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ARAŞTIRMA / RESEARCH

Relationship between serum neuron specific enolase levels and brain injury in patients with hyponatremia

Hiponatremili hastalarda serum nöron spesifik enolaz düzeyleri ile beyin hasarı arasındaki ilişki

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Abstract

Purpose: In this study, we aimed to investigate the effects of serum neuron specific enolase on the prediction of central nervous system injury and the clinical course in patients to have hyponatremia.
Materials and Methods: 75 adult patients with serum sodium levels less than 135 mEq/L were evaluated. The patients were grouped according to serum neuron specific enolase levels (group 1 ≤ 17.0 ng/mL and group 2 > 17.0 ng/mL). The groups were compared according to demographic and laboratory data.
Results: The incidence of hypertension, heart failure, and loss of consciousness was significantly higher in group 2 patient. High neuron specific enolase levels were related to lower serum sodium levels. The mean sodium levels were 129.5 ± 4.3 mEq/L and 126 ± 4.5 mEq/L in groups 1 and 2, respectively. Of the patients in group 2 (n = 45), 8 patients with loss of consciousness (low Glasgow Coma Scale scores) (i.e. <15)) had significantly higher serum neuron specific enolase levels than the rest of the patients in group 2 (n = 37) (37.1 ± 6.9 and 18.6 ± 8.8).
Conclusion: High neuron specific enolase levels are associated with lower sodium levels and low Glasgow Coma Scale scores. In patients with hyponatremia, we think that neuron specific enolase monitoring can predict which patients may experience a change in consciousness.
Keywords: Emergency department, hyponatremia, loss of consciousness, neuron specific enolase

Öz

Amaç: Bu çalışmada hiponatremili hastalarda serum nöron spesifik enolazın santral sinir sistemi hasarını öngörmesi ve klinik gidiş üzerindeki etkilerini araştırmayı amaçladık.
Gereç ve Yöntem: Bu prospektif çalışmada, serum sodyum seviyeleri 135 mEq/L'nin altında olan 75 yetişkin hasta değerlendirildi. Hastalar serum nöron spesifik enolaz düzeylerine göre gruplandırıldı (grup 1 ≤ 17.0 ng/mL ve grup 2 > 17.0 ng/mL). Gruplar demografik ve laboratuvar verilerine göre karşılaştırıldı.
Bulgular: Grup 2 hastalarında hipertansiyon, kalp yetmezliği ve bilinç kaybı insidansı anlamlı olarak daha yüksekti. Yüksek nöron spesifik enolaz seviyeleri, daha düşük serum sodyum seviyeleri ile ilişkiliydi. Ortalama sodyum seviyeleri grup 1 ve 2'de sırasıyla 129.5 ± 4.3 mEq/L ve 126 ± 4.5 mEq/L idi. Grup 2'deki hastalardan (n = 45), bilinç kaybı olan (düşük Glasgow Koma Skalası skorları) (GKS <15) 8 hastada, grup 2'deki diğer hastalara göre (n = 37) serum nöron spesifik enolaz seviyeleri anlamlı olarak daha yüksekti (37.1 ± 6.9 ve 18.6 ± 8.8).
Sonuç: Sonuçlarımız, yüksek nöron spesifik enolaz düzeylerinin daha düşük sodyum düzeyleri ve düşük Glasgow Koma Skalası skorları ile ilişkili olduğunu göstermektedir. Hiponatremili hastalarda nöron spesifik enolaz monitörizasyonunun hangi hastaların bilinç değişikliği yaşayabileceğini öngörebileceğini düşünüyoruz.
Anahtar kelimeler: Acil servis, hiponatremi, bilinç kaybı, nöron spesifik enolaz

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INTRODUCTION

Hyponatremia is the most common fluid and electrolyte imbalance disorder and occurs in 15-20% of patients admitted to hospital emergency departments (EDs)[1,2]. The symptoms are usually nonspecific, and the diagnosis of hyponatremia is often incidentally detected during routine laboratory measurements of patients presenting to the clinic or ED[1,3,4]. Clinical manifestations of hyponatremia are associated with central nervous system (CNS) dysfunction, and mild hyponatremia (sodium (Na) = 134-125 mEq/L), which does not develop rapidly, is usually asymptomatic. Nausea, vomiting, headache, lethargy, disorientation, agitation, muscle cramps, and convulsions are the main symptoms in rapidly developing and severe hyponatremia (sodium (Na) < 115 mEq/L)[2,5,6].

Since there is an effective osmolality difference between the brain and plasma in hyponatremia, water moves into the cell, and the brain cells begin to swell. The neurological symptoms of hyponatremia therefore correspond with the severity of cerebral edema[1,3,6]. The more the severity of hyponatremia, the more degeneration of cells occurs. In addition, neuronal damage is high in acute hyponatremia in which an osmolality difference occurs rapidly. Therefore, loss of consciousness is more common in acute hyponatremia than in chronic hyponatremia[2,6].

Neuron specific enolase (NSE) is the γγ isoform of the glycolytic enzyme enolase with a molecular weight of 78 kDa and is expressed primarily in neurons, in central and peripheral neuroendocrine cells, and in certain rare tumors[7-9]. In recent years, biomarkers of brain injury have received considerable attention as potential tools for determining prognosis[10]. NSE is one of the markers which can directly predict the functional damage of neurons and has been extensively studied in recent years to predict prognosis of neuronal damage. NSE levels have been extensively studied in many diseases that cause neuronal damage, such as stroke, brain trauma, and hemorrhage, and malignancies, such as lung cancer, neuroblastoma, multiple myeloma, and serum NSE levels have been found to be high in these diseases[7,10-15]. Already, NSE has been used as a tumor marker in tumors originating from APUD for a long time[8]. In addition, it has been reported that serum NSE levels may be high in neuroendocrine neoplasms, renal cell carcinoma, Guillain-Barre syndrome and some other diseases[14].To the best of our knowledge, there are no studies in the literature on NSE as an indicator of brain injury in hyponatremia patients.

In this study, we aimed to investigate the effects of serum NSE on the prediction of CNS injury and the clinical course in patients admitted to our ED who were accidentally found to have hyponatremia on laboratory tests.

MATERIALS AND METHODS

Study population

In this prospective study, 75 of the 193 patients with serum Na levels less than 135 mEq/L who were referred to the ED of the Cukurova University Faculty of Medicine were included. First of all, our working group; consisted of patients who applied to the emergency department with complaints of headache, nausea, vomiting, dizziness, weakness, and fatigue. Only 8 of 75 patients with incidental hyponatremia had impaired consciousness. Of these patients, 4 had disorientation, 3 had somnolence, and 1 had coma. This study was conducted in accordance with the Declaration of Helsinki. It was approved by the ethics committee of the hospital (Cukurova University Faculty of Medicine Ethics Committee; Approval date: 05 December 2015– Meeting number: 37, Decision No: 1) and it was conducted between December 2014 and January 2017, and all patients or relatives gave written informed consent. Detailed clinical data, including patient characteristics, medical histories, physical examinations, laboratories, diagnostic tests, procedures, medication use, clinical outcomes, and adherence to performance indicators, were collected.

This study included 193 patients with serum Na levels below 135 mEq/L, who applied to the Emergency Department of Çukurova University Faculty of Medicine. However, 118 patients with reasons that may increase NSE levels other than hyponatremia were excluded from the study (Table 2). CNS conditions that may increase NSE levels except for hyponatremia such as CNS infections, acute ischemic stroke, traumatic brain injury, subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), meningitis, Alzheimer's disease, epileptic seizures, brain tumors or metastases to the brain that cause neurological damage of the CNS, malignancy, pseudo-hyponatremia. In addition, since NSE is also

present in blood cells, hemolyzed samples were excluded.

Specimen collection

Venous blood samples were obtained by vascular puncture from the patients who applied to the emergency department of Çukurova University, Faculty of Medicine for the reasons mentioned above, and were collected in EDTA (Ethylenediaminetetraacetic acid) tubes and 5 mL vacuum collection tubes without anticoagulant for serum separation (Becton Dickinson Vacutainer® ref. 369032) in standardized conditions to minimize sources of pre-analytical variation. The EDTA samples immediately underwent routine hematological tests. The tubes without anticoagulant were allowed to clot at room temperature for 15-20 min, were separated by centrifugation at 3000 *g* for 10 min, and kept refrigerated if analyzed within 12 h. Otherwise, the serum sample was frozen (-20°C) and analyzed within a week.

Measurement of the analytes

Hematological tests were determined with a Beckman Coulter LH 780 (Beckman Coulter Inc., CA, USA) full-automated analyzer with the electrical impedance method. Four serum analytes (i.e. glucose, creatinine, Na, and potassium (K)) were analyzed with Beckman Coulter kits, which were manufactured to use on a Beckman UniCel DXC 800 Synchron (Beckman Coulter Inc., CA, USA) auto-analyzer.

The analytical method used for each analyte included Na, K, and the ion selective electrodes as an indirect method (reference number: A28937). The other analytes were analyzed with the enzymatic or colorimetric methods. Serum NSE levels were analyzed with an electrochemiluminescence immunoassay (ECLIA) using a standard assay kit for in vitro diagnostics (NSE kit catalogue number: 12133113122, Roche Diagnostics GmbH, Mannheim, Germany) with a fully-automatized Cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). To minimize analytical errors, the same lots of reagents, standards, and quality control materials were used throughout the analyses.

The distribution of NSE concentrations in 547 healthy patients was 16.3 ng/mL (95th percentile) with a 95% confidence interval of 15.7-17.0 ng/mL in a study conducted by Roche in three clinical centers in Germany[16]. The detection limit was 0.04 µg/L for NSE. We recalculated translocation hyponatremia due to hyperglycemia[1].

Statistical analysis

All analyses were performed by the SPSS 15.0 statistical software package (SPSS Inc., Chicago, IL, USA). Group data were defined as mean ±standard deviation (mean±SD). Parametric demographic data and laboratory findings were evaluated with the Student t-test, and categorical data were evaluated with the chi-square test. Measurements methods were compared by correlation analysis. A linear regression analysis was performed to determine the independent predictors of serum Na and GCS score. Statistical significance was set at a value of $P < 0.05$.

RESULTS

The baseline demographic and laboratory variables of patients are shown in Table 1. The mean age of patients was 61.1 ± 18.3 years. Thirty-seven patients (49.3%) had hypertension (HT); 21 patients (28.0%) had diabetes mellitus; 23 patients (30.7%) had coronary artery disease; and 30 patients (40.0%) had heart failure. Eight patients (10.7%) experienced a loss of consciousness, and 19 patients (25.3%) had dyspnea.

Table 1. Demographic and laboratory findings of the all patients.

	Patients
Age (years) (mean±SD)	61.1 ± 18.3
Female / male (n)	35 / 40
Hypertension (n, %)	37 (49.3)
Diabetes mellitus (n, %)	21 (28.0)
Coronary artery disease (n, %)	23 (30.7)
Heart failure (n, %)	30 (40.0)
Diuretic use (n, %)	26 (34.7)
Unconsciousness (n, %)	8 (10.7)
Shortness breath (n, %)	19 (25.3)
Haemoglobin (g/L) (mean±SD)	11.4 ± 2.1
Glucose (mg/dL) (mean±SD)	141.7 ± 66.2
Creatinine (mg/dL) (mean±SD)	1.01 ± 0.49
Sodium (mEq/L) (mean±SD)	127.8 ± 4.6
Potassium (mEq/L) (mean±SD)	4.2 ± 0.6
NSE (ng/mL)* (mean±SD)	20.5 ± 10.0

*NSE: Neuron specific enolase

Excluded patients (118 pts) were summarized in Table 2. The demographic and laboratory data of patients with an NSE level > 17.0 ng/mL and NSE level ≤ 17.0 ng/mL are compared and shown in Table 3. In group 2 patients with high NSE levels, the

frequency of HT, heart failure, and loss of consciousness was significantly higher than it was in group 1 (p = 0.024, 0.018, and 0.019, respectively). The serum creatinine level was also high, and the serum Na level was low (p = 0.008 and 0.006, respectively) in the same group.

Table 2. Diagnoses of excluded patients (n=118)

Diagnosis	n
CNS* infections	4
Acute ischemic stroke	5
Traumatic brain injury	16
Subarachnoid hemorrhage	5
Intracranial hemorrhage	10
Epileptic seizures	3
Alzheimer's disease	10
Brain tumours or metastases	28
Pseudohyponatremia	5
Drug use	18
Haemolyzed samples	14

*CNS: Central nervous system

Of the NSE levels of patients in group 2 (n = 45), the serum NSE levels of 8 patients with a loss of consciousness (Glasgow Coma Scale (GCS) score <15) were significantly higher than the rest of the patients in group 2 (n = 37) (37.1 ± 6.9 and 18.6 ± 8.8, p < 0.001), and the serum NSE levels were above the normal limits in all patients with a loss of consciousness. The correlation analysis revealed an inverse relationship between the serum Na level and the NSE level, as the NSE level increased as the serum Na level decreased (p <0.001, r = -0.478). When the data were examined in more detail, it was observed that the NSE level was quite high, although the serum Na level was not very low, especially in three patients with a loss of consciousness (Figure 1).

Linear Regression Analysis was applied to the variables with p<0.05 (significant) in Table 3.When independent risk factors affecting the NSE level were evaluated by linear regression analysis, it was seen that the serum Na level and presence of heart failure were independent risk factors (Table 4).

Table 3. Comparison of NSE ≤ 17.0 and NSE > 17.0 patients of baseline demographic and laboratory variables.

	Group 1 NSE ≤ 17.0 (n = 30)	Group 2 NSE > 17.0 (n = 45)	P
Age (years) (mean±SD)	56.5 ± 18.2	64.1 ± 18.0	0.080
Female / male (n)	13 / 17	27 / 18	0.156
Hypertension (n, %)	10 (33.3)	27 (60.0)	0.024 *
Diabetes mellitus (n, %)	6 (20.0)	15 (33.3)	0.295
Coronary artery disease (n, %)	7 (23.3)	16 (35.6)	0.313
Heart failure (n, %)	7 (23.3)	23 (51.1)	0.018 *
Diuretic use (n, %)	7 (23.3)	19 (42.2)	0.137
Unconsciousness (n, %)	0 (0.0)	8 (17.8)	0.019 *
Shortness breath (n, %)	6 (20.0)	13 (28.9)	0.430
Haemoglobin (g/L) (mean±SD)	12.5 ± 2.2	11.6 ± 1.9	0.061
Glucose (mg/dL) (mean±SD)	136.1 ± 67.6	145.5 ± 65.7	0.553
Creatinine (mg/dL) (mean±SD)	0.85 ± 0.33	1.12 ± 0.54	0.008 **
Sodium (mEq/L) (mean±SD)	129.5 ± 4.3	126.6 ± 4.5	0.006 **
Potassium (mEq/L) (mean±SD)	4.1 ± 0.6	4.2 ± 0.6	0.564

* p < 0.05, ** p < 0.01; Student t-test

Table 4. Independent risk factors affecting NSE level.

	Odds ratio	SE	95% Cl	P
Constant	143.106	28.010	(87.268) - (198.944)	0.000
Sodium	-0.894	0.225	(-1.342) - (-0.447)	0.000*
Heart failure	-5.185	2.095	(-9.362) - (-1.009)	0.016**

* p < 0.01, ** p < 0.05

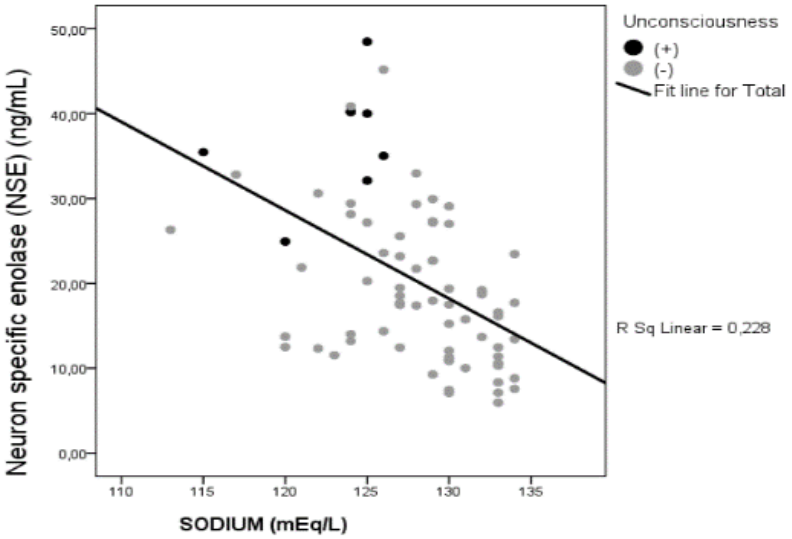

Figure 1. Linear regression analysis for the independent risk factors affecting the NSE level.

DISCUSSION

In our study, the serum NSE levels were remarkably high in patients admitted to our ED who were found to have hyponatremia by routine laboratory tests.

In this study, we found that the serum NSE level increased with decreasing serum Na levels. In addition, NSE levels were higher in patients with impaired consciousness regardless of level of hyponatremia. Studies have shown that the reference ranges of NSE levels may differ in different populations[14]. These differences may be due to population disparities and/or inter-individual variation in the cohort used to construct the interval[14,16].

However, the serum NSE levels of patients with a loss of consciousness in our study were quite high and significantly higher than the upper limit of the reference interval provided by the Roche NSE kit, which is 17.0 ng/mL[16]., and then the upper limit set by Liu et al in a reference interval study in a Chinese population[14].

In clinical practice, if significant hyponatremia concomitantly occurs with consciousness problems, this is considered to be acute hyponatremia. In our cohort, the presence of neuronal damage and the level of NSE were significantly higher in patients who had significant hyponatremia accompanied with loss of consciousness, and that subgroup of patients was thought to have acute hyponatremia.

These findings in our study show that NSE, which is a brain injury marker, increases significantly when serum Na levels decrease, especially in acute decreases.

Studies have shown that during hyponatremia, the Na-K-ATPase system in glial cells plays an important role in cellular ion homeostasis. Due to this enzyme requiring ATP, neuronal damage can be prevented by allowing ions to escape out of the glial cell during hyponatremia. However, this enzyme cannot function adequately in hypoxemic conditions, and further neuronal damage occurs[17]. Therefore, accurate and rapid diagnosis and treatment of hyponatremia is very important in preventing any permanent brain damage[3].

In our study, there were two independent risk factors that determined the NSE level in the logistic regression analysis: hyponatremia and heart failure. In heart failure, the mechanism of neurogenic cell death and the associated increase in serum NSE levels, independent of hyponatremia, was thought to be due

to inhibition of the Na-K-ATPase system in glial cells[17]. Normally, low concentrations of NSE may also be physiologically present in the blood, since small amounts of NSE are present in erythrocytes and platelets[18,19]. However, the actual increase is caused by neuronal damage. NSE is known to increase in the systemic circulation after incidents that cause neurological damage, such as ischemic stroke, cerebral hemorrhage, and traumatic and hypoxic brain injury[7,12,20].

NSE levels have been found to be consistently elevated both in brain lesions and in patients with severe secondary brain injury. Thus, NSE levels are not only a marker of primary brain injury, but also reflect the progression of secondary brain damage. In this respect, NSE may have important potential as a prognostic and therapeutic indicator in neurological intensive care units [10].

In a meta-analysis study by Mercier et al., they stated that high serum neuron-specific enolase concentrations were associated with mortality and a Glasgow Outcome Scale score (< 4) in traumatic brain injury cases [9]. In addition, NSE has been shown to have prognostic significance in cerebrovascular stroke[13]. NSE in the cerebrospinal fluid (CSF) and serum has been correlated with poor outcomes in patients with cardiac arrest[21-23].

The level of NSE during CNS problems due to metabolic causes was investigated in a study conducted by Grandi et al.[22]. In this study, NSE levels were examined in patients with delirium in intensive care units, and the values were significantly higher in the non-delirious controls. As a result of this study, the authors concluded that neuronal cell destruction may occur during delirium[22].

In a study by Zhang et al., it was determined that hyponatremia accompanying traumatic brain injury worsened the patient's condition and increased the death rate[25]. In our study, we determined NSE levels to detect brain damage in patients with hyponatremia.

Our study has some limitations that may have affected the results. The first of these is the relatively low number of unconscious patients, and the other is that the NSE reference range may differ between different races

In conclusion, our results suggest that high NSE levels are associated with low hyponatremia levels and low GCS scores. Elevated levels of NSE as an indicator of neuronal damage may be helpful in predicting the development of impaired consciousness as sodium levels decrease in patients. In patients with hyponatremia, we think that neuron specific enolase monitoring can predict which patients may experience a change in consciousness. Future studies on this subject can be conducted with larger samples and by dividing the patient group with hyponatremia into 3 groups as mild, moderate and severe. In addition, the effects of NSE on predicting prognosis and mortality in patients with hyponatremia can be investigated.

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