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ORIGINAL ARTICLE/ÖZGÜN ARAŞTIRMA

S100B protein levels in patients admitted to an emergency service due to seizures

Acil servise nöbet şikayeti ile başvuran hastalarda S100B protein düzeyi

Fatma SARI DOĞAN, Arzu DENİZBAŞI ALTINOK, Özge ECMEL ONUR, Özlem GÜNEYSEL, Haldun AKOĞLU

ABSTRACT

Objectives: Various levels of dysfunction and damage can occur in the central nervous system of patients experiencing seizures. It is known that these impairments can be assessed by measurement of biochemical markers. S100B proteins have been extensively studied in recent years. We have assessed whether there is a change in serum S100B protein levels during seizures which lead to cerebral hypoperfusion and/or hypoxia.

Patients and Methods: A total of 56 patients admitted to an emergency service due to seizures and more than 18 years of age were included in the study. The control group consisted of 20 patients who were admitted to the emergency service due to complaints other than seizures.

Results: There was a significant difference between the groups in terms of gender, hemoglobin levels and S100B levels, whereas there was no significant difference in terms of glucose, sodium and potassium levels. The S100B levels were significantly lower in the patient group compared to the control group. Hemoglobin levels was significantly lower in the control group compared to the patient group.

Conclusion: Serum S100B protein concentration was found to be significantly lower in patients compared to controls.

Key words: Seizure, S100B protein, Emergency

ÖZET

Amaç: Nöbet geçiren hastalarda santral sinir sisteminde farklı düzeylerde disfonksiyon ve hasar oluşabilmektedir. Bu hasarlanmaların biyokimyasal belirteçlere bakılmak suretiyle değerlendirilebileceği bilinmektedir. Son yıllarda giderek artan bir şekilde "beyine özel göstergeler" araştırılmaktadır. Bu çalışmada serebral hipoperfüzyon ve/veya hipoksiye neden olan nöbet durumlarında serum S100B protein düzeylerinde değişiklik oluşup oluşmadığının belirlenmesi amaçlanmıştır.

Hastalar ve Yöntem: Acil servise nöbet şikayetiyle başvuran ≥18 yaşında 56 hasta çalışmaya alınmıştır. Kontrol grubunu nöbet dışı bir şikayetle acil servise başvuran 20 hasta oluşturmuştur.

Bulgular: Gruplar arasında cinsiyet, hemoglobin değerleri ve S100B proteini açısından anlamlı olarak fark bulunmuştur. Bunun yanında glukoz, sodyum ve potasyum değerleri açısından gruplar arasında anlamlı olarak bir fark yoktur. Hasta grubu S100B değerleri, kontrol grubuna göre istatistiksel açıdan anlamlı olarak düşük bulunmuştur. Hemoglobin değerleri ise, kontrol grubunda, hasta grubuna göre anlamlı olarak düşük bulunmuştur.

Sonuç: Hasta grubu serum S100B protein konsantrasyonu, kontrol grubundan anlamlı olarak düşük bulunmuştur.

Anahtar Kelimeler: Nöbet, S100B protein, Acil

Introduction

Epilepsy , a common neurological disorder throughout the world, is also an important public health issue associated with a large economical burden due to the requirement of lifetime drug treatment and concomitant diseases. Epileptic seizures which occur as partial or generalized forms may be life-threatening[1]. Almost 28% of all patients with epilepsy require emergency treatment annually[2]. Seizures may cause severe and persistent damage in the central nervous system (CNS). Several biochemical markers are used for the assessment of this damage. S100 proteins are among the markers investigated for this purpose.

S100B is a multigenic family of calcium-modulated proteins of the EF-hand type expressed in vertebrates. Members of this protein family modulate enzyme activities by interacting with numerous effector proteins. They affect the structural dynamics of the cytoskeleton, modulate

Fatma Sarı Doğan (✉)
Department of Emergency Medicine, Göztepe Training and Research Hospital, İstanbul, Turkey
e-mail*: fatmasdogan@gmail.com*

Arzu Denizbaşı Altınok, Özge Ecmel Onur
Department of Emergency Medicine, School of Medicine, Marmara University, İstanbul, Turkey

Özlem Güneysel, Haldun Akoğlu
Department of Emergency Medicine, Lütfü Kırdar Training and Research Hospital, İstanbul, Turkey

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cell growth and differentiation and establish calcium homeostasis [3-5]. S100B is a homodimer protein which is primarily released from astrocytes, is found in large amounts in the CNS and has autocrine and paracrine effects of glia cells neurons and microglia [5, 6]. Release of S100B from astrocytes occurs under metabolic stress conditions such as oxygen and glucose deprivation7.

Following brain injury, S100B transferred to the cerebrospinal fluid (CSF) and then to the circulation [3, 4]. High CSF and serum levels of S100B have been reported in Alzheimer's disease, stroke, traumatic brain injury and acute subarachnoid hemorrhage [8-11].

Central nervous system dysfunction and injury occurs in patients sustaining generalized seizures.

This study assessed serum S100B protein levels in patients admitted to an emergency service due to seizures.

Patients and Methods

Study Design

The present study was designed as a prospective controlled study. The study was approved by the Ethical Board of Marmara University, School of Medicine and all patients provided informed consent.

Study Setting and Population

The study was conducted in the Hospital of the Marmara University, Faculty of Medicine. Adult patients (≥18 years of age) admitted to the emergency service due to seizures were included in the study. Subjects with a history of central nervous system trauma, cerebrovascular events, malignant melanoma or an intracranial mass and those subjects who were diagnosed as a conversion disorder or syncope at the time of admission were excluded.

Totally 234 patients were admitted to the emergency unit due to seizures during the one-year study period. During the assessment performed at time of emergency admission, it was noted that the primary complaint was not a seizure in 20 patients. Another 65 patients were excluded due to an intracranial mass, 70 patients due to a cerebrovascular accident (CVA) and 21 patients due to head injury. A total of 58 patients were included, but 2 patients were also excluded because appropriate blood samples could not be obtained. Data from 56 patients were included in final analysis. The control group consisted of 20 patients who had been admitted to the emergency service due to complaints other than seizures.

Study protocol

Demographic innormation about the patients was recorded and blood samples were obtained for the measurement of serum S100B protein level in addition to a complete blood count and routine biochemistry tests. All patients underwent a neurological examination and were treated accordingly following necessary radiological evaluations.

The venous blood samples collected for serum S100B protein level measurement were immediately centrifuged and serum samples were stored at -40ºC. After drawing the serum samples, a S100B protein level analysis was performed using a CanAg S100BB EIA (Fujirebio Diagnostics) kit according to the instructions provided by the manufacturer.

Key Outcome Measures

Serum S100B protein levels of patients and controls were compared.

Data Analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS) for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). Between-group comparisons were performed by the Mann Whitney U test or by the independent samples t-test depending on their distribution. The statistical significance level was set as $p<0.05$.

Results

Men constituted 57.1% of patients (n=56) and 30% of control subjects (n=20) included in the study. Characteristics of patient and control groups are presented in Table I. The mean ages of patient and control groups were similar. Significant differences were noted between the groups in terms of gender, hemoglobin level and S100B levels. The S100B levels were significantly lower in the patient group compared to the control group. Hemoglobin levels were significantly lower in the control group compared to the patient group. No significant differences were noted between the groups in terms of glucose, sodium and potassium levels.

Table I. Characteristics of patient and control groups

	Patient Group (n=56)	Control Group (n=20)	p
Gender			
Male	32 (57.1)	6 (30.0)	0.037
Female	24 (42.9)	14 (70.0)	
Age (years)	55.46±21.08	60.65±15.68	0.255
S100B (ng/L)	42.75±53.51	51.05±44.27	0.006
Glucose (mg/dL)	115.05±29.97	124±32.01	0.264
Sodium (mEq/L)	137.48±6.88	137.25±8.70	0.904
Potassium (mEq/L)	4.17±0.60	4.24±0.65	0.690
Hemoglobin (g/dL)	12.94±2.08	11.37±1.87	0.005

Results are expressed as either n (%) or mean±standard deviation.

Discussion

In recent years, S100B protein has been largely focused on as a biochemical marker of cerebral disorders. Increased serum S100B protein level may reflect either glial damage or

astrocytic reactions to neural injury. Serum S100B protein levels increase after trauma and after stroke. In previous studies, serum S100B protein level was associated with severity of trauma and disease prognosis [3-7].

As a marker of epilepsy S100B protein has been studied in a few studies which have reported controversial results [12-20]. It is not clear whether S100B protein has a role in the pathophysiology of epilepsy or whether S100B has an antiepileptic action . In our study we found that serum S100B levels in patients suffering from seizures were significantly lower compared to the control group.

In our study, in order to elucidate the role of S100B protein in epileptogenesis, knockout (KO) and wild-type (WT) mice have been compared and the results have supported the hypothesis that astrocytes have some kind of an antiepileptic activity through S100B21. In another study, a rat seizure model using pentylenetetrazol (PTZ) has been used and significant increases in CSF S100B levels have been noted between 10-360 minutes after the seizures returning to control levels at 24 hours [12].

The mean age of the patient group was 55.46±21.08 years in our study. In another study, Leutmezer et al. prospectively investigated changes in postictal serum S100B protein concentration in 10 patients with mesial temporal lobe epilepsy (TLE) 16 . The mean age in this study was 12 (range: 7-22) years and 8 out of 10 samples from subjects were found to have high serum S100B concentration and no statistically significant changes were noted16but this finding could not be explained in this study.

Portela et al. [22] have reported a negative correlation between age and serum S100B concentration. Thus, the difference between our results and the results of Leutmezer et al. 16 might be due to the difference in mean age of the two patient groups. Our age group was older than Leutmezer's group.

Serum S100 protein concentration was prospectively measured in 9 adult patients following tonic clonic seizures at 5 minutes, 6 hours, 24 hours, 48 hours by a radioimmunoassay (RIA) method and no statistically significant differences were found compared to the control group [15]. It was concluded that serum S100 protein levels cannot be considered as a promising marker to indicate brain dysfunction following seizures [15]. We used an enzyme immunoassay (EIA) method to measure serum S100B protein levels, which were found to be significantly lower in patients who were suffering from seizures. However, as each study included control groups, the discrepancy of the results cannot be attributed to the difference in measurement method (RIA or EIA).

There were more men in the patient group in our study. It has been suggested in some studies that the higher prevalence of epilepsy in men can be associated with their greater involvement in social life and consequently greater trauma [23].

In a study conducted in patients with drug-resistant partial seizures, Otto et al. have found in contrast to our findings that there was a statistically significant increase in serum S100 concentration following seizures, and that serum S100 concentration reached a peak level at the initial 60 minutes after the seizure and then gradually decreased in the following hours [13]. Blood samples were obtained at time of admission to the emergency service in our study. While some patients were suffering from seizures during their assessment in the emergency service, others had been admitted in the postictal period and the exact time of seizures was not recorded in the patient's history. The difference in time of sampling may explain the difference of our results and those reported by Otto et al. [13].

High S100B levels noted in previous studies might have resulted from an increase due to a passive leak related to acute seizures or active release to limit the seizure. No significant difference has have been noted in S100B levels of patient and control groups in some of the studies [14-16]. The lower S100B level found in our study may be due to the depletion and therefore reduction of S100B which is actively released for protection following seizure.

Limitations

In the present study, the diagnosis of seizure was based on history and neurological examination and not by electroencephalography (EEG), and this may be considered as a limitation. The control group was not selected from healthy adults and was formed by patients admitted to the emergency service due to complaints other than seizures. It should be noted however that pathologies that have been previously reported to cause an increase in S100B level were all excluded. Thus, we do not believe that this might have led to any bias.

Conclusion

In conclusion, the serum S100B protein concentration has been found to be statistically significantly lower in patients suffering from seizures compared to controls; however, this result has no clear-cut explanation. Further research is warranted in order to clarify the role of S100B released from astrocytes in seizure mechanisms and to determine whether it acts as a neuroprotective or neurodegenerative agent. Future studies are required to provide a definitive statement for serum S100B levels in the postictal period in patients with seizures as "reduced, not changed or increased" and to use serum S100B protein level as a biomarker in patients with seizures.

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