Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery

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Xue-Wu Chen, Jun-Wu Shi, Ping-Shan Yang, Zhu-Qi Wu *

Department of Orthopedics, The Central Hospital of Wenzhou City, 32 Dajian Lane, Wenzhou 325000, China

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ABSTRACT

Leptin is considered to be a modulator of the immune response. Hypoleptinemia increases the risk for Alzheimer's disease and vascular dementia. The present study aimed to investigate the ability of plasma leptin level to predict delirium in elderly patients after hip fracture surgery. Postoperative delirium (pod) was evaluated using the Confusion Assessment Method. Prolonged postoperative delirium (ppod) was defined as delirium lasting more than 4 weeks. Plasma leptin levels of 186 elderly patients and 186 elderly controls were measured by an enzyme-linked immunosorbent assay. Plasma leptin level was substantially lower in patients than in controls (4.6 ± 2.2 ng/ml vs. 7.5 ± 1.8 ng/ml, $P < 0.001$). It was identified as an independent predictor for pod [odds ratio, 0.385; 95% confidence interval (CI), 0.286–0.517; $P < 0.001$] and ppod (odds ratio, 0.283; 95% CI, 0.152–0.527; $P < 0.001$) using a multivariate analysis, and had high area under receiver operating characteristic curve for pod [area under curve (AUC), 0.850; 95% CI, 0.790–0.898] and ppod (AUC, 0.890; 95% CI, 0.836–0.931). The predictive value of leptin was markedly bigger than that of age for pod (AUC, 0.705; 95% CI, 0.634–0.770; $P = 0.002$) and ppod (AUC, 0.713; 95% CI, 0.642–0.777; $P = 0.019$). In a combined logistic-regression model, leptin improved the AUC of age to 0.890 (95% CI, 0.836–0.931) ($P < 0.001$) for pod and 0.910 (95% CI, 0.860–0.947) ($P = 0.005$) for ppod. Thus, preoperative plasma leptin level may be a useful, complementary tool to predict delirium and also prolonged delirium in elderly patients after hip fracture surgery.

1. Introduction

Delirium is a common complication in elderly patients after hip fracture surgery, characterized by fluctuating changes in cognition, consciousness and attention [11,15]. Although patients usually recover after resolution of the underlying cause, delirium appears to be an important risk factor for dementia, even in people without prior cognitive impairment [4,5,18]. In elderly patients after hip fracture surgery, a chronic type of delirium, which is called prolonged delirium (lasting > 4 weeks), is reported to exist and is known to be associated with greater mortality and poor functional recovery [13]. So far, the suggested pathophysiological mechanisms of delirium are mostly hypothetical, but lately there is a lot of interest in the neuroinflammatory system [20,29]. Leptin is a hormone with broad effects on several neurotransmitter systems and on a number of neural functions [10,32]. This 16 kD protein is produced mainly by white adipose tissue and is the key regulator of body weight via its effects on the hypothalamic arcuate nucleus

[6,12]. Leptin is also considered to be a modulator of the immune response and hypoleptinemia can increase the production of proinflammatory cytokines that could result to cognitive impairment [2,24,25,28]. Recent report has demonstrated leptin levels were significantly lower in elderly patients with delirium [26]. The present study aimed to further investigate the ability of plasma leptin level to predict delirium and also prolonged delirium in elderly patients after hip fracture surgery.

2. Materials and methods

2.1. Study population

This study included these patients aged 65 years and older who underwent surgery for a femoral neck fracture or an intertrochanteric fracture from January 2011 to December 2013 in The Central Hospital of Wenzhou City. The patients, who had a documented history of dementia, delirium or depressive illness, had leptin measurements unavailable, were unable to speak or understand Chinese or had missing of follow-up, were excluded. Some volunteers aged 65 years and older without a documented history of dementia, delirium or depressive illness were recruited as

* Corresponding author. Tel.: +86 0577 88070335; fax: +86 0577 88070335.
  E-mail address: xsywxzr@163.com (Z.-Q. Wu).

control group. Patients or controls were included in this study after they or their relatives provided written informed consent. This protocol was approved by the Ethics Committee of The Central Hospital of Wenzhou City before implementation.

2.2. Clinical assessment

Recorded possible confounding factors included age, gender, body mass index, medical comorbidity, fracture type, surgical delay, type of anesthesia, duration of anesthesia, amount of blood loss, type of operation (hip arthroplasty or internal fixation), hospitalization after surgery, and surgical risk on the American Society of Anesthesiologists (ASA) rating scale [22] (Classes I and II or Classes III and IV). Medical comorbidities were assessed using the modified Charlson's Comorbidity Index, which is calculated by summing points awarded for disease conditions as follows: 1 point for myocardial infarction, congestive heart failure, deep vein thrombosis, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, arthritis, ulcers, or diabetes; 2 points for cancer or stroke; and 3 points for cirrhosis. Thus, possible total scores range from 0 to 15, where higher scores indicate a poorer health status [3].

2.3. Delirium evaluation

Delirium was evaluated using the Confusion Assessment Method (CAM) [3]. CAM scores are determined using a diagnostic algorithm consisting of four features: (1) acute and fluctuating changes in mental status, (2) inattention, (3) disorganized or incoherent thinking, and (4) an altered level of consciousness. CAM scores are considered to indicate delirium if Features 1 and 2 are present and either Feature 3 or 4 is present. Transient delirium was defined as delirium lasting for 4 weeks or less postoperatively and prolonged delirium was defined as delirium lasting more than 4 weeks [13]. Postoperative delirium was assessed at 1, 2, 3, and 7 days postoperatively, as well as at 1 month after first diagnosis of postoperative delirium.

2.4. Immunoassay methods

Venous blood of patients was drawn before administration of the anaesthestic agent, 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 minutes 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.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The results were reported as counts (percentage) for the categorical variables, and mean ± standard deviation for the continuous variables. Comparisons were made by using (1) chi-square test or Fisher exact test for categorical data, and (2) Student t test for continuous variables. The relations of leptin to delirium and prolonged delirium 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 determine the best threshold of leptin values to predict delirium and prolonged

delirium with calculated area under curve (AUC). A 2-tailed probability value of <0.05 was considered as statistically significant.

3. Results

3.1. Study population characteristics

This study eventually included 186 patients aged 65 years and older who underwent surgery for a femoral neck fracture or an intertrochanteric fracture as well as 186 controls aged 65 years and older. Table 1 showed the main demographic, clinical, and laboratory characteristics of these elderly patients after hip fracture surgery. There were not statistically significant differences in the age, gender, body mass index and modified Charlson's Comorbidity Index between the patients and the controls (all $P > 0.05$). Fig. 1 showed plasma leptin levels were statistically significantly lower in patients than in controls ($P < 0.0001$).

3.2. Postoperative delirium prediction

70 elderly patients (37.6%) had postoperative delirium after hip fracture surgery. Table 2 showed that lower plasma leptin levels and other variables were highly associated with postoperative delirium after hip fracture surgery. When the above variables found to be significant in the univariate analysis were introduced into the logistic model, a multivariate analysis selected age (OR, 1.137; 95% CI, 1.073–1.205; $P < 0.001$), and plasma leptin level (OR, 0.385; 95% CI, 0.286–0.517; $P < 0.001$) as the independent predictors for postoperative delirium after hip fracture surgery.

Just as shown in Fig. 2, a ROC curve identified that plasma leptin level predicted postoperative delirium after hip fracture surgery with high AUC. The predictive value of the leptin concentration was markedly higher that of age (AUC, 0.705; 95% CI, 0.634–0.770; $P = 0.002$). In a combined logistic-regression model, leptin improved the AUC of age to 0.890 (95% CI, 0.836–0.931) ($P < 0.001$).

Table 1
The main demographic, clinical, and laboratory characteristics of elderly patients after hip fracture surgery.

	All patients
Cases	186
Male	47 (25.3%)
Age (year)	76.7 ± 8.0
Body mass index (kg/m^2)	22.4 ± 2.8
Diagnosis	
Femoral neck fracture	94
Intertrochanteric fracture	92
Modified Charlson's Comorbidity Index	1.2 ± 1.2
American Society of Anesthesiologists Scale	
I	10
II	102
III	73
IV	1
Type of anesthesia	
Spinal	109
General	77
Duration of anesthesia (min)	97.4 ± 18.1
Amount of transfusion (mL)	319.9 ± 154.7
Delay of surgery (days)	5.7 ± 5.3
Hospitalization after surgery (days)	14.0 ± 3.6
Type of surgery	
Arthroplasty	147
Internal fixation	39
Plasma leptin level (ng/mL)	4.6 ± 2.2

Numerical variables were presented as mean ± standard deviation. Categorical variables were expressed as counts (percentage).