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Low plasma leptin level at admission predicts delirium in critically ill patients: A prospective cohort study

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ABSTRACT

The pathophysiology of delirium remains poorly understood. Low leptin level has been associated with features leading to delirium such as dysregulated immune functions and loss of neuroprotective effects. The purpose of the present study was to investigate the relationship between plasma leptin level at intensive care unit (ICU) entry and subsequent occurrence of delirium in critically ill patients. This single-center prospective cohort study in China allocated 336 critically ill patients admitted to ICU between 05/2015 and 05/2016 into a delirium group (n = 102) and non-delirium group (n = 234) based on whether delirium occurred during their stay at the ICU. Patients were examined at least twice daily and delirium was diagnosed using the Confusion Assessment Method for the ICU (CAM-ICU). Blood samples were obtained after ICU entry. Plasma leptin concentrations were measured by ELISA. Delirium occurred in 30.4% (102/336) of patients. Patients who developed delirium showed significantly lower leptin level at ICU entry than those who did not (6.1 ± 3.2 vs. 9.2 ± 5.9 ng/mL; $P < 0.001$). Low plasma leptin level at ICU entry was independently associated with subsequent occurrence of delirium (OR, 0.865; 95%CI, 0.802–0.934; $P < 0.001$). Other independent risk factors for delirium included increasing age (OR, 1.050; 95%CI, 1.020–1.080; $P = 0.001$) and Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score (OR, 1.148; 95%CI, 1.092–1.208; $P < 0.001$). Patients who developed delirium had a prolonged duration of ICU stay and higher mortality. Low plasma leptin level at ICU entry was associated with the occurrence of delirium in critically ill patients.

1. Introduction

Delirium is a serious and commonly observed clinical syndrome in critically ill patients characterized by fluctuating changes in cognition, attention and consciousness [20]. The reported incidence of delirium in critically ill patients has varied from 20% to 80% across different study populations and institutions [15,28,35,38,42]. In patients in the intensive care unit (ICU), the occurrence of delirium will lead to multiple negative outcomes, including longer hospital stays [9,28], increased mortality [11] and chronic cognitive impairment [14]. For these reasons, it is very important to explore the potential pathophysiologic mechanisms underlying the occurrence of delirium in critically ill patients and identify risk factors for the development of delirium in these patients. Although the pathophysiology of delirium remains incompletely understood, recently there has been considerable interest in the possible role of inflammation [7,27,37], especially the neuroinflammatory system [26,40].

Leptin is a circulating 16 kD protein mostly secreted from white adipose tissue [22]. In addition to playing a role in energy regulation, leptin also has neuroprotective effects [8]. Furthermore, leptin can affect cognitive function [16] and worsen learning and memory performance [18]. These functions of leptin raise the possibility that it might be involved in the development of delirium. Recent studies have reported that leptin levels were significantly lower in non-ICU patients with delirium [6,34]. However, the relationship between plasma leptin level and the occurrence of delirium in critically ill patients has not been fully demonstrated. Therefore, the purpose of this prospective cohort study was to examine the relationship between plasma leptin level at ICU entry and the subsequent development of delirium in critically ill patients.

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation-II score; BMI, body mass index; CAM-ICU, Confusion Assessment Method for the intensive care unit; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; RASS, Richmond Agitation Sedation Scale; ROC, receiver operating characteristic

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2. Materials and methods

2.1. Study population

This prospective observational study was conducted in a mixed ICU at the First Peoples' Hospital of Chenzhou, Hunan Province, China. The protocol was approved by the Ethics Committee of the First People's Hospital of Chenzhou before implementation. Patients or their family members gave written informed consent. All patients admitted to the ICU between May 2015 and May 2016 were screened for potential eligibility. A total of 336 consecutive patients were included in the study and were divided into two groups based on whether delirium occurred during their stay at the ICU: a non-delirium group (n = 234) and a delirium group (n = 102).

2.2. Inclusion and exclusion criteria

Patients aged 18 years or older, admitted to the ICU between May 2015 and May 2016, were included. The exclusion criteria were as follows: (1) did not give consent or declined treatment during the period of observation; (2) documented history of severe dementia, mental illness before ICU admission or habitual benzodiazepine use; (3) leptin measurements unavailable or follow-up information missing; (4) severe hearing disability or inability to understand Chinese; (5) expected to stay in the ICU for less than 48 h; (6) acute onset brain diseases such as brain trauma, subarachnoid hemorrhage, stroke, encephalitis or intracranial hemorrhage; (7) delirium that was diagnosed by the Confusion Assessment Method for the ICU (CAM-ICU) at the time of ICU admission; (8) pregnancy or lactation; (9) admitted to the ICU after cardiopulmonary resuscitation; and (10) coma or toxic at the time of ICU admission.

2.3. Clinical assessment

On ICU entry, the demographic data and baseline characteristics of the eligible patients were collected, including age, gender, body mass index (BMI), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, degree of education, alcohol consumption, cigarette smoking, type of underlying clinical condition (medical or surgical), living status (alone or with others) and length of hospital stay before ICU admission. Beyond that, other possible confounding factors were also recorded, including previous medical history, tracheal intubation, and the use of sedatives or opiates. These variables were considered to be associated with the development of delirium, in accordance with previous studies [28,41]. The primary outcome variable was the incidence of delirium. The secondary outcome variables were length of stay (LOS) in the ICU and 28-day mortality rate. Patients were followed up for a maximum of 28 days or until death. Clinical examinations and data collection were performed by two clinicians (XL and CA).

2.4. Evaluation of delirium

At each time point (see below), delirium was evaluated by one of two clinicians (XL and CA) using CAM-ICU [10]; both clinicians had completed a 1-week formal training program in the use of CAM-ICU to ensure consistency in the assessment. The CAM-ICU tool considers four features: (1) acute and fluctuating changes in mental status; (2) inattention; (3) disorganized thinking; and (4) an altered level of consciousness. Delirium was diagnosed if features 1 and 2 were present and either feature 3 or 4 was present. Prior to the evaluation of delirium, the level of sedation was assessed by means of the Richmond Agitation Sedation Scale (RASS) [12]. This is a 10-point scale with four levels of anxiety or agitation (+1 = restless to +4 = combative), one level representing an alert and calm state (0), and five levels of sedation (−5 = unarousable to −1 = drowsy). If the patient was deeply sedated or unarousable (−4 or −5 on the RASS), the assessment was stopped and repeated later. If RASS was above −4 (i.e., −3 to +4), the assessment was continued to the evaluation of delirium. During the study phase, patients were assessed for delirium immediately on admission to the ICU and at least twice daily (at 6–8 a.m. and at 6–8 p.m.) until the 28th day or death. If delirium was diagnosed, the patients received treatment that comprised nonpharmacologic and pharmacologic strategies. The former included early mobilization, family visits, minimization of unnecessary noise or stimuli, timely removal of the tracheal tube and physical restraints, and use of a scheduled pain protocol; and the latter included the administration of haloperidol or olanzapine tablets. The clinicians who assessed delirium were blinded to the treatment details and plasma leptin results.

2.5. Measurement of plasma leptin level

Venous blood was collected between 6 a.m. and 7 a.m. on the day after ICU entry following overnight fasting, and aliquots of plasma were centrifuged at 3000 × *g* for 30 min and then stored at −70 °C until assayed. The plasma concentration of leptin was determined by enzyme-linked immunosorbent assay using a commercial kit (R & D Systems Inc., Minneapolis, MN, USA) in accordance with the manufacturer's instructions. The laboratory investigator (TL) who carried out the measurements of plasma leptin was completely blinded to the clinical information throughout the study.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation (SD) and were compared between the delirium and non-delirium groups using the Student's *t*-test or the Mann-Whitney *U* test. Categorical variables are presented as count (percentage) and were compared between groups using the Chi-squared test or Fisher's exact test. The association between leptin level at ICU entry and the development of delirium was assessed using a logistic regression model with calculation of the odds ratio (OR) and 95% confidence interval (CI). All variables that might interact with delirium and leptin were added to the logistic regression model; these variables included age, gender, BMI, APACHE-II score, degree of education, living status, history of alcohol consumption and smoking, type of medical condition (medical or surgical), previous medical history, length of hospital stay before ICU admission, tracheal intubation, and use of sedatives or opiates. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of plasma leptin concentration for predicting the development of delirium. A two-tailed *P* value of less than 0.05 was considered significant.

3. Results

3.1. Study population characteristics

A total of 610 consecutive patients were screened during the 12-month study period. Of those, 262 patients were subsequently excluded according to the exclusion criteria. Among the remaining 348 eligible patients, 12 were excluded for inadequate blood sample for measurement of plasma leptin concentration or refusal to participate. Therefore, 336 patients were enrolled in this study (Fig. 1).

Based on CAM-ICU assessments, 102 patients developed delirium during the 28-day observation period, resulting in an overall delirium rate of 30.4% (102/336). Table 1 shows the main demographic and clinical characteristics of the 336 patients included in the analysis. Patients who developed delirium were significantly older (67.9 ± 15.1 years *vs.* 55.9 ± 15.5 years; $P < 0.001$) and had higher APACHE-II score (18.8 ± 5.9 *vs.* 13.3 ± 5.7; $P < 0.001$) than those without delirium. Furthermore, the delirium group contained a higher