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The prognostic value of plasma nesfatin-1 concentrations in patients with traumatic brain injury

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ABSTRACT

Background: Nesfatin-1 is related to inflammation. Its increased circulating concentrations are associated with the severity and prognosis of subarachnoid hemorrhage. In-hospital major adverse events (IMAEs), including acute traumatic coagulopathy, progressive hemorrhagic injury and posttraumatic cerebral infarction, are correlated with mortality after traumatic brain injury (TBI). The present study was designed to investigate the changes of plasma nesfatin-1 concentrations and further assess its association with inflammation, trauma severity, in-hospital mortality and IMAEs following TBI.
Methods: We measured plasma nesfatin-1 concentrations of 100 severe TBI patients and 100 controls. Progressive hemorrhagic injury and posttraumatic cerebral infarction were diagnosed based on a follow-up computerized tomography scan. Acute traumatic coagulopathy was identified according to a coagulation test.
Results: Plasma nesfatin-1 concentrations were significantly higher in patients than in controls and associated highly with Glasgow coma scale (GCS) scores and plasma C-reactive protein concentrations. Nesfatin-1 was indicated as an independent predictor for in-hospital mortality and IMAEs. In accordance with area under receiver operating characteristic curve, its predictive value was similar to GCS scores.
Conclusion: Increased plasma nesfatin-1 concentrations are associated closely with inflammation, trauma severity and clinical outcomes, indicating that nesfatin-1 might be involved in inflammation and become a good prognostic biomarker following TBI.

1. Introduction

Severe traumatic brain injury (STBI), one of the most leading causes of disability and mortality, is characterized by inflammation involved in the progression of secondary brain injury [1–3]. Acute traumatic coagulopathy (ATC), progressive hemorrhagic injury (PHI) and posttraumatic cerebral infarction (PTCI), identified as in-hospital major adverse events (IMAEs), are associated with inflammation and high mortality after head trauma [4–10]. Nesfatin-1, an 82-amino acid peptide, is highly expressed in several brain areas, including the hypothalamic paraventricular nucleus, supraoptic nucleus, arcuate nucleus, lateral hypothalamic area, and nucleus tractus solitarius in the brainstem [11,12] and primarily identified to regulate food intake [13,14]. Recently, nesfatin-1 was found to play an important role in inflammatory process. It was shown that the neurons of the central nesfatinergic system are sensitive to peripheral inflammatory stimulus; thus, the activation of nesfatin-1-expressing neurons in the brainstem and hypothalamus may have a potential role in the complex neuronal circuitry as a coordinated response to infection or inflammation [15]. Increased or decreased nesfatin-1 concentrations in the peripheral blood are associated with some inflammatory diseases including acute myocardial infarction, polycystic ovary syndrome and knee osteoarthritis [16–18]. Interestingly, nesfatin-1 possesses anti-inflammatory and anti-apoptotic effects in brain tissue of rats with subarachnoid hemorrhage and traumatic brain injury [19,20]. Importantly, plasma nesfatin-1 concentrations were recently found to be increased and associated with the severity and mortality of spontaneous subarachnoid hemorrhage [21]. To date, there is a paucity of data available on the change of circulating nesfatin-1 concentrations in head trauma.

Abbreviations: GCS, Glasgow coma scale; STBI, severe traumatic brain injury.

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2. Methods

2.1. Study population

Our study included these patients with isolated head trauma, postresuscitation Glasgow coma scale (GCS) score of ≤8, ≥2 head computed tomography (CT) scans in the first 72 h and at least 4 head CT scans in the first week after injury at The Hangzhou First People's Hospital from May 2010 to July 2015. Isolated head trauma was defined as CT scan — confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an extracranial abbreviated injury scale score <3. This study had excluded patients <18 y, those with admission time ?6 h since trauma, those with existing previous head trauma, neurological disease including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication, or presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. Additionally, a total of 100 gender- and age-matched healthy controls were recruited in this study. This study was performed in accordance with the ethical standards of the responsible committee on human experimentation in The Hangzhou First People's Hospital. Written informed consent was obtained from someone responsible for them.

2.2. Clinical and radiological assessments

Head trauma severity was assessed using initial postresuscitation GCS score. Abnormal cisterns, midline shift >5 mm and traumatic subarachnoid hemorrhage were recorded on initial CT scan. Diagnoses of PHI and PTCI were made on the follow-up CT scan. PHI was defined as any increase in size or number of the hemorrhagic lesion, including newly developed ones [22]. Diagnosis of PTCI was made according to the following criteria: (1) distinctly hypodense lesions within a defined cerebral vascular territory; (2) hypodense lesions located in boundary zones between the defined cerebral vascular territories or situated in the terminal zones of perforating arteries within the deep white matter [23]. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information.

2.3. Immunoassay methods

Venous blood was drawn from patients on admission and from controls at study entry. Coagulation test or blood routine test were completed using the routine laboratory assay. ATC was defined as an activated partial thromboplastic time >40 s and/or international normalized ratio >1.2 and/or a platelet count $<120 \times 10^9$/l [24,25]. Blood samples for nesfatin-1 assessment were placed on ice, centrifuged at 3000 × *g*, and plasma aliquoted and frozen at −70 °C. A commercially available kit was used to measured plasma nesfatin-1 concentrations (Phoenix Pharmaceuticals). All samples were assayed in duplicate. The person carrying out the assays was completely blinded to the clinical information.

2.4. Statistical analysis

All statistical analyses were performed with SPSS 19. and MedCalc 9.6.4.0. The categorical and continuous variables are presented as counts (percentage) and mean ± SD respectively. Intergroup comparisons were assessed by Student's *t*-test for plasma nesfatin-1 concentrations. Bivariate correlations were analyzed by Spearman's correlation coefficient or Pearson's correlation coefficient. Receiver operating characteristic (ROC) curves were configured to evaluate the predictive values of plasma nesfatin-1 concentrations for the in-hospital mortality, ATC, PHI and PTCI with calculated area under curve (AUC). Multivariable logistic regression analyses were performed to determine factors that could be considered as independent predictors of the in-hospital mortality, ATC, PHI and PTCI. 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 nesfatin-1 concentrations to GCS scores. A P v < 0.05 was considered significant.

3. Results

3.1. Participant characteristics

A total of 100 patients were enrolled, including 59 men and 41 women. The mean age was 37.1 ± 15.2 y (range, 18–76 y). In addition, 100 gender- and age-matched healthy controls were recruited in this study. In this group of patients, the mean postresuscitation GCS score was 4.8 ± 1.6 (range, 3–8). 42 patients (42.0%) had unreactive pupils; 51 patients (51.0%), abnormal cisterns; 45 patients (45.0%), midline shift >5 mm; 58 patients (58.0%), traumatic subarachnoid hemorrhage. The mean admission time was 2.5 ± 1.4 h (range, 0.5–6 h). The mean plasma-sampling time was 5.1 ± 2.7 h (range, 1.5–10.5 h). The mean time from trauma to the first CT scan was 3.2 ± 1.7 h (range, 1.1–7.2 h). The mean blood glucose concentration was 13.0 ± 4.6 mmol/l (range, 4.0–27.1 mmol/l). The mean plasma C-reactive protein concentration was 18.2 ± 6.1 mg/l (range, 9.6–35.4 mg/l). The mean plasma fibrinogen concentration was 2.8 ± 0.9 g/l (range, 1.3–4.4 g/l). The mean plasma D-dimer concentration was 3.9 ± 1.4 mg/l (range, 2.0–8.9 mg/l). During treatment in hospital, 22 (22.0%) patients deceased; ATC, PHI and PTCI were found in 42 (42.0%), 31 (31.0%) and 14 (14.0%) patients respectively.

3.2. The change of plasma nesfatin-1 concentrations

Plasma nesfatin-1 concentrations were significantly higher in patients than in controls (2.4 ± 0.9 vs. 0.9 ± 0.3 ng/ml, $P < 0.001$), in non-survivors than in survivors (3.0 ± 0.9 vs. 2.2 ± 0.8 ng/ml, $P < 0.001$), in patients with ATC than in those without ATC (2.9 ± 0. vs. 2.0 ± 0.8 ng/ml, $P < 0.001$), in patients with PHI than in those without PHI (3.0 ± 0.8 vs. 2.1 ± 0.8 ng/ml, $P < 0.001$), and in patients with PTCI than in those without PTCI (3.2 ± 0.9 vs. 2.2 ± 0.8 ng/ml, $P < 0.001$). Moreover, plasma nesfatin-1 concentrations were highly associated with plasma C-reactive protein concentrations ($r = 0.393$, $P < 0.001$) and GCS scores ($r = -0.401$, $P < 0.001$).

3.3. Mortality prediction

According to Table 1, some variables including GCS scores and plasma nesfatin-1 concentrations were associated with in-hospital

Table 1
The factors associated with in-hospital mortality using a univariate binary logistic regression.

	Odds ratio	95% confidence interval	*P* value
Sex (male/female)	1.005	0.384–2.630	NS
Age (y)	1.017	0.986–1.049	NS
Glasgow Coma Scale scores	0.240	0.115–0.501	<0.001
Unreactive pupils	7.208	2.388–21.756	<0.001
Abnormal cisterns	6.136	1.899–19.828	0.002
Midline shift >5 mm	4.506	1.585–12.807	0.005
Traumatic subarachnoid hemorrhage	4.275	1.326–13.786	0.015
Admission time (h)	1.196	0.864–1.654	NS
Plasma-sampling time (h)	1.057	0.891–1.253	NS
Time from trauma to the first CT scan (h)	0.530	0.332–0.847	0.008
Blood glucose level (mmol/l)	1.122	1.014–1.241	0.026
Plasma C-reactive protein level (mg/l)	1.094	1.016–1.179	0.017
Plasma fibrinogen level (g/l)	0.898	0.525–1.536	NS
Plasma D-dimer level (mg/l)	0.933	0.656–1.326	NS
Plasma nesfatin-1 level (ng/ml)	3.008	1.626–5.565	<0.001