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Admission plasma levels of the neuronal injury marker neuron-specific enolase are associated with mortality and delirium in sepsis

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ABSTRACT

Purpose: Neuron-specific enolase (NSE) concentrations are prognostic following traumatic and anoxic brain injury and may provide a method to quantify neuronal injury in other populations. We determined the association of admission plasma NSE concentrations with mortality and delirium in critically ill septic patients.
Methods: We performed a retrospective analysis of 124 patients from a larger sepsis cohort. Plasma NSE was measured in the earliest blood draw at intensive care unit admission. Primary outcomes were 30-day mortality and intensive care unit delirium determined by chart review.
Results: Sixty-one patients (49.2%) died within 30 days, and delirium developed in 34 (31.5%) of the 108 patients who survived at least 24 hours and were not persistently comatose. Each doubling of the NSE concentration was associated with a 7.3% (95% confidence interval [CI] 2.5-12.0, $P = .003$) increased risk of 30-day mortality and a 5.2% (95% CI 3.2-7.2, $P < .001$) increased risk of delirium. An NSE concentration >12.5 μg/L was independently associated with a 23.3% (95% CI 6.7-39.9, $P = .006$) increased risk of 30-day mortality and a 29.3% (95% CI 8.8-49.8, $P = .005$) increased risk of delirium.
Conclusions: Higher plasma NSE concentrations were associated with mortality and delirium in critically ill septic patients, suggesting that NSE may have utility as a marker of neuronal injury in sepsis.

1. Introduction

Sepsis is one of the most common reasons for hospitalization in the United States and often leads to organ failure and death [1-3]. Acute brain dysfunction, manifesting as coma and/or delirium, is one of the most common organ failures in sepsis and is associated with increased mortality [4-8] as well as long-term cognitive impairment in survivors [7,9].

Although the pathogenic mechanisms of acute brain dysfunction and subsequent long-term cognitive impairment are poorly understood, imaging studies comparing intensive care unit (ICU) survivors with matched controls reveal volume loss in the superior frontal lobes and hippocampus [10,11]. The degree of volume loss is linked to the duration of acute brain dysfunction and severity of post-ICU cognitive impairment [10,11]. In combination with animal studies showing neuronal degeneration and apoptosis during sepsis [12], these data suggest that neuron cell death plays an important role in the pathophysiology of acute brain dysfunction and how it may lead to long-term cognitive impairment.

Early recognition and intervention aimed at limiting organ injury are a major priority for patients and clinicians; however, prompt detection of brain injury in critically ill patients with sepsis remains challenging. The frequent need for deep sedation during early critical illness limits the neurologic examination and may delay delirium recognition [5,6]. Neuroimaging during early critical illness is impractical because patients often require respiratory and cardiovascular support, making safe transport difficult [13]. Thus, novel approaches to identify brain injury during early critical illness are needed. Peripheral blood is easily accessible, and measurement of organ-specific proteins allows for timely recognition of organ injury, such as measurement of troponin for cardiac injury or transaminases and bilirubin for hepatic injury [14,15]. Following brain injury, neuron cell membrane integrity is compromised, allowing brain-specific proteins to leak into the interstitial space from which they enter peripheral blood via the brain's glymphatic system [16] or diffusion across a disrupted blood-brain barrier [17].

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Neuron-specific enolase (NSE) is one of the more promising peripheral blood markers of neuronal injury because it is a cytosolic enzyme nearly exclusive to neurons and neuroendocrine cells and is expressed in high levels in the brain [18]. NSE has proven useful for determining brain injury severity and aiding early prognosis following traumatic brain injury [19,20] and cardiac arrest [21-23]. A prior study demonstrated that high serum NSE concentrations were associated with mortality in sepsis but found no association with sepsis-associated encephalopathy [24]. We sought to further investigate NSE as a marker of neuronal injury in critical illness by determining the association of plasma NSE concentration at ICU admission with 30-day mortality and delirium in a cohort of critically ill patients with sepsis.

2. Methods

2.1. Study design

We performed a retrospective analysis of patients enrolled in the Molecular Epidemiology of Severe Sepsis in the ICU (MESSI) study between January and September 2011 [25,26]. The MESSI study is an ongoing prospective cohort of patients admitted to the medical ICU at the Hospital of the University of Pennsylvania, an urban academic tertiary referral center, with severe sepsis as defined by the American College of Chest Physicians consensus criteria [2]. Patients were enrolled if they had ≥2 systemic inflammatory response syndrome criteria, a known or strongly suspected infection, and evidence of organ dysfunction or shock [2]. Exclusion criteria included a lack of commitment to life-sustaining treatment at the time of admission, primary reason for admission unrelated to sepsis (ie, cardiac arrest, head injury), and previous enrollment. We excluded transfers from outside hospital ICUs given the objective to evaluate plasma NSE concentrations at initial ICU presentation. We excluded 1 patient with neuroendocrine cancer because NSE is a neuroendocrine tumor marker [27].

This study was approved by the Institutional Review Board of the University of Pennsylvania with a waiver of timely informed consent. Informed consent was obtained from patients or their surrogates as soon as feasible, and patients or their surrogates could withdraw from the study at any time.

2.2. Data collection

Research personnel collected data using structured case report forms with standardized definitions. Demographics and medical history were collected at the time of enrollment. We collected continuous analgesic and sedative infusion dosages during the ICU stay through day 15. Opiate dosages were converted into equivalent doses of fentanyl, and benzodiazepine dosages were converted into equivalent doses of lorazepam [7]. We reviewed nursing and physician documentation during the ICU stay through day 15 to determine delirium status. During the study period, nurses assessed level of consciousness as part of standard care at least once per shift using the Richmond Agitation-Sedation Scale (RASS) [28]. Patients were considered persistently comatose if they had a RASS score of ≤−4 throughout the study period. Nurses assessed for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) [29], but at the time of this study, the CAM-ICU was not performed every shift as part of our standard care. We defined patients as having delirium if the patient's bedside nurse documented at least 1 positive CAM-ICU assessment or if the patient's attending physician documented a diagnosis of delirium in their daily progress note at least once during the study period.

Acute Physiology and Chronic Health Evaluation (APACHE) III scores were calculated based on data within the first 24 hours of ICU admission. Acute kidney injury (AKI) was defined by Acute Kidney Injury Network creatinine and renal replacement therapy criteria [30]. Acute respiratory distress syndrome (ARDS) was defined using the Berlin definition with the added requirement of invasive mechanical ventilation [31].

2.3. Plasma biomarker measurement

Residual citrated plasma was collected from the earliest blood draw at or just before ICU admission. This corresponds to the initial blood draw at presentation to the emergency department for patients directly admitted to the ICU and to blood drawn during or just after decompensation for patients transferred to the ICU from the medical ward. Plasma was collected in citrated Vacutainers, centrifuged within 30 minutes for clinical testing, and then kept at 4°C for 12 to 48 hours before storage at −80°C until analysis. NSE concentrations were measured using a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) with an intra-assay coefficient of variation of 6.1%. The lower limit of detection for NSE was 0.038 μg/L. Samples with visible evidence of hemolysis were excluded [32].

2.4. Statistical analysis

Comparisons of baseline characteristics were made using Pearson χ^2 for categorical data and the Wilcoxon rank sum test for continuous data. We used multivariable logistic regression to test the association of the plasma NSE concentration, defined as both a continuous and a categorical variable, with 30-day mortality and ICU delirium. We calculated standardized risks and risk differences (RDs) using regression risk analysis [33,34]. We used locally weighted scatterplot smoothing curves to determine if continuous variables required transformation before inclusion in logistic regression models [35]. We log (base 2) transformed the NSE concentration and therefore report our results when using NSE as a continuous variable as the RD for each 2-fold increase in the NSE concentration. In our analyses using NSE as a categorical variable, we defined a high NSE concentration as a concentration >12.5 μg/L, which represents the 95th percentile in healthy subjects [36] and has been used in several prior studies in critically ill patients [19-22,24].

We adjusted for illness severity using the APACHE III score in multivariable mortality models and adjusted for APACHE III score and treatment with sedative and analgesic medications as categorical exposures in multivariable delirium models. We also assessed potential confounding by sedative and analgesic medications in delirium models when defined as the cumulative and mean daily dose during the study period. Additional potential confounders were selected a priori based on existing literature and were retained in multivariable models if they resulted in a ≥10% change in the point estimate in bivariate analysis (Tables S1-S4 in the data supplement) [37].

In secondary analyses, we performed sensitivity analyses to test whether the association of NSE with 30-day mortality was driven by early deaths or modified by assumptions about survival of patients who were lost to follow-up. We also performed sensitivity analyses to test whether the association of NSE with delirium was modified by early deaths. Given the possibility that delirium was underdiagnosed, we assessed potential misclassification of the delirium outcome using logistic regression with an expectation-maximization algorithm (Stata logitem command) [38]. This method accounts for potential outcome misclassification by incorporating the sensitivity and specificity of the outcome measure in the model [38]. We varied the sensitivity of our delirium classification from 0.1 to 1.0 and determined the sensitivity at which our results would become nonsignificant. We assumed that delirious patients were correctly classified (specificity 1.0). We also tested the association of the plasma NSE concentration with coma using multivariable logistic regression and with the number of coma/delirium-free days using negative binomial regression.

All analyses were performed using Stata version 12.1 (College Station, TX). A 2-sided P value < .05 was considered statistically significant.