Clinica Chimica Acta 425 (2013) 85–89

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

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

# Admission plasma visfatin level strongly correlates with hematoma growth and early neurologic deterioration in patients with acute spontaneous basal ganglia hemorrhage

Shui-Jun Gu, Hong-Fei Xuan, Ming Lu *, Xin-Zhi Chen, Wei-Feng Dong, Xiao-Feng Yan, Yun Si, Guo-Liang Gao, Dian-Xiang Hu, Jian-Qing Miao

*Department of Neurosurgery, The first people's Hospital of Xiaoshan District of Hangzhou City, 199 Shixin South Road, Xiaoshan District, Hangzhou 311200, China*

ARTICLE INFO

*Article history:*
Received 25 June 2013
Received in revised form 23 July 2013
Accepted 23 July 2013
Available online 31 July 2013

*Keywords:*
Intracerebral hemorrhage
Hematoma growth
Early neurologic deterioration
Visfatin
Biomarker

ABSTRACT

*Background:* Visfatin, a proinflammatory mediator, has been associated with poor clinical outcomes after acute brain injury. The present study is designed to investigate the potential association between plasma visfatin levels and the risk of hematoma growth (HG) and early neurologic deterioration (END) after intracerebral hemorrhage.
*Methods:* There were 85 patients as cases who presented with first-time hemorrhagic stroke that were assessed within 6 h after the incident. The control group consisted of 85 healthy volunteers. HG was defined as hematoma enlargement >33% at 24 h. END was defined as an increase of ≥ 4 points in National Institute of Health Stroke Scale score at 24 h from symptoms onset. Plasma visfatin levels were determined using enzyme immunoassay.
*Results:* Plasma visfatin levels were significantly higher in patients compared to controls. Plasma visfatin level emerged as an independent predictor of HG [odds ratio (OR), 1.154; 95% confidence interval (CI), 1.046–3.108; $P = 0.009$] and END (OR, 1.195; 95% CI, 1.073–3.516; $P = 0.005$). For predicting HG, area under curve (AUC) of plasma visfatin level (0.814; 95% CI: 0.715–0.890) was similar to that of hematoma volume (0.839; 95% CI, 0.743–0.909) ($P = 0.703$). For predicting END, AUC of plasma visfatin level (0.828; 95% CI: 0.730–0.901) was similar to that of hematoma volume (0.863; 95% CI, 0.771–0.928) ($P = 0.605$). Visfatin did not improve AUC of hematoma volume for predicting HG and END (both $P > 0.05$).
*Conclusion:* Plasma visfatin level represents a novel biomarker for predicting HG and END.


## 1. Introduction

Spontaneous acute intracerebral hemorrhage (ICH) is defined as non-traumatic bleeding into the brain tissue. It is the deadliest and most disabling form of stroke and affects approximately a million people worldwide annually [1–5] with the outcome determined by hematoma growth (HG) [6–9] and early neurologic deterioration (END) [10–12]. Visfatin (also termed pre-B-cell colony-enhancing factor or nicotinamide phosphoribosyltransferase) is a pleiotropic mediator acting on many inflammatory processes including osteoarthritis, acute myocardial infarction, acute lung injury, sepsis and pneumonia [13–16]. Visfatin, predominantly produced and secreted in visceral fat, is also expressed in animal and human brain [17,18]. Moreover, higher visfatin levels in plasma are associated with ischemic stroke and long-term clinical outcomes after severe traumatic brain injury, ICH and ischemic stroke [19–22]. Moreover, plasma visfatin, associated with a genetic polymorphism −1535C > T, is correlated with C-reactive protein in traumatic brain injury [23]. The aim of the present study was to investigate the relationship between visfatin levels and HG in patients with acute ICH and their impact on END.

## 2. Subjects and methods

### 2.1. Study population

Our study included 85 patients who presented with acute spontaneous basal ganglia hemorrhage for the first time and were assessed within 6 hours after the incident. Controls consisted of 85 healthy individuals matched for age and sex. Cases presented with ICH from May 2010 through January 2013 to the first people's Hospital of Xiaoshan District of Hangzhou City and controls were randomly selected from healthy volunteers. Patients with inflammatory diseases, infectious diseases, renal or liver problems and those under anticoagulant treatment, with a Glasgow Coma Scale (GCS) score <9, without a follow-up computerized tomography (CT) scan, dying < 24 h, and undergoing a surgical procedure were excluded. The study was approved by the Human Research Ethics Committee at the first people's Hospital of Xiaoshan District of Hangzhou City. All participants or family members formally consented to participate in all stages of the study.

* Corresponding author. Tel.: +86 571 83807999; fax: +86 571 83807064.
*E-mail address:* sjghxml@163.com (M. Lu).

0009-8981/$ – see front matter 
http://dx.doi.org/10.1016/j.cca.2013.07.025

### 2.2. Assessment

The severity of the stroke was assessed with use of the GCS and the National Institute of Health Stroke Scale (NIHSS) at baseline. END was defined as the increase of ≥ 4 points in the NIHSS score at 24 hours from symptoms onset. Brain CT was performed according to standard techniques. All patients underwent 2 cranial CT scans: an initial CT scan on admission (<6 hours), and at 24 hours from symptoms onset (follow-up CT scan). Hematoma volume was measured according to the previously reported formula $A \times B \times C \times 0.5$ [24]. HG was defined as an increase of >33% in the volume of intraparenchymal hemorrhage as measured by CT compared with the initial scan [25].

### 2.3. Visfatin measurement

Blood samples were collected from controls at study entry and from patients on admission. Samples were then centrifuged, coded and stored at −70 °C. A commercially available kit was used to measured plasma visfatin levels (Human visfatin enzyme-linked immunosorbent assay kit, AdipoGen Pharmaceuticals, Belmont and Seoul Korea). The intra-assay and inter-assay CVs were <4.5% and <7.2%, respectively.

### 2.4. Statistical analysis

The results were reported as counts (percentage) for the categorical variables, mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed for the continuous variables. All statistical analyses were performed with the use of computer software (SPSS 15.0 and MedCalc 9.6.4.0). Statistical significance for intergroup differences was assessed by $\chi^2$ or Fisher exact test for categorical variables, and by Student's *t*, or Mann–Whitney *U* test for continuous variables. Correlations between plasma visfatin levels and other variables were analyzed using Spearman correlation coefficient or Pearson correlation coefficient. Receiver operating characteristic (ROC) curves were used to describe visfatin concentrations as a potential predictive factor of the END and HG and the optimal cut-off point was estimated 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, the additive benefit of visfatin to hematoma volume was estimated. A $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Study population

A total of 85 patients with new onset ICH and no histories of any such prior incident as well as 85 age- and sex-matched healthy individuals were recruited for the study. Clinical characteristics of the patient group are tabulated in Table 1. Twenty-five patients (29.4%) had HG and 20 patients (23.5%) experienced END.

### 3.2. Levels of visfatin in plasma

Fig. 1 showed the higher level of plasma visfatin in all patients, those with HG or without HG and those with END or without END versus healthy controls (12.7 ± 5.0 ng/ml, all $P < 0.001$) using Student's *t* test.

### 3.3. The correlative analysis of visfatin

As tabulated in Fig. 2, a significant correlation was found between visfatin plasma levels and other factors including NIHSS score, GCS score, plasma C-reactive protein level and hematoma volume in study ICH group using Spearman correlation coefficient or Pearson correlation coefficient as appropriate.

**Table 1**
Baseline characteristics and potential baseline factors associated with presence or absence of hematoma growth and early neurologic deterioration.

| Baseline characteristics | All patients ($n = 85$) | Hematoma growth | | | Early neurologic deterioration | | |
|---|---|---|---|---|---|---|---|
| | | Presence ($n = 25$) | Absence ($n = 60$) | *P* values | Presence ($n = 20$) | Absence ($n = 65$) | *P* values |
| Age (y) | 65.9 ± 9.5 | 71.4 ± 7.8 | 63.6 ± 9.4 | 0.002 | 71.5 ± 8.3 | 64.2 ± 9.3 | 0.006 |
| Male sex | 47 (55.3%) | 14 (56.0%) | 33 (55.0%) | NS | 12 (60.0%) | 35 (53.9%) | NS |
| Body mass index (kg/m$^2$) | 25.8 ± 2.2 | 26.4 ± 1.9 | 25.5 ± 2.3 | NS | 26.3 ± 1.8 | 25.6 ± 2.3 | NS |
| Antiplatelet pretreatment | 18 (21.2%) | 6 (24.0%) | 12 (16.7%) | NS | 5 (25.0%) | 13 (20.0%) | NS |
| Statin pretreatment | 14 (16.5%) | 5 (20.0%) | 9 (15.0%) | NS | 4 (20.0%) | 10 (15.4%) | NS |
| Hypertension | 76 (89.4%) | 22 (88.0%) | 54 (90.0%) | NS | 19 (95.0%) | 57 (87.7%) | NS |
| Diabetes mellitus | 19 (22.4%) | 7 (28.0%) | 12 (20.0%) | NS | 5 (25.0%) | 14 (21.5%) | NS |
| GCS score | 13 (3) | 12 (3) | 13 (4) | 0.002 | 11 (3) | 13 (4) | 0.002 |
| NIHSS score | 17 (5) | 18 (4) | 16 (6) | 0.035 | 18 (3) | 16 (6) | 0.023 |
| Hematoma volume (ml) | 29.9 ± 13.0 | 38.6 ± 8.7 | 23.5 ± 12.0 | <0.001 | 40.8 ± 7.9 | 24.0 ± 11.7 | <0.001 |
| Intraventricular extension | 30 (35.3%) | 15 (60.0%) | 15 (25.0%) | 0.002 | 12 (60.0%) | 18 (27.7%) | 0.008 |
| Admission time (h) | 1.6 ± 0.9 | 1.6 ± 0.9 | 1.7 ± 1.0 | NS | 1.8 ± 0.9 | 1.5 ± 0.9 | NS |
| Plasma-sampling time (h) | 3.8 ± 2.0 | 3.4 ± 1.9 | 3.9 ± 2.0 | NS | 3.4 ± 2.0 | 3.9 ± 2.0 | NS |
| Systolic arterial pressure (mm Hg) | 163.7 ± 25.2 | 168.7 ± 23.1 | 161.6 ± 25.9 | NS | 172.4 ± 23.2 | 161.0 ± 25.2 | NS |
| Diastolic arterial pressure (mm Hg) | 88.1 ± 12.2 | 89.9 ± 10.4 | 87.3 ± 12.9 | NS | 90.6 ± 11.3 | 87.3 ± 12.4 | NS |
| Blood glucose level (mmol/l) | 12.5 ± 3.7 | 14.2 ± 3.7 | 11.8 ± 3.4 | 0.005 | 14.9 ± 3.5 | 11.7 ± 3.4 | 0.001 |
| Hemoglobin (g/dl) | 13.1 ± 2.3 | 12.9 ± 2.2 | 13.3 ± 2.4 | NS | 12.9 ± 2.1 | 13.2 ± 2.4 | NS |
| Leukocyte count ($\times 10^9$/l) | 8.2 ± 2.9 | 8.2 ± 3.8 | 8.2 ± 2.5 | NS | 8.4 ± 4.0 | 8.1 ± 2.5 | NS |
| Platelet count ($\times 10^9$/l) | 203.0 ± 36.7 | 202.2 ± 41.8 | 203.4 ± 34.7 | NS | 199.3 ± 40.8 | 204.2 ± 35.6 | NS |
| Prothrombin time (s) | 15.2 ± 2.5 | 15.1 ± 2.5 | 15.2 ± 2.6 | NS | 15.1 ± 2.7 | 15.2 ± 2.5 | NS |
| Activated partial thromboplastin time (s) | 33.6 ± 5.9 | 34.0 ± 5.5 | 33.4 ± 6.1 | NS | 34.7 ± 5.2 | 33.2 ± 6.1 | NS |
| C-reactive protein (mg/l) | 14.5 ± 5.3 | 17.1 ± 7.0 | 13.4 ± 4.0 | 0.017 | 17.5 ± 7.2 | 13.5 ± 4.2 | 0.028 |
| Fibrinogen (g/l) | 3.0 ± 1.3 | 2.9 ± 0.9 | 3.0 ± 1.4 | NS | 2.9 ± 1.0 | 3.0 ± 1.4 | NS |
| Visfatin (ng/ml) | 86.2 ± 30.5 | 110.5 ± 32.8 | 76.1 ± 23.0 | <0.001 | 114.8 ± 33.3 | 77.4 ± 23.6 | <0.001 |

Numerical variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as counts (percentage). Numerical variables were analyzed by Student's *t* or Mann–Whitney *U* test. Categorical variables were analyzed by $\chi^2$ test or Fisher exact test. n indicates number of patients; NIHSS, National Institutes of Health Stroke Scale, GCS, Glasgow Coma Scale.