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Title: Serum Neuron Specific Enolase and S-100B concentratios in Hemodialysis and Peritoneal Dialysis Patients

Turkish Title: Hemodiyaliz and Peritondiyalizi Hastalarında Serum Neuron Specific Enolase and S-100B düzeyleri

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Özet

Giriş ve Amaç: Nöron Spesifik Enolaz (NSE) ve S-100B beyinden kaynaklanan proteinlerdir. Nörolojik beyin hasarında düzeyleri artar. Çalışmanın amacı son dönem böbrek yetmezliği bulunan, hemodializ (HD) ve periton diyalizi (PD) uygulanan hastalarda serum S-100B ve NSE düzeylerini belirlemek ve bunların uygulanan diyaliz tipinden nasıl etkilendiğini göstermektir

Yöntem ve Gereçler: Çalışma grubu, yaş ve cinsiyet eşleştirilmiş HD tedavisi uygulanan 20, PD uygulanan 26 hasta ve 21 sağlıklı kontrolden oluştu. Kan örnekleri HD hasta grubunda diyaliz öncesi ve sonrasında, PD ve kontrol grubunda sabah açlık kanı olarak alındı. Elde edilen serum örneklerinde rutin biyokimya parametreleri aynı

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gün 2 saat içinde ölçüldü. Serum S-100B and NSE düzeyleri çalışılacakları güne kadar -80°C'de saklandı. Serum S-100B ve NSE düzeyleri kemilüminesans immunuassay yöntemiyle ölçüldü. Rutin biyokimya testleri kolorimetrik yöntem ile biyokimya analizöründe ölçüldü.

Bulgular: HD ve PD grupları ile kontrol grubu karşılaştırıldığında S-100B (sırasıyla; 0.11±0.06 ng/mL, 0.13±0.09 ng/mL ve 0.05±0.03 ng/mL) ve NSE (sırasıyla; 12.7±5.99 ng/mL, 9.26±5.52 ng/mL ve 6.82±2.36ng/mL) düzeyleri, hasta gruplarında anlamlı yüksekti. S-100B ve NSE düzeyleri HD sonrası, HD öncesi düzeylerinden yüksekti (P< 0.001). S-100B and NSE düzeyleri arasında zayıf ama anlamlı korelasyon vardı (r=0.290; p=0.006).

Tartışma ve Sonuç: Bu çalışmada serum S-100B ve NSE düzeyleri HD ve PD hastalarında yüksek bulundu. Kronik böbrek yetmezliği (KBY) olan hastalarda artmış S-100B ve NSE düzeyleri serebrovasküler olaylar ile ilişkili olabilir. Ayrıca serebrovasküler olayların belirlenmesine önemli belirteçler olabilir.

Anahtar Kelimeler: S-100B, nöron spesifik enolaz, son dönem böbrek yetmezliği, hemodiyaliz, periton diyalizi, beyin hasarı

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Abstract

Objective: Neuron specific enolase (NSE) and S-100B are brain derived proteins and increase in neurological tissue injuries. In this study, we aimed to investigate the serum values of NSE and S-100B in hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients with end stage renal disease (ESRD) and the effect of different dialysis procedures on these parameters.

Methods: 20 HD patients, 26 CAPD patients and 21 healthy controls matched by age and gender were included in the study. Venous blood samples from pre- and post-hemodialysis session and only fasting blood samples from CAPD and control subjects were obtained. The routine biochemical parameters were measured within two hours for all serum samples. The remaining serum samples were stored at -80oC until the day of analysis of the S-100B and NSE assays. Serum S-100B and NSE values were performed by analyzer using chemiluminescence immunoassay method. Other routine biochemical tests were measured in a chemistry analyzer by colorimetric methods.

Results: Serum S-100B (HD: 0.11±0.06 ng/mL, CAPD: 0.13±0.09 ng/mL and control: 0.05±0.03 ng/mL) and NSE (HD: 12.7±5.99 ng/mL, CAPD: 9.26±5.52 ng/mL and control: 6.82±2.36 ng/mL) concentrations were higher in HD and CAPD patients compared to control subjects. S-100B and NSE concentrations were also higher in post-

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HD group than pre-HD ($p< 0.001$). There was a weak but significant correlation between S-100B and NSE concentrations ($r=0.290$; $p=0.006$).

Conclusion: Serum S-100B and NSE concentrations were higher in HD and CAPD patients. Increased concentrations of serum S-100B and NSE can be associated with neurological tissue injury in these patients. Therefore, these markers can be valuable for determining the possible risk of cerebrovascular event in patients with chronic renal disease.

Keywords: S-100B, neuron specific enolase, end stage renal failure, hemodialysis, continuous ambulatory peritoneal dialysis, brain damage

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INTRODUCTION

Neuron Specific Enolase (NSE) and S-100B are specific brain-derived proteins that in recent decades have gradually gained importance as neurochemical markers (1). The serum concentrations of these analytes are increased in traumatic brain injury and following clinical conditions that result in brain injury, such as cardiac arrest and cardiopulmonary bypass surgery (CPBS) (2, 3). S-100B is a calcium-binding protein, approximately 21 kDa in weight and composed of subunits A and B. Subunit B is

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synthesized mainly by astroglial and microglial cells and is highly specific for the central neurological system (CNS) (4, 5). The half-life of S-100B in serum is reported to be about two hours, and it is metabolized and excreted through the kidneys. Its concentrations are normally undetectable in serum samples, but can reach measurable levels following certain clinical conditions such as strokes, subarachnoid hemorrhage, head injury, and extracorporeal circulation (6-8).

Neuron Specific Enolase (NSE) is a dimeric isoenzyme of the glycolytic enzyme enolase that is approximately 78 kDa in weight and has a biological half-life of about 24 hours. It is highly localized in neurons and neuroendocrine cells, and constitutes 1.5% of soluble proteins in brain tissue (9). When brain tissues are injured, NSE diffuses cerebrospinal fluid (CSF) and systemic circulation (1, 10). Recent studies have suggested that increased NSE concentrations in serum and CSF can be used as a sensitive and quantitative marker for parenchymal damage in brain tissue, cerebral infarction and intracerebral bleeding (9, 11).

Chronic renal disease is defined as an irreversible and progressive decrease (<60mL/min/1.73 m2) in the glomerular filtration rate (GFR). When the chronic and progressive deterioration reaches an advanced stage, it is called a chronic renal failure (CRF). CRF is associated with dangerous disturbances in the fluid and electrolytes balance, as well as in metabolic-endocrine functions. It is well known that decreased

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GFR is a risk factor for cerebrovascular and cardiovascular diseases. Cerebrovascular diseases are considered as one of the most important causes for higher morbidity and mortality in patients with end-stage renal disease (ESRD). It has been reported that there is a relationship between ESRD and several cerebral pathologies, including stroke, cerebral microvascular disease, silent lacunar infarct, white matter lesions and cerebral microvascular bleedings (12).

Controlling these risk factors plays a key role in the prevention of cerebral diseases and in improving the quality of life for patients with ESRD. Magnetic resonance imaging (MRI) is still the most valuable diagnostic tool, and is commonly used in the diagnosis of cerebrovascular diseases in these patients. As neurochemical markers, serum S-100B and NSE can be useful for early diagnosis of brain injury.

The purpose of this study was to determine serum NSE and S-100B concentrations in patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD), to compare these values with the control group, and to assess these neurochemical markers before and after a single HD session.

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METHODS

Subjects

Twenty patients undergoing hemodialysis and 26 patients undergoing peritoneal dialysis were included in the study. Twenty-one healthy controls, matched by age and gender and with no systemic disease such as hypertension, chronic renal disease, diabetes mellitus, cardiovascular or neurovascular disease were selected for the study. The study was approved by the Ethics Committee of Ankara Hospital (Approval Number: 3020) in accordance with the regulations of the Ministry of Health. All patients were informed about the study procedures before being included.

Blood Sampling and Biochemical Analysis

Fasting venous blood samples were obtained from the patients before and after a hemodialysis session, while only fasting blood samples were obtained from the CAPD and control subjects. Blood samples were drawn into evacuated serum separator tubes containing clot activator (SST Vacutainer®, Becton Dickinson). All blood samples were centrifuged at 1500 g for 10 minutes and sera were separated and used for routine biochemical testing within two hours. The remaining serum samples were stored at -80ºC until the day of analysis of the S-100B and NSE assays.

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Serum glucose, urea, creatinine (Cre), uric acid (UA), total protein (TP), albumin (Alb), sodium (Na) and potassium (K) concentrations were measured with original reagent using an Olympus AU 2700 analyzer (Mihsima Olympus Co. Ltd. JAPAN).

S-100B and NSE Procedure

Serum S-100B and NSE measurements were conducted using an immunochemistry (Liaison® Sangtec 100, DiaSorin AB Bromma, Sweden). The minimal detection concentration was 0.02 ng/mL for S-100B and 0.04ng/mL for NSE. The intra-assay coefficient of variation (CV) was 3.7% for S-100B and 0.9 % for NSE. The inter-assay CV's for S100-B and NSE were 5.7 % and 5.3 %, respectively.

Dialysis Procedure

All patients underwent hemodialysis three times per week for a duration of four hours a day, using a synthetic low-flux hollow-fiber filter (polysulfone membrane) (surface area 1.25 m^2), a mean blood flow speed of 200-300 mL/min, and a dialysate flow speed of approximately 500 mL/min during the HD procedure. For peritoneal dialysis patients, CAPD involves four or five dwells per day of 2-2.5 liters per dwell.

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Statistical Analysis

Descriptive statistics were used to analyze the data. The Kolmogorov-Smirnov test was used for normality testing of the data. Differences between the means of groups were analyzed using the Mann-Whitney U test. The Spearman correlation was used to evaluate the association between variables. Pre- and post-HD values were compared using the Wilcoxon Sign test. Values of $p<0.05$ were considered to be statistically significant. Statistical analyses were conducted using SPSS version 15.0.

RESULTS

Demographic information for the patients included in this study and the biochemical test results are given in Table 1 and Table 2, respectively. Serum S-100B and NSE concentrations are given in Table 3. Serum S-100B and NSE concentrations were higher in HD patients compared with the control subjects (P=0.001, P=0.002). Serum S-100B and NSE concentrations were higher in CAPD patients compared with the control subjects (p=0.002, p=0.009). Serum S-100B and NSE concentrations were a significantly diffirent between CAPD and HD patients (p=0.023, p<0.001) (Table 3). There was a significant positive correlation between S-100B and NSE concentrations (r=0.290; p=0.006). S-100B and NSE concentrations were also significantly higher

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following a single HD session ($p<0.001$) (Table 4). The S-100B and NSE results are shown in Figure 1.

DISCUSSION

The dialysis process can affect and change number of biochemical factors. Several of these changes are useful, while others can be harmful and increase the severity of the disease.

In the current study, both S-100B and NSE concentrations found to have increased in the patients with HD and CAPD. When we evaluated the difference between the types of dialysis, we found that serum S-100B concentrations were higher and NSE concentrations were lower in the CAPD group in comparison to the HD group. Kidneys normally metabolize both S-100B and NSE; therefore, in renal failure, it can be expected that their concentrations in the serum are higherdue to decreased renal clearance. When the relationship between chronic renal disease and cerebrovascular disorders are taken into consideration in these patients, increasing concentrations of serum S-100B and NSE may be associated with neurological tissue injury.

In this study, we also evaluated the hemodialysis effect and found that both serum S-100B and NSE concentrations were higher in post-HD compared with pre-HD. This could be the result of the hemodilution effect, which normally occurs in pre-HD and partial hemoconcentration due to dialysis therapy. Another factor contributing to higher

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concentrations of these parameters in post-HD could be the insufficient permeability of the synthetic hollow-fiber membrane to the S-100B and NSE proteins, which can result in their ineffective removal; however, in literature, there is no study investigating the effect of dialysis on serum S-100B and NSE.

Cerebrovascular diseases one of the most common reasons for higher morbidity and mortality in patients with ESRD (1, 13). The early diagnosis of cerebrovascular disease is important for improving the prognosis and quality of life of these patients. In a previous study, Ikram et al. (14) observed that there was a relationship between decreased GFR levels and the findings of MRI, including cerebral microvascular lesions. Some other studies have reported that decreased GFR is related to an increased prevalence of subclinical lacunar cerebral infarcts detected using MRI (15, 16). In another study, decreased GFR was found to be associated with silent cerebral infarcts (17). Kim et al. (18), investigated the connection between depression symptoms and serum S-100B concentrations and found that S-100B concentrations increased in ESRD due to glial pathology and dysfunction of the blood brain barrier . According to these previous studies, we can say that the varying degrees of reduction in GFR levels were linked to the cerebral pathologies of patients with chronic renal disease. In the diagnosis of cerebrovascular diseases, measuring serum S-100B and NSE provides significant advantage, as it is easy to perform and non-invasive; however, there is no study in

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literature investigating S-100B and NSE concentrations in patients with ESRD, and the present study is the first in this field.

In this study, we determined that serum S-100B and NSE concentrations increased in patients undergoing HD and CAPD therapy compared to the controls. Therefore, these markers could be valuable in determining the possible risk of a cerebrovascular event in patients with chronic renal disease. Nevertheless, one of the limitations of this study was that further studies are needed to compare the serum S-100B and NSE parameters with the MRI findings of patients with chronic renal failure. Another limitation was that study size was relatively small.

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Table 1. Baseline demographics of control and patien groups

Variableles	**Control**	**CAPD**	**HD**
n	21	26	20
Gender			
Female (%)	9 (43%)	12 (46%)	9 (45%)
Male (%)	12 (57%)	14 (54%)	11 (55%)
Age (year; mean±SD)	47.9 ± 8.5	46.8 ± 13.3	49.37 ± 15.17
Body-mass	27.7 ± 3.7	25.35 ± 5.2	22.58 ± 3.2
Dialysis duration (years)			
<1	-	4	5
1-5	-	17	10
5- 10	-	5	5
Smoking (%)	4 (19%)	6 (23%)	2 (10%)
Diabetes mellitus (%)	-	6 (23%)	5 (25%)
Bone disease (%)	-	3 (12%)	4 (20%)
Cardiovascular disease (%)	-	2 (8%)	1 (5%)
Hypertension (%)	2	12 (46%)	14 (70%)
Dyslipidemia (%)	3	3 (12%)	8 (40%)
Tyroid disease (%)	2	3 (12%)	-
Family history (%)	-	1 (4%)	3 (15%)
Drugs used (%)			
Antilipidemics	-	3 (12%)	8 (40%)
Antihypertensive	-	21(81%)	14 (70%)
• Beta blockers	-	3 (12%)	2 (10%)
• ACE inhibitors	-	5 (19%)	6 (30%)
• Angiotensin II receptor	-	4 (13%)	2 (10%)
• Calcium channel	-	9 (35%)	6 (30%)
• Adrenergic receptor	-	4 (13%)	-

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Insuline	-	6 (23%)	5 (25%)
Folic acids and derivatives	-	13(50%)	20(100%)
Drugs containing iron	-	10 (38%)	20(100%)
Phosphate chelators	-	24 (92%)	20(100%)
Vitamine D analogues		24 (92%)	20 (100%)
Erythropoietin analogues	-	5 (9%)	20(100%)
Antiaggregants	-	1 (4%)	-
Aspirin	-	2 (8%)	-
Tricyclic antidepressants	-	2 (8%)	-
T3 agonists	-	2(8%)	-

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Table 2. The measuring analytes concentrations in control and patient groups

Analytes (measuring units)	Control (n=21) M (IQR)	CAPD (n=26) M (IQR)	p*	HD (n=20) M (IQR)	p*
Glucose (mmol/L)	5.2 (1.6)	7.2 (4.7)	<0.001	6.9 (6.7)	<0.001
Urea (mmol /L)	10.6 (3.2)	40.2 (12.4)	<0.001	46.7 (10.2)	<0.001
Crea (µmol/L)	88 (18)	778 (239)	<0.001	787 (265)	<0.001
UA (mmol/L)	0.29 (0.06)	0.34 (0.07)	0.042	0.33 (0.06)	0.042
TP (g/L)	69 (5)	67 (9)	0.062	68 (6)	0.070
Alb (g/L)	42 (4)	37 (4)	0.001	36 (4)	0.001
Na (mmol/L)	139.3(2.5)	138. 6 (3.4)	0.125	136.0 (5.0)	0.102
K (mmol/L)	4.4 (0.4)	4.3 (0.5)	0.086	5.4 (0.8)	0.001
Systolic blood pressure (mmHg)	115 (12)	132 (19)	0.001	142 (19)	0.001
Diastolic blood pressure (mmHg)	75 (6)	82 (9)	0.001	80 (11)	0.001

*p value: comparing control and study groups; M: Median; IQR: Inter quartile range

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Table 3. Comparison of serum S-100B and NSE concentrations in control and patient groups

Analytes (measuring units)	**Control n=21 M (IQR)**	**CAPD n=26 M (IQR)**	**p***	**HD n=20 M (IQR)**	**p***	**p****
S-100B (ng/mL)	0.05 (0.03)	0.13 (0.09)	0.002	0.11 (0.06)	0.001	0.023
NSE (ng/mL)	6.82 (2.36)	9.26 (5.52)	0.009	12.7 (5.99)	0.002	< 0.001

*p value: comparing control and study groups; **p value: comparing CAPD and HD;

M: Median; IQR: Inter quartile range

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Table 4. Comparison of serum S-100B and NSE concentrations in pre-HD and Post-HD

Analytes (measuring units)	**Pre-HD n=20 M (IQR)**	**Post-HD n=20 M (IQR)**	**p***
S-100B (ng/mL)	0.11 (0.06)	0.13 (0 .07)	< 0.001
NSE (ng/mL)	12.7 (5.99)	15.84 (11.72)	< 0.001

*p value: comparing pre-HD and Post- HD; M: Median; IQR: Inter quartile range

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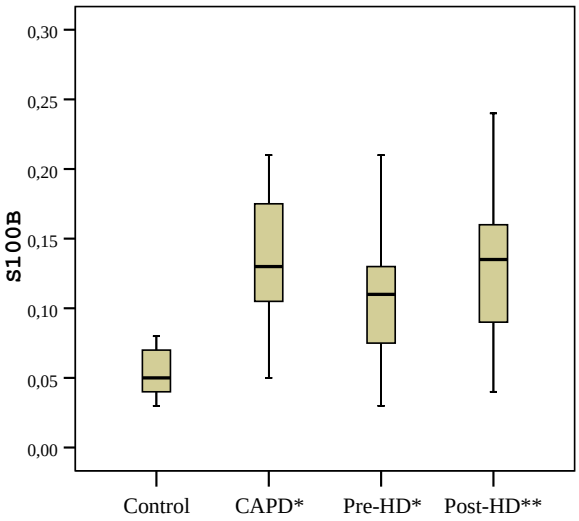

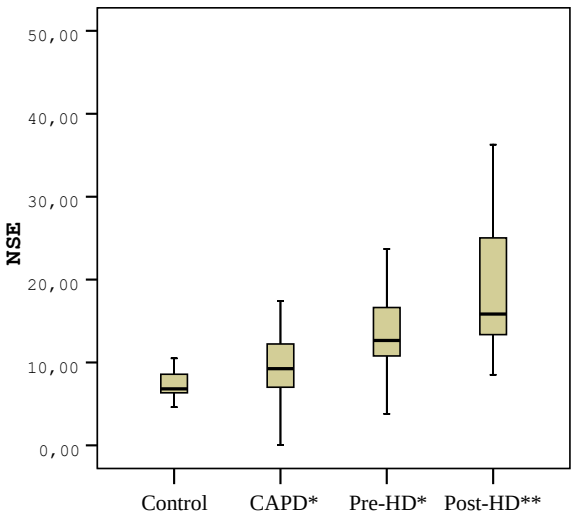

Figure 1. Serum S-100B and NSE concentrations of patient and control groups in study

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