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Elevated serum S-100B levels in children with temporal lobe epilepsy

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ABSTRACT

Purpose: An elevated level of S-100B in serum is generally considered to be a biochemical marker of nervous tissue damage. According to our knowledge, no studies have evaluated the serum S-100B protein concentration in children with temporal lobe epilepsy. The objective of this study was to measure the serum levels of S-100B protein in pediatric cases with temporal epilepsy.
Methods: This case-controlled cross-sectional study was performed at the Department of Pediatric Neurology, Harran University School of Medicine, Sanliurfa, in Turkey. Serum S-100B protein levels were studied in 19 (12 females, 7 males) children with temporal lobe epilepsy and in 25 (15 females, 10 males) healthy control subjects. Serum samples were collected within 30 min after a complex partial seizure, and serum S-100B protein levels were measured with an electrochemiluminescence immunoassay for the quantification of protein (ECLIA kit, Roche® Diagnostics, Germany).
Results: The mean serum concentration of S-100B protein was 0.12 ± 0.02 μg/L in the temporal lobe epilepsy group and 0.07 ± 0.01 μg/L in the control group. The patients showed significantly elevated S-100B protein levels compared with healthy controls ($P < 0.001$).
Conclusion: Our data suggest that increased S-100B protein levels in the serum might reflect neuronal damage in the brains of children with temporal lobe epilepsy. These results do confirm the previous findings of elevated S-100B protein levels in adult patients with temporal lobe epilepsy.

1. Introduction

Partial epilepsy is defined as seizures that occur as a result of neuronal discharge in a certain region of the brain, the clinical and electroencephalography (EEG) findings of which are related to this anatomic localization. To date, the pathogenesis of partial epilepsy has not been fully explained. Recently, many studies have shown the existence of astrocytosis, particularly in mesial temporal lobe epilepsy (MTLE).[1,2] Astrocytosis has a primary importance in the etiology of temporal lobe epilepsy. Reactive astrocytosis causes deficits in neuronal inhibition by causing local synaptic dysfunction. Thus, an imbalance in the excitatory and inhibitory synapses may cause epileptiform discharges in these patients.[3]

A number of proteins have been proposed as peripheral biochemical markers of neuronal damage and glial activation, including S-100B and neuron-specific enolase (NSE). S-100B is a calcium-binding protein found primarily in astroglial and schwann cells.[4,5] Some reports have evaluated serum S-100B protein levels in adults with epilepsy, including temporal lobe epilepsy (TLE) and symptomatic and idiopathic partial epilepsies, but the results are inconclusive.[8,9] In this study, to investigate possible neuronal and/or glial damage at the cellular level in TLE, we measured the levels of S-100B protein, which is a biochemical marker of neuronal damage, in patients with TLE.

2. Methods and materials

This case-controlled cross-sectional study was performed at the Department of Pediatric Neurology, Harran University School of Medicine, Sanliurfa, Turkey. The study groups consisted of 19 patients (12 females, 7 males) with TLE and a control group of

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25 healthy individuals (16 females, 9 males). All of the individuals in the patient group had been diagnosed with TLE on the basis of their clinical seizure semiology, video-EEG monitoring, and high-resolution magnetic resonance imaging (MRI) results. Video-EEG monitoring revealed ictal discharges in 10 cases. The ictal EEG results indicated repetitive spikes and spike-and-wave discharges in the left and/or right temporal lobes of these patients. Ictal recordings could not be obtained in the remaining 9 patients. Patients with simple partial epilepsy and patients who displayed extratemporal epileptiform activity in EEG analyses were excluded from the study. Patients with non-epileptic disorders, such as electrolyte disturbances, metabolic disorders, acute brain disease or trauma, and non-epileptic paroxysmal events mimicking epilepsy, were excluded from the study.

Research ethics approval was obtained from the Ethics Committee of the Medical School of Harran University. Written informed consent was obtained from all children/legal guardians. Serum samples were taken within 30 min after a seizure for S-100B measurement.[7] Venous blood was extracted into serum tubes and centrifuged for 10 min at 5000 rpm. Samples were then stored at −20 °C until analysis. Hemolyzed samples were not evaluated for S-100B. Serum S-100B protein levels were measured with an electrochemiluminescence immunoassay for the quantification of protein (ECLIA kit, Roche® Diagnostics, Germany). The assays were performed according to the manufacturer's instructions.

The data were analyzed using SPSS® for Windows version 11.5 (Chicago, IL, USA). The values for each group are expressed as the mean ± SD. The Kolmogorov–Smirnov test was used to determine whether the data were distributed normally. Non-parametric tests were used because the distribution of the groups was not homogeneous. The differences between groups were analyzed using the Mann–Whitney *U*-test. The results are expressed as the mean ± S.D. $P < 0.05$ was considered as statistically significant.

3. Results

The age of the subjects ranged from 3 to 16 years (11.0 ± 6.0 years) in the study group and 4 to 16 years (8.50 ± 6.0 years) in the control group. No statistically significant differences were found between the groups in terms of age or gender distribution ($P = 0.189$).

All of the patients exhibited typical clinical features of complex partial seizures. In total, seven patients had a one year history of TLE. A three year history of TLE was present in five cases, and a five year history of TLE was present in six cases. One patient had a seven year history of TLE. Only four patients reported experiencing aura; this phenomenon manifested in the form of epigastric discomfort in three cases and as an abnormal odor in one instance. The patients experienced an average monthly epileptic seizure frequency of 7.5 ± 5.2 (range: 1–20). The demographic details of the patient and control groups are given in Table 1. The mean serum concentration of S-100B protein was 0.12 ± 0.02 μg/L in the temporal lobe epilepsy group and 0.07 ± 0.01 μg/L in the control group. We found that the serum levels of S-100B protein were significantly elevated in children with temporal lobe epilepsy compared to controls ($P < 0.001$) (Table 1). Interictal EEG demonstrated unilateral temporal epileptiform activity in 12 cases and bilateral temporal epileptiform activity in 7 cases. Two of the patients were taking sodium valproate, four were taking carbamazepine, seven were taking sodium valproate + carbamazepine, and six were taking sodium valproate + levetiracetam. Brain MRI was carried out for all temporal lobe epilepsy patients. Brain MRI findings compatible with mesial temporal sclerosis were observed in three patients, and findings compatible with millimetric non-specific gliosis were observed for one patient. Two patients with mesial temporal sclerosis had a history of febrile convulsion.

Table 1
The demographic characteristics and serum S-100B levels of the patients with temporal lobe epilepsy and the healthy controls.

Parameters	Patients ($n = 19$)	Controls ($n = 25$)	*P*-value
Age in years[a]	11.0 ± 6.0	8.50 ± 5.0	$P = 0.189$
Gender, *n* (%)			
Male	7 (36.8)	9 (36.0)	
Female	12 (63.1)	16 (64.0)	
Number of AED[a]	2.0 ± 1.0	–	
Duration (years)[a]	2.7 ± 1.8	–	
Epileptic seizure frequency (per month)[a]	7.5 ± 5.2	–	
Interictal EEG, *n* (%)			
Unilateral temporal	14 (73.6)	–	
Bilateral temporal	5 (26.4)	–	
Epilepsy type, *n* (%)		–	
Simple partial	–	–	
Complex partial	19 (100)	–	
Brain MRI finding, *n* (%)			
No abnormality	15 (78.9)	–	
Mesial sclerosis	3 (15.7)	–	
S-100B level (μg/L)[a]	0.12 ± 0.02	0.07 ± 0.01	$P < 0.001$

[a] These table values are expressed in the form of means ± SD.

The receiver operating curve (ROC) analysis of S-100B levels in TLE patients determined that the area under the ROC curve was 0.980. This analysis revealed that S-100B levels ≥ 0.095 in epileptic patients indicated the presence of TLE with a sensitivity of 94.7% and a specificity of 96% (area under the curve of 0.980; 95% confidence interval of 0.00–1.00) (Fig. 1).

4. Discussion

S-100B is a structural protein of the central nervous system. It is primarily an astrocytic protein and is widely used as a parameter of glial activation.[5] Animal models of epilepsy and postsurgery brain specimens from epileptic patients have also demonstrated elevated S-100B protein levels in brain tissue.[10,11] In previous studies, elevated S-100B protein levels were associated with various neurological diseases, including traumatic brain injury,

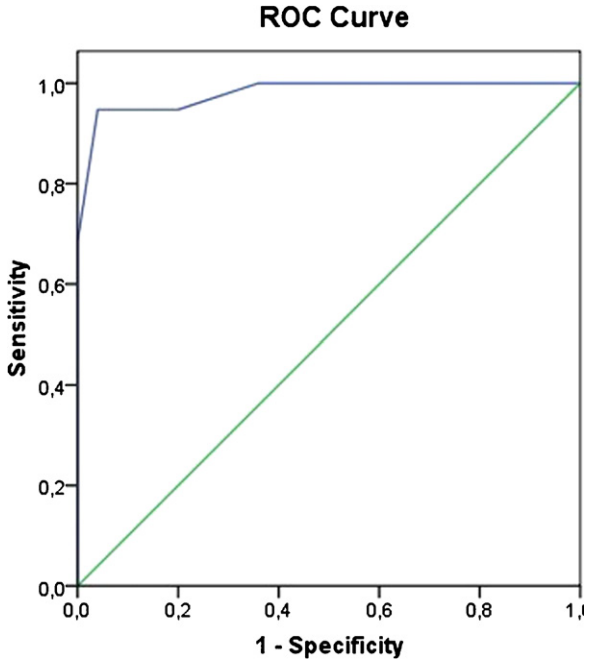

Fig. 1. The graph demonstrating receiver operating curve (ROC) analysis of S-100B levels in temporal lobe epilepsy patients with an area under the curve of 0.980.

subarachnoid hemorrhage, cerebral infarction, neurodegenerative processes, central nervous system (CNS) infections and many other brain disorders.[6,12,13] However, only a limited number of studies have examined serum S-100B protein levels in adult patients with partial epilepsy. Portela et al.[9] reported normal serum S-100B protein levels in patients with focal epilepsy, while Lu et al.[8] reported elevated plasma S-100B protein levels in patients with MTLE when compared with controls. Steinhoff et al.[14] reported high cerebrospinal fluid (CSF) S-100B levels in patients with TLE compared to controls. In the study by Lu et al.,[8] the concentration of S-100B protein was shown to correlate with the severity of epilepsy, and patients with hippocampal sclerosis had higher plasma S-100B levels than those with MTLE without hippocampal sclerosis.

In our study, we found a significant elevation of serum S-100B protein levels in children with TLE. To our knowledge, this study is the first to report that serum S-100B protein levels are elevated after TLE in children. In our series, the serum S-100B levels in children with TLE were much higher than those of the control group. S-100B protein acts locally in the brain, however, and its short serum half-life (only approximately 25–113 min) poses challenges for its measurement.[15] The presence of this protein in blood serum points to the functional and/or morphological disruption of the blood–brain barrier. High concentrations of extracellular S-100B proteins may result from the activation of cell metabolism, cell death and disease.[16] An increased serum concentration of S-100B may be indicative of neuronal damage in an epileptic brain.

Leutmezer et al.[17] studied the serum S-100 levels in 10 patients with TLE at baseline and at 30 min, 3 h, 6 h, 12 h, and 24 h after an epileptic seizure and found no significant differences in the serum S-100 levels at these various time points. Conversely, Palmio et al.[18] found a significant difference in serum S-100 levels between a TLE patient group and an XTLE (extratemporal lobe epilepsy) patient group. In this previously published study, the serum levels of both NSE and S-100 in the TLE group demonstrated a statistically significant increase following an epileptic seizure, whereas in the XTLE group, no significant changes in NSE and S-100 levels were observed after an epileptic seizure.

Our clinical samples for S-100B measurement in children were obtained from serum. These serum samples were acquired 30 min after an epileptic seizure. Our results are consistent with the previous studies that indicated elevated S-100B protein levels after TLE-related seizures in adult patients. The observation of high S-100B levels in children with TLE led us to hypothesize that brain damage risks are related to the occurrence of epileptic seizures (Fig. 2). Baseline levels of S-100B could not be measured in the TLE cases in our study. However, a significant difference has been found between the patient and control groups with respect to S-100B levels. Our study marks the first investigation in which S-100B levels were measured in children with TLE, and its findings have contributed to the literature regarding this topic.

Through ROC analysis, the current study has also demonstrated that serum S-100B levels may possess predictive value that could supplement the results of radiological and non-radiological tests (e.g. conventional MR imaging, clinical examinations, or EEG scanning) in TLE patients. A disadvantage of this study is that it was conducted with only a small number of patients. This limitation has restricted the defined cut-off value of the ROC analysis.

In conclusion, the serum S-100B protein level may be a biochemical marker for neuronal damage in childhood TLE. It is clear that there is a need for further studies with a larger patient population.

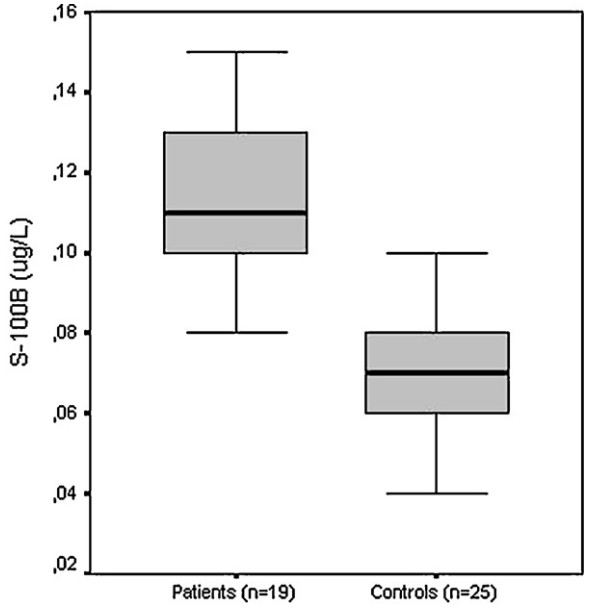

Fig. 2. The boxplot graphic of serum S-100B level in the patients with temporal lobe epilepsy and in the controls. The differences between the two groups are significant ($P < 0.001$).

Contributors

Calik M proposed the study and wrote the first draft. Iscan A helped the writing. All authors contributed to the design and interpretation of the study. Calik M is the guarantor.

Competing interest

No conflict of interest.

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References

1. Briellmann RS, Kalnins RM, Berkovic SF, Jackson GD. Hippocampal pathology in refractory temporal lobe epilepsy: t2-weighted signal change reflects dentate gliosis. *Neurology* 2006;**67**:134–6.
2. Choi J, Nordli DR, Alden TD, DiPatri A, Laux L, Kelley K, et al. Cellular injury and neuroinflammation in children with chronic intractable epilepsy. *Journal of Neuroinflammation* 2009;**6**:38.
3. Ortinski PI, Dong J, Mungenast A, Yue C, Takano H, Watson DJ, et al. Selective induction of astrocytic gliosis generates deficits in neuronal inhibition. *Nature Neuroscience* 2010;**13**:584–91.
4. Hu J, ferreira A, Van Eldik LJ. S100beta induces neuronal cell death through nitric oxide release from astrocytes. *Journal of Neurochemistry* 1997;**69**:2294–301.
5. Van Eldik LJ, Wainwright MS. The janus face of glial-derived S100B: beneficial and detrimental functions in the brain. *Restorative Neurology and Neuroscience* 2003;**21**:97–108.
6. Sandler SJ, Figaji AA, Adelson PD. Clinical applications of biomarkers in pediatric traumatic brain injury. *Childs Nervous System* 2010;**26**:205–13.
7. Böttiger BW, Möbes S, Glatzer R, Bauer H, Gries A, Bartsch P, et al. Astroglial protein S-100 is a an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. *Circulation* 2001;**103**:2694–8.
8. Lu C, Li J, Sun W, Feng L, Li L, Liu A, et al. Elevated plasma S100B concentration is associated with mesial temporal lobe epilepsy in Han Chinese: a case–control study. *Neuroscience Letters* 2010;**484**:139–42.
9. Portela LV, Tort AB, Walz R, Bianchin M, trevisol-bittencourt PC, Wille PR, et al. Interictal serum S100B levels in chronic neurocysticercosis and idiopathic epilepsy. *Acta Neurologica Scandinavica* 2003;**108**:424–7.
10. Somera–Molina KC, Nair S, Van Eldik LJ, Watterson DM, wainwright MS. Enhanced microglial activation and proinflammatory cytokine upregulation are linked to increased susceptibility to seizures in neurologic injury in a 'two-hit' seizure model. *Brain Research* 2009;**1282**:162–72.
11. Griffin WS, Yeralan O, Sheng JG, Boop FA, Mrak RE, Rovnaghi CR, et al. Overexpression of the neurotrophic cytokine S100 beta in human temporal lobe epilepsy. *Journal of Neurochemistry* 1995;**65**:228–33.

12. Moritz S, Warnat J, Bele S, Graf BM, Woertgen C. The prognostic value of NSE and S100B from serum and cerebrospinal fluid in patients with spontaneous subarachnoid hemorrhage. *Journal of Neurosurgical Anesthesiology* 2010;**22**:21–31.
13. Leclerc E, Sturchler E, Vetter SW. The S100B/RAGE axis in Alzheimer's disease. *Cardiovascular Psychiatry and Neurology* 2010;**2010**:539–81.
14. Steinhoff B, Tumani H, Otto M, Mursch K, Wiltfang J, Herrendorf G, et al. Cisternal S-100 protein and neuron-specific enolase are elevated and site-specific markers in intractable temporal lobe epilepsy. *Epilepsy Research* 1999;**36**:75–82.
15. Gazzolo D, Michetti F, Bruschettini M, Marchese N, Lituania M, Mangraviti S, et al. Pediatric concentrations of S100B protein in blood: age-and sexrelated changes. *Clinical Chemistry* 2003;**49**:967–70.
16. Marchi N, Cavaglia M, Fazio V, Bhudia S, Hallene K, Jangiro D. Peripheral markers of blood–brain barrier damage. *Clinica Chimica Acta* 2004;**342**:1–12.
17. Leutmezer F, Wagner O, Baumgartner C. Serum S-100 protein is not a suitable seizure marker in temporal lobe epilepsy. *Epilepsia* 2002;**43**:1172–4.
18. Palmio J, Keranen T, Alapirtti T, Hulkkonen J, Makinen R, Holm P, et al. Elevated serum neuron-specific enolase in patients with temporal lobe epilepsy: a video-EEG study. *Epilepsy Research* 2008;**81**:155–60.