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Plasma copeptin concentration and outcome after pediatric traumatic brain injury

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ABSTRACT

Higher plasma copeptin level has been associated with poor outcomes of critical illness. The present study was undertaken to investigate the plasma copeptin concentrations in children with traumatic brain injury (TBI) and to analyze the correlation of copeptin with disease outcome. Plasma copeptin concentrations of 126 healthy children and 126 children with acute severe TBI were measured by enzyme-linked immunosorbent assay. Twenty-one patients (16.7%) died and 38 patients (30.2%) had an unfavorable outcome (Glasgow Outcome Scale score of 1–3) at 6 months. Plasma copeptin level was obviously higher in patients than in healthy children (46.2 ± 20.8 pmol/L vs. 9.6 ± 3.0 pmol/L, $P < 0.001$). Plasma copeptin level was identified as an independent predictor for 6-month mortality [odds ratio (OR) 1.261, 95% confidence interval (CI) 1.112–1.538, $P = 0.005$] and unfavorable outcome (OR 1.313, 95% CI 1.146–1.659, $P = 0.003$). The predictive value of copeptin was similar to that of Glasgow Coma Scale (GCS) score for 6-month mortality [area under curve (AUC) 0.832, 95% CI 0.755–0.892 vs. AUC 0.873, 95% CI 0.802–0.926, $P = 0.412$] and unfavorable outcome (AUC 0.863, 95% CI 0.790–0.918 vs. AUC 0.885, 95% CI 0.816–0.935, $P = 0.596$). Copeptin improved the AUC of GCS score for 6-month unfavorable outcome (AUC 0.929, 95% CI 0.869–0.967, $P = 0.013$), but not for 6-month mortality (AUC 0.887, 95% CI 0.818–0.936, $P = 0.600$). Thus, plasma copeptin level represents a novel biomarker for predicting 6-month clinical outcome in children with TBI.

1. Introduction

Arginine vasopressin plays a crucial role in the endocrine stress response to a variety of diseases such as different shock states [4] and contributes to the regulation of osmotic and cardiovascular homeostasis [1,7]. Since arginine vasopressin is highly instable with a short half-life of 4–20 min, reliable determination of arginine vasopressin concentration is not used in clinical practice [22]. Copeptin is co-synthesized with arginine vasopressin in the hypothalamus and is released into the portal circulation of the neurohypophysis [19]. Copeptin is relatively stable in serum and thereby reliably mirrors vasopressin levels [9,16]. Previous studies in adults have demonstrated that copeptin is increased after ischemic stroke [10,23], intracerebral hemorrhage [6,27], aneurysmal subarachnoid hemorrhage [26], and traumatic brain injury (TBI) [5,12,25]; in these groups of patients, high copeptin levels were highly predictive for poor functional outcome and mortality. However, at present there is a paucity of data available on circulating plasma copeptin concentrations in pediatric TBI patients. The present study was undertaken to investigate the plasma copeptin concentrations in children with TBI and to analyze the correlation of copeptin with pediatric TBI outcome.

2. Materials and methods

2.1. Study population

From January 2010 to January 2012, all isolated head trauma children (aged below 15 years and over 5 years) with a post-resuscitation Glasgow Coma Scale (GCS) score of 8 or less were initially assessed in the Department of Neurosurgery, The Children's Hospital, Zhejiang University, School of Medicine. Exclusion criteria were the disagreement of the parents (legal representatives) with participation of their children in this study, recent infection, admission time >6 h, previous head trauma, and history of seizure.

Children were eligible as controls if they presented to our hospital and had blood collected as part of well-child care (e.g., as part of a 1-year well-child examination which includes measurement of hemoglobin) between January 2011 and May 2011. Exclusion criteria were the disagreement of the parents (legal representatives)

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with participation of their children in this study, recent infection, previous head trauma, and history of seizure.

The study protocol and informed consent approach were approved by the Ethics Committee of The Children's Hospital, Zhejiang University, School of Medicine before implementation. The parents provided written informed consent for their children to participate in this trial.

2.2. Clinical and radiological assessment

At admission, we recorded age, gender, vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure), body temperature in °C, GCS score [20], pediatric trauma score [21], injury severity score [2].

All computerized tomography (CT) scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information. Midline shift >5 mm, abnormal basal cisterns (compressed or absent cisterns) and traumatic subarachnoid hemorrhage were recorded. CT classification was performed using Traumatic Coma Data Bank criteria on initial postresuscitation CT scan according to the method of Marshall et al. [14].

2.3. Immunoassay method

The informed consents were obtained from their parents in all cases before the blood were collected. Venous blood was drawn at study entry in the control group and on admission in the patients. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at $3000 \times g$ for 30 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. Copeptin was detected with a novel commercial chemiluminescence assay (B.R.A.H.M.S. Aktiengesellschaft, Hennigsdorf/Berlin, Germany) as described previously [16]. Briefly, a polyclonal antibody against a peptide representing amino acids 132–147 of preproAVP was used as solid-phase antibody, and a polyclonal antibody raised against a peptide representing amino acids 149–164 of preproAVP was used as a tracer. Dilutions of a peptide representing amino acids 132–164 of preproAVP in normal horse serum served as standards. The analytical detection limit of the assay was 1.7 pmol/L. The person carrying out the assays was completely blinded to the clinical information.

2.4. End point

Participants were followed up until death or completion of 6 months after head trauma. The end points were unfavorable outcome and death after 6 months. The functional outcome was defined by Glasgow outcome scale (GOS) score. GOS was defined as follows: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery [8]. GOS Scores were dichotomized in favorable and unfavorable outcomes (GOS of 4–5 vs. GOS of 1–3). The person who determined the outcome was completely blinded to the clinical information.

2.5. Statistical analysis

Statistical analysis was done using the SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The categorical variables are presented as percentages, and the continuous variables are presented as mean ± standard deviation if normally distributed or median (interquartile range) if not normally distributed. Statistical significance for intergroup differences was assessed by chi-square or Fisher exact test for categorical variables, and by Student's *t* or Mann–Whitney *U* test for continuous variables. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma copeptin level that optimally predicted mortality and functional outcome. Multivariable logistic regression analyses were performed to determine factors that could be considered as independent predictors of mortality and functional outcome, 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). A p value of <0.05 was considered significant for all tests.

3. Results

3.1. Patient characteristics

During the study period, a total of 152 consecutive head trauma children were initially evaluated. Of these, 26 patients were excluded for the following reasons shown in Fig. 1, and 126 patients were finally included in the analysis. The main baseline demographic, clinical, and radiologic characteristics of the series are summarized in Table 1. Overall, 21 patients (16.7%) died and 38 patients (30.2%) had an unfavorable outcome at 6 months. One hundred and twenty-six healthy children were eligible as controls. The intergroup differences in the age and sex were not statistically significant. Plasma copeptin level was obviously higher in patients than in healthy children (46.2 ± 20.8 pmol/L vs. 9.6 ± 3.0 pmol/L, $P < 0.001$).

3.2. Impact of plasma copeptin level on 6-month mortality

Potential predictors of 6-month mortality are shown in Table 1. Patients who experienced 6-month mortality had higher glucose, C-reactive protein and copeptin level, lower GCS score, and more frequently showed unreactive pupils, CT classification 5 or 6, abnormal cisterns, midline shift >5 mm and traumatic subarachnoid hemorrhage on initial CT scan, and need more mechanical ventilation. Multivariate logistic regression analysis showed that variables independently related to 6-month mortality were plasma copeptin level (OR 1.261, 95% CI 1.112–1.538, $P = 0.005$) and GCS score (OR 0.352, 95% CI 0.215–0.695, $P = 0.001$). ROC curves identified cutoff points for plasma copeptin level on admission as the value that better predicted 6-month mortality (Fig. 2). The predictive value of the copeptin concentration was thus similar to that of GCS score (area under curve 0.873, 95% CI 0.802–0.926, $P = 0.412$). Copeptin did not improve the predictive value of GCS score (area under curve 0.887, 95% CI 0.818–0.936, $P = 0.600$).

3.3. Impact of plasma copeptin level on the unfavorable outcome at 6 months

Potential predictors of 6-month unfavorable outcome are shown in Table 1. Patients who experienced 6-month unfavorable outcome had higher glucose, C-reactive protein and copeptin level, lower GCS score, and more frequently showed unreactive pupils, CT classification 5 or 6, abnormal cisterns, midline shift >5 mm and traumatic subarachnoid hemorrhage on initial CT scan, and need more mechanical ventilation. Multivariate logistic regression analysis showed that variables independently related to 6-month unfavorable outcome were plasma copeptin level (OR 1.313, 95% CI 1.146–1.659, $P = 0.003$) and GCS score (OR 0.308, 95% CI 0.197–0.616, $P = 0.001$). ROC curves identified cutoff points for plasma copeptin level on admission as the value that better predicted 6-month unfavorable outcome (Fig. 3). The predictive value of the copeptin concentration was thus similar to that of GCS score