Clinica Chimica Acta 412 (2011) 1626–1631

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Plasma adiponectin as an independent predictor of early death after acute intracerebral hemorrhage

Wen-Hong Wang [a], Wen-Hua Yu [b], Xiao-Qiao Dong [b,*], Zu-Yong Zhang [b], Qiang Zhu [b], Zhi-Hao Che [b], Quan Du [b], Hao Wang [b]

[a] Department of Neurosurgery, The Affiliated Zhongda Hospital of Southeast University, 87 Dingjiaqiao Road, Nanjing, 210009, China
[b] Department of Neurosurgery, The First Hangzhou Municipal People's Hospital, Nanjing Medical University, 261 Huansha Road, Hangzhou, 310000, China

ARTICLE INFO

Article history:
Received 16 November 2010
Received in revised form 11 May 2011
Accepted 11 May 2011
Available online 19 May 2011

Keywords:
Adiponectin
Intracerebral hemorrhage
Prognosis
Stroke

ABSTRACT

Background: Hyperadiponectinemia or hypoadiponectinemia is associated with different diseases. There is a paucity of data on circulating plasma adiponectin concentrations in human intracerebral hemorrhage (ICH). We investigated the plasma adiponectin concentrations in patients with intracerebral hemorrhage, and analyzed the correlation of adiponectin with the severity of brain injury and early mortality after ICH.
Methods: Thirty controls and 86 patients with acute ICH were included. Plasma samples were obtained on admission and at days 1, 2, 3, 5, and 7 after ICH. Their concentrations were measured by enzyme-linked immunosorbent assay.
Results: After ICH, plasma adiponectin level of the patients increased immediately within 6 h, peaked within 24 h, plateaued at day 2, and decreased gradually thereafter. It was substantially higher than that in the controls in a period of 7 days. A multivariate analysis showed plasma adiponectin level was an independent predictor for 1-week mortality (odds ratio, 1.199; 95% CI: 1.035–1.389; $P=0.015$) and that it was associated with Glasgow coma scale (GCS) score ($t=-3.596$, $P=0.001$) and plasma C-reactive protein level ($t=4.194$, $P<0.001$). A receiver operating characteristic curve identified that a plasma adiponectin level >16.4 μg/ml predicted the 1-week mortality of patients with a sensitivity of 65.6% and a specificity of 90.7% (AUC, 0.789; 95% CI: 0.688–0.870). The predictive value of adiponectin concentration was significantly lower than that of GCS score ($P=0.007$) and hematoma volume ($P=0.022$). Adiponectin could not improve the predictive values of GCS score ($P=0.317$) and hematoma volume ($P=0.226$).
Conclusions: Adiponectin is an independent indicator of early death and may play an anti-inflammatory role after intracerebral hemorrhage.

1. Introduction

Adiponectin, also designated Acrp30, AdipoQ, apM1, and GBP28, is a plasma protein of approximately 30 kd and is the most abundant gene product in adipose tissue [1]. Adiponectin is noted for its direct link to insulin sensitivity and for its anti-inflammatory property [2,3]. Lower plasma adiponectin levels are reported to be associated with development of obesity, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and hypertension [4–11]. In short, adiponectin is associated with many of the traditional cardiovascular risk factors. Further evidence has shown that hypoadiponectinemia is associated with atherosclerotic cardiovascular events such as myocardial infarction and brain infarction [12–14]. However, recent epidemiologic studies have shown contradictory results. Some of them revealed that hyperadiponectinemia rather than hypoadiponectinemia is associated with liver cirrhosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus, all of which are conditions predisposed to wasting [15–18]. Furthermore, release of adiponectin from fat tissue is increased under conditions of malnutrition [19,20]; plasma adiponectin concentration rises in the inflammatory state [21]. Therefore, adiponectin can act as a mirror reflecting the degree of systemic wasting, and thus can predict death [22,23].

Jernås et al. [24] studied adiponectin in 8 patients with subarachnoid hemorrhage, and they found that plasma level of adiponectin may influence the development of insulin resistance. However, at present there is a paucity of data available on circulating plasma adiponectin concentrations in patients with intracerebral hemorrhage (ICH).

2. Materials and methods

2.1. Study population

The study group consisted of consecutive patients with spontaneous basal ganglia hemorrhage evaluated in the emergency room of the First Hangzhou Municipal People's Hospital within the first 6 h from

Abbreviations: ICH, intracerebral hemorrhage; IVE, intraventricular extension of intraparenchymal hematoma; LPS, lipopolysaccharide.

* Corresponding author. Tel.: +86 571 87065701.
E-mail address: dxqhyy@163.com (X.-Q. Dong).

0009-8981/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2011.05.016

stroke onset. A total of 100 patients with spontaneous basal ganglia hemorrhage were initially evaluated between June 2006 and December 2008. Exclusion criteria included existing neurological disease, head trauma, use of antiplatelet or anticoagulant medication, and systemic diseases including uremia, liver cirrhosis, malignancy, and chronic heart or lung disease, with exception of diabetes mellitus, hypercholesterolemia, obesity and hypertension. Diabetes mellitus was thought to be treated with oral hypoglycemic drugs or insulin, or as previously diagnosed. Hypercholesterolemia was defined when cholesterol-lowering drugs were used or a fasting total cholesterol level was >200 mg/dl. Obesity was defined when body mass index was >25.0 kg/m^2. Hypertension was considered when antihypertensive drug therapy was prescribed or previous documented blood pressure was >140/90 mm Hg (systolic/diastolic). The patients who were not subjected to measurement of adiponectin were also excluded. Finally, 86 patients were included in the study.

The control group consisted of 30 inpatients who admitted to our hospital via emergency service of the First Hangzhou Municipal People's Hospital due to acute soft tissue injury than strokes between January 2008 and December 2009. Inclusion criteria included diabetes mellitus, or/and hypercholesterolemia, or/and obesity or/and hypertension. Exclusion criteria included previous neurological diseases, head trauma, use of antiplatelets or anticoagulant medication, presence of other systemic diseases including uremia, liver cirrhosis, malignancy, and chronic heart or lung disease. Informed consent to participate in the study was obtained from the patients or their relatives. This protocol was approved by the Ethics Committee of the hospital.

2.2. Clinical and radiological assessment

On arrival at the emergency department, vascular risk factors, concomitant medication, Glasgow coma scale (GCS) score, body temperature, heart rate, respiratory rate, and blood pressure were recorded.

CT scans were performed according to the neuroradiology department protocol. Investigators who read the films were blinded to clinical information. ICH volume was measured according to the previously reported formula $A \times B \times C \times 0.5$ [25]. Hydrocephalus, intraventricular extension of intraparenchymal hematoma (IVE) and hematoma growth were also recorded. A diagnosis of hydrocephalus was made by consensus of two doctors (inter-reliability coefficient = 0.907)

2.3. Intracerebral hemorrhage management

The treatment of the patients included surgical therapy, mechanical ventilation, blood pressure control, intravenous fluids, hyperosmolar agents, H_2 blockers, early nutritional support, and physical therapy. Intubation and mechanical ventilation were prescribed to the patients according to their level of consciousness and ability to protect airway and arterial blood gas levels [26]. As soon as elevated intracranial pressure was shown by clinical and radiological examinations, osmotherapy with intravenous mannitol was given. The mean arterial pressure was 130 mm Hg (systolic arterial pressure below 170 mm Hg) [27]. The patients were subjected to evacuation of hematoma and/or external ventricular drainage when appropriate. External decompression depended on the intracranial pressure of the patients and the preference of neurosurgeons.

2.4. Determination of adiponectin in plasma

Informed consents were obtained from the patients or their relatives before collection of blood. In the control group, venous blood was taken at study entry. In the ICH patients, venous blood was drawn on admission (defined as day 0) and at 8:00 AM at days 1, 2, 3, 5, and 7 after ICH. The blood samples were immediately placed into sterile EDTA tubes and centrifuged at 1500 *g* for 20 mins at 4 °C to collect plasma. The plasma was stored at −70 °C. The concentration of total adiponectin in plasma was analyzed by the enzyme-linked immunosorbent assay using commercial kits (R&D systems, Minneapolis, Minn, USA) in accordance with the manufactures' instructions.

2.5. End point

Outcome was assessed as mortality in one week. The cause of death for all patients during the study was ICH.

2.6. Statistical analysis

Statistical analysis was performed with SPSS 10.0 (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. All values were expressed as median (lower quartile, upper quartile), mean ± standard deviation or counts (percentage) unless otherwise specified. Comparisons were made by (1) the chi-square test or Fisher exact test for categorical data, (2) unpaired Student's *t* test for continuous normally distributed variables, and (3) the Mann–Whitney *U* test for continuous non-normally distributed variables. Correlations of adiponectin with other variables were assessed by Spearman's rank-order correlation coefficient test and multivariate linear regression. The relation of adiponectin to one-week mortality was assessed in a logistic-regression model. For multivariate analysis, we included the significantly different outcome predictors as assessed in univariate analysis. A receiver operating characteristic curve was configured to establish the cutoff point of plasma adiponectin with optimal sensitivity and specificity for predicting one-week mortality. A *P* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patients and controls

In the 86 patients enrolled, 66 were men and 20 women. Their median age was 65 years (range 42–80 years). The median admission time for these patients was 2.7 h (range 0.3–6 h). On admission, their median GCS score was 8 (range 5–13) and median ICH volume, 48 ml (range 20–80 ml). IVH was observed in 60 patients (69.8%), hydrocephalus in 38 (44.2%), hemorrhage growth in 13 (15.1%), rebleeding in 6 (7.0%), seizure in 6 (7.0%), pneumonia in 10 (11.6%), and deep vein thrombosis in 7 (8.1%). Forty-seven patients were subjected to mechanical ventilation. All of the patients underwent surgery including evacuation of hematoma (73 patients), external decompression (46), and external ventricular drainage (52). The median time for surgery was 3.9 h (range 1.5–8.8 h) and the median plasma-sampling time, 3.1 (range, 1.0–6.9 h). Demographic, clinical, laboratory and radiological data from baseline CT scans are shown in Table 1.

Thirty patients served as controls, 20 men and 10 women. Their median age was 64 years (range 44–79 years). Hypertension was seen in 26 patients (86.7%), diabetes mellitus in 9 (30.0%), and hypercholesterolemia in 10 (33.3%). The mean body mass index was 25.4 (range 22.2–29.4). Laboratory data are shown in Table 1.

There were no statistically significant differences in age ($P = 0.278$), gender ($P = 0.117$), diabetes mellitus ($P = 0.827$), hypercholesterolemia ($P = 0.141$), hypertension ($P = 0.285$) and body mass index ($P = 0.339$) between the two groups. Systolic arterial pressure, diastolic arterial pressure and mean arterial pressure in the ICH group were significantly higher than those in the control group (all $P < 0.001$). The levels of blood glucose ($P < 0.001$), creatine kinase ($P < 0.001$), plasma C-reactive protein ($P < 0.001$), fibrinogen ($P = 0.001$), and D-dimer ($P < 0.001$) in the control group were significantly lower than those in the ICH group on admission (Table 1).