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RESEARCH ARTICLE

Serum S-100B levels in children with Subacute Sclerosing Panencephalitis

Subakut Sklerozan Panensefalit'li çocuklarda serum S-100B düzeyleri

İbrahim Hocanlı[1], Mustafa Çalık[2], Alpay Çakmak[1], Hakim Çelik[3], Abdürrahim Kocyiğit[3], Akın İşcan[2]

ABSTRACT

Objectives: S-100B a protein prevalent in the central nervous system is a peripheral biomarker for blood-brain barrier disruption and neuronal damage. The objective of the study was to investigate the S-100B levels in patients with subacute sclerosing panencephalitis.

Materials and methods: A group of 40 patients with SSPE and 40 healthy controls were recruited. Serum S-100B protein concentrations were measured using a commercially available electrochemiluminescence immunoassay (ECLIA) kit, as supplied and according to the manufacturer's standards.

Results: Median S-100B levels were 0.095 ± 0.017 µg/L in patients with SSPE and 0.097±0.019 µg/L in the control group. This difference was not statistically significant (p>0.05). The patient group was further subdivided into two subgroups according to the presence or absence of brain atrophy. The S-100B levels were 0.096 ± 0.018 µg/L in the subgroup with atrophy and 0.094±0.014 µg/L in the subgroup without atrophy. This difference was also not statistically significant (p>0.05).

Conclusions: Our results suggest that serum S-100B is not a reliable marker for neuronal damage in SSPE. *J Clin Exp Invest 2012; 3 (3): 331-334*

Key words: Subacute sclerosing panencephalitis, S-100B level, serum biomarker

ÖZET

Amaç: S-100B santral sinir sisteminde yaygın olarak bulunan, kan beyin bariyeri yıkımında ve nöronal hasarda periferik belirteç olarak kullanılan bir proteindir. Bu çalışmanın amacı, Subakut sklerozan panensefalitli hastalarda S-100B düzeylerini araştırmaktır.

Gereç ve yöntem: Çalışmada, SSPE' li 40 hasta ile 40 sağlıklı kontrol grubu alındı. Serum S-100B protein konsantrasyonları elektrokemiluminesan immunoassay (ECLIA) yöntemi ile üretici standartlarına göre ölçüldü.

Bulgular: Ortalama S-100B seviyeleri SSPE'li hasta grubunda 0.095 ± 0.017 µg/L, kontrol grubunda ise 0.097 ± 0.019 µg/L bulundu. Aralarında istatistiksel olarak anlamlı farklılık bulunmadı (p>0.05). Hasta grubu beyin atrofisinin varlığına göre iki altgruba ayrıldı. S-100B seviyeleri beyin atrofisi olan grupta 0.096±0.018 µg/L, atrofisi olmayan grupta ise 0.094±0.014 µg/L idi. Bu farklılık istatistiksel olarak anlamlı değildi (p>0.05).

Sonuç: Bizim sonuçlarımız, S-100B'nin SSPE' de nöronal hasarda güvenilir bir belirteç olmadığını göstermektedir.

Anahtar kelimeler: Subakut sklerozan panensefalit, S-100B seviyesi, serum biomarker

INTRODUCTION

Subacute sclerosing panencephalitis (SSPE) is a progressive neurologic disorder of childhood and early adolescence that develops as a sequel to early childhood measles infection. The incidence of SSPE has declined substantially since the development of the measles vaccination. However, it still remains a problem in developing countries. The diagnosis of the disease is based on clinical and neuroimaging findings, electroencephalography (EEG) results, and the titer of measles antibodies in the cerebrospinal fluid (CSF) and serum. There is currently no objective laboratory finding monitoring the course of the disease. No peripheral biomarker is currently in use apart from imaging methods.[1]

S-100B is a calcium-binding protein primarily present in nervous tissue. Elevated S-100B levels are detected as a marker of injury to the astrocytes even after mild head injury [2], in children with septic encephalopathy and in newborns after prolonged

[1] Harran University School of medicine, Department of Pediatrics Şanlıurfa, Turkey
[2] Harran University School of medicine, Department of Pediatric neurology Şanlıurfa, Turkey
[3] Harran University School of medicine, Department of Biochemistry and Clinical Biochemistry, Şanlıurfa, Turkey

Correspondence: Mustafa Çalık,
Harran University School of medicine, Department of Pediatric neurology Şanlıurfa, Turkey Email: m.calik80@hotmail.com

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labor [3], and they are also associated with a number of other diseases, e.g. migraine, epilepsy, cardiomyopathy, cancer and inflammatory and autoimmune diseases.[4,5]

In this study, we measured the levels of S-100B protein which is a biochemical marker of neuronal damage in SSPE patients and control subjects.

MATERIALS AND METHODS

Study population

This prospective study was conducted at the Pediatric Neurology Department of Harran University School of Medicine, Sanliurfa, in Turkey. The study was conducted from October 2004 to December 2010. The case group consisted of 40 children who were admitted to the hospital following SSPE. The control group was consisted of 40 healthy children. SSPE was diagnosed by the Dyken Criteria.[6] Neurological disability index (NDI) developed by Dyken et al. was used in scoring the clinical neurological abnormalities of the cases. The method recommended by Jabbour [7] was used in clinical staging. The study was conducted according to the principles approved by Harran University Hospital ethics committee. Informed consent was obtained from the parents or guardians. Patients were excluded from the study if findings showed septic encephalopathy, hypoxia, and recent neurosurgery operation.

Data collection

The clinical data collected on all patients included the following: 1) demographics (age and gender), mean age of having measles, and measles vaccination status; 2) Serum measles IgG levels and CSF measles IgG levels 3) EEG and brain magnetic resonance imaging (MRI). A brain MRI was performed using a Siemens 1.5 Tesla system device (Signa; GE Medical Systems, Milwaukee, WI). An EEG was performed using a Nihon-Kohden device that took digital recordings from 16 surface electrodes placed according to the international 10-20 system.

Sample collection

Serum samples were collected from patients upon admission. Standard hematological and biochemical analyses of peripheral blood were also documented. Blood samples were obtained from the 40 healthy age- and sex-matched control children. The serum samples were centrifuged, and the supernatants were frozen at -70°C until assayed.

Analyzing S-100B levels

Serum S-100B protein concentrations were measured using a commercially available electrochemiluminescence immunoassay (ECLIA) kit, Roche Diagnostics (Germany) as supplied and according to the manufacturer's standards. The sensitivity of the kit was 0.005-0.105 µg/L.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 11.5 (SPSS, Chicago, IL, USA). Distribution of the samples in the groups was analyzed with one sample of Kolmogorov-Smirnov test. The data were expressed as arithmetic means and standard deviations. When the two groups are compared; the variables that showed normal distribution were evaluated using the t-test and the S-100B variable that did not show a normal distribution was evaluated via Mann-Whitney U test. Whereas, the relationship between the qualifier variables was examined using Chi-square test. $P< 0.05$ value was accepted to be statistically significant.

RESULTS

The study group consisted of 24 males and 16 females. The mean age of diagnosis of SSPE was 8.2 ± 2.3 (age range 4-13 years). A history of measles was present in 33 patients (82.5%). In seven patients, no information regarding measles could be obtained. The mean age of having measles was 19 ±15.4 months. A measles vaccination had been administered to 16 (40%) patients. The history for measles vaccination was unclear in 24 out of 40 patients. The mean duration of the latent period between having measles and SSPE was 6.3±2.4 (2.7-11.5 years).

The serum S-100B levels were 0.095±0.017 µg/L in the group of patients with SSPE and 0.097±0.019 µg/L in the control group. No statistically significant difference in S-100B levels was found between the SSPE group and control group ($P=0.692$) (Table 1). No statistically significant correlations were determined between the levels of S-100B and age of diagnosis, age of having measles, NDI, and duration of the latent period ($P>0.05$).

Brain MRI analysis revealed intensity changes in the cortico-subcortical, cortico-subcortical plus corpus callosal, and cortico-subcortical plus periventricular regions in 36 (90%), 15 (37.5%) and 14 (35%) of the subjects, respectively. Atrophy characterized by enlargement of cortical sulci was found in 12 subjects out of 40, in addition to intensity chang-

es. The group of patients with SSPE was divided into two different subgroups according to the presence of brain atrophy.

Table 1. Age, sex, body mass index and S-100B level in patient and control groups

	Patients (n=40)	Controls (n=40)	*P*-value
Age (years)	11.30±1.80*	10.91±1.80*	0.338
Sex (B/G)	24/16	22/18	0.651
BMI (kg/m²)	17.65±2.86	17.4±1.79	0.659
S-100B (µg/L)	0.095± 0.017*	0.097±0.019*	0.692

* Given as the mean ± SD, BMI: Body mass index

The S-100B levels were 0.096±0.018 µg/L in the subgroup of cases with SSPE and atrophy and 0.094±0.014 µg/L in the subgroup of cases with SSPE lacking atrophy. The NDI scores of subjects with atrophy (determined using brain MRI analysis) were significantly higher compared to subjects without atrophy (P<0.001). No statistically significant difference in S-100B levels was determined between the subgroup with atrophy and the subgroup without atrophy (P=0.299) (Table 2).

Table 2: Comparison of S-100B levels and neurological disability index scores in 40 patients with and without atrophy determined using brain MRI

	Atrophy present (n=28)	No atrophy (n=12)	*P*-value
NDI score (points)	55.2±13.0	33.8±1.0	0.001
S-100B (µg/L)	0.096±0.018*	0.094± 0.014*	0.299

* Given as the mean ± SD, NDI: Neurological disability index

DISCUSSION

Subacute sclerosing panencephalitis is a devastating disease, beginning as minor disturbances in behavior in a previously healthy child. Subsequently, myoclonic attacks develop and become increasingly more frequent. Dementia follows, and within months or a few years, the child is comatose and void of higher brain functions. Clinical findings and brain imaging methods have had great importance in the monitoring of patients diagnosed with SSPE. Even though imaging methods make significant contributions to the display of brain damage in patients, the severity of the sickness does not always coincide with the brain MRI findings.[8,9]

Studies on neurobiochemical and immunologic markers correlated with brain damage have gained interest in recent years.[4,5] Some proteins are thought of as peripheral biochemical markers of neuronal damage and glial injury or activation. According to this opinion, an available peripheral evaluation would represent a milestone for the diagnosis and follow-up of central nervous system diseases.[10]

S-100B is the most analyzed brain-derived peripheric biochemical marker in brain damage. S-100B is a low molecular weight protein mainly derived from the brain (intrathecal fraction = ~99%; CSF/serum ratio: 18:1). In healthy subjects, natural autoantibodies to S-100B of IgG class are present in serum. However, the exact source of S-100B in the blood is unknown. At normal concentrations, S-100B is able to protect hippocampal neurons against glutamate toxicity.[11] It has been demonstrated that S-100B suppresses copper-induced oxidative stress. At higher levels (micromolar), S-100B causes exacerbation of neuroinflammation, oxidative stress and neuronal apoptosis. Increases in S-100B levels may reflect the extent of glial damage or astrocytic reactions to neural injury (reactive astrogliosis).[12]

It has been found that in animal models, CSF increases rapidly due to traumatic or focal ischemic events and that in hypoxic ischaemic encephalopathy, this increase occurs prior to radiologic and clinical findings.[13,14] It has been hypothesized that high serum S-100B levels are an indicator of neuron breakdown or more likely an indicator of the regenerative activity that takes place in response to an unknown degenerative process.[5]

Recent studies indicate that oxidative damage causing an increase in reactive oxygen products plays an important role in the pathogenesis of neurodegenerative diseases such as SSPE.[15,16] In this regard, it is thought that the inflammatory reactions responsible for the pathogenesis of SSPE might be related to the biological functions of S-100B. Furthermore, the S-100B protein levels may show the neuronal damage that develops during the inflammatory process.[17]

Yuksel et al. [18] suggest that there is no difference in the CSF S-100B and Tau protein levels of newly diagnosed SSPE patients in comparison with control groups. Our findings are consistent with this study. No statistically significant relationship was determined in terms of S-100B levels of SSPE patients and control groups in our study, which aimed to examine the effect of neuron damage on system-

ic circulation in SSPE via S-100B measurements in peripheric blood.

It is known that S-100B concentrations increase in acute schizophrenia and decrease in chronic schizophreni.[19] In a study by Chaves et al. [20] on Alzheimer patients, serum S-100B levels were lower compared to healthy controls, whereas the serum S-100B levels showed no correlation with morphological changes, such as cortical atrophy determined by brain MRI. Even though it was stated in previous studies that the S-100B levels were high for acute encephalitis patients, the fact that it was determined to be normal in our study may be due to the fact that SSPE is a subacute viral encephalitis.[21]

In conclusion, even though the existence of atrophy in brain MRI findings is an indicator of neuron loss, no statistically significant difference was determined in our study between the S-100B levels of patients with atrophy and those with no atrophy development. This finding indicates that serum S-100B levels cannot be taken as a criterion for demonstrating the functional losses along with the reflection of atrophy. Even though the results obtained in this study indicate that serum S-100B levels cannot be used as a peripheral marker for the evaluation of brain damage in SSPE, the study does not conclusively demonstrate that S-100B does not contribute to the pathogenic process in SSPE. This topic can be clarified in future studies.

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