31.4%) had HG and 24 patients (23.5%) experienced END.

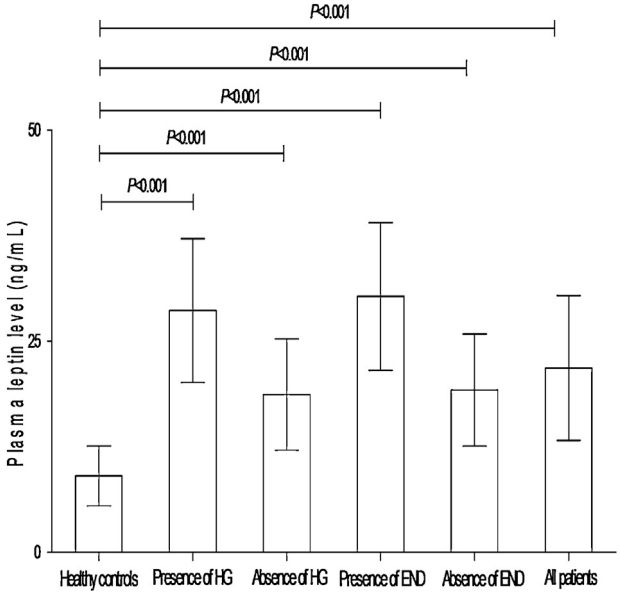

Fig. 1. The change of plasma leptin levels in intracerebral hemorrhage. HG indicates hematoma growth; END, early neurological deterioration.

3.2. The change of plasma leptin level in ICH patients

The admission leptin levels were significantly increased in all patients (21.8 ± 8.6 ng/mL), those with HG (28.6 ± 8.5 ng/mL) and END (30.3 ± 8.8 ng/mL), and without HG (18.7 ± 6.6 ng/mL) and END (19.2 ± 6.6 ng/mL) compared with healthy control individuals (9.0 ± 3.6 ng/mL, all $P < 0.001$) (Fig. 1).

3.3. The correlative analysis of leptin with other variables

A significant correlation emerged between plasma leptin level and NIHSS score ($r = 0.611$, $P < 0.001$), between plasma leptin level and GCS score ($r = -0.582$, $P < 0.001$), between plasma leptin level and hematoma volume ($r = 0.548$, $P < 0.001$) as well as between plasma leptin level and plasma C-reactive protein level ($r = 0.430$, $P < 0.001$) (Fig. 2).

3.4. Association of leptin with HG

Higher baseline plasma leptin level was associated with HG, as well as other variables shown in Table 1. A multivariate analyses selected hematoma volume (OR, 1.209; 95% CI, 1.108–3.124; $P = 0.002$) and baseline plasma leptin level (OR, 1.182; 95% CI, 1.061–2.598; $P = 0.008$) as the independent predictors for HG. A ROC curve showed that the plasma leptin level predicted HG of patients with high predictive value (Fig. 3). The predictive value of the leptin concentration was similar to that of hematoma volume (AUC, 0.850; 95% CI, 0.766–0.908) ($P = 0.911$). In a combined logistic-regression model, leptin improved the AUC of hematoma volume to 0.881 (95% CI, 0.802–0.937), but the difference was not significant ($P = 0.299$).

3.5. Association of leptin with END

Higher baseline plasma leptin level was associated with END, as well as other variables shown in Table 1. A multivariate analyses selected hematoma volume (OR, 1.223; 95% CI, 1.115–3.409; $P = 0.001$) and baseline plasma leptin level (OR, 1.193; 95% CI,

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