Serum S100B levels in children with simple febrile seizures

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1. Introduction

Febrile seizures (FS) are the most common convulsive disorder during childhood with a prevalence in children of approximately 3–4%. FS usually develop in children from six months to five years of age following an increase in body temperature higher than 38°C. Based on the seizure type FS are divided into simple and complex. Simple febrile seizures (SFS) are single and generalized seizures with a duration lasting less than 15 min. Complex febrile seizures are partial, or prolonged seizures that repeat within 24 h. Although the prognosis associated with FS is generally considered good, the long-term effects of FS on brain development have not yet been clearly identified, particularly its effects associated with neuronal damage and neurocognitive functions. The relationship between FS and mesial temporal sclerosis (MTS) has been one of the most contentious issues in epileptology. For instance, some evidence suggests that prolonged FS directly damage the hippocampus and surrounding structures, while other authors contend that an independent underlying pathology may be responsible for FS and development of MTS. A number of proteins have been proposed as peripheral biochemical markers of neuronal damage and glial activation including S100B and neuron specific enolase (NSE). Therefore, the concentrations of these molecules in the blood and central nervous system (CNS) may represent an important step forward in the diagnosis and monitoring of CNS diseases. S100B is a calcium binding protein found primarily in the astroglial and Schwann cells. Previous studies found that the serum S100B concentrations were elevated and associated with the severity of adverse neurologic outcome in hypoxic and traumatic brain damage as well as ischemic stroke. There are some reports on the evaluation of serum S100B concentrations in adults with epilepsy including temporal lobe epilepsy (TLE), symptomatic and idiopathic partial epilepsies, but the results are diverging.

While several studies have examined the serum NSE levels in FS, no studies have yet examined the S100B levels in FS. Therefore, the purpose of this study was to investigate whether SFS affects the serum concentration of S100B.

2. Methods

The present study included thirty-nine children with SFS and sixty control subjects who were admitted to the pediatric emergency department of our hospital between September 2009 and March 2010. Children were defined as febrile seizure patients...
if seizures occurred during fever with an axillary temperature of 38 °C or higher. Simple febrile seizures were defined as generalized tonic, tonic–clonic or atonic activity without focal features, shorter than 15 min duration without recurrence subsequent 24 h. All the patients were admitted to our emergency room within 30 min after the initiation of febrile seizure. Intracranial infections were excluded by clinical or laboratory findings, and lumbar punctures were performed in 24 of 39 patients. All patients were followed in the emergency room for at least 24 h. The control group was composed of 30 patients who had a fever without a seizure (control a) and 30 healthy subjects (control b). Both groups were age- and sex-matched according to the study group. The exclusion criteria for this study included children who had evidence of history of febrile seizures, metabolic diseases, developmental retardation, and head trauma or a febrile seizure three days prior to admission. This study was approved by the Ethics Committee of Baskent University, and informed consent was obtained from all patients’ legal guardians before patient enrolment in the study.

Two serum samples were obtained for S100B from study group at 0–1 h (0.7 ± 0.12) and 6–24 h (9 ± 0.4) following seizure. Serum samples were drawn once in the control groups. All the blood samples were centrifuged for 10 min at 3000 rpm, and the serum was frozen at −80 °C until the assays were performed. S100B (Headquarters BioVendor Medical, Germany) specimens were analyzed using a human S100B Enzyme-linked Immuno Sorbent Assay (ELISA). Serum S100B concentration is expressed as pg/ml (mean ± SD), and we found that 95% of healthy individuals displayed serum S100B levels lower than 50 pg/ml.

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Levene test was used to analyze variance homogeneity. Mann–Whitney’s U test was used to compare two independent groups. Wilcoxon test was employed to compare two independent groups, and Kruskal–Wallis was used to compare groups containing more than two independent groups. Spearman correlation coefficients were also calculated to examine bivariate relationships, and the correlation between biochemical parameters and S100B concentrations of the study groups was conducted using Spearman’s coefficient. For the two-way analysis, Pearson chi-square test, probability ratio test or Fisher’s Exact test were used. A P-value less than 0.05 was deemed significant.

3. Results

Our study included 39 children (17 males, 22 females) with simple febrile seizure, and the controls included 30 children (13 males, 17 females) in control group a and 30 children (13 males, 17 females) in control group b. The age of the subjects in this study ranged from 6 to 36 months (17.4 ± 7.3 months) in the study group, 6 to 36 months (17.9 ± 9.4 months) in control group a, and 6 to 37 months (17.1 ± 9.8 months) in the control group b. No statistically significant difference was detected between the groups for sex or age (Table 1).

Table 1 shows serum S100B levels in study group and control groups. No significant differences were observed between the mean S100B serum concentrations at 0–1 h (32.6 ± 7.8 pg/ml) and 6–24 h (32.1 ± 5.8 pg/ml) in the study group. In addition, no significant differences were found in serum S100B concentrations between the study group, control group a (32.1 ± 8.8 pg/ml) and control group b (29.5 ± 7.8 pg/ml).

The frequency and duration of febrile convulsion were as follows: 1 min (1 patient), 2 min (4 patients), 3 min (4 patients), 5 min (19 patients), and 10 min (11 patients). No correlation was detected between the duration of febrile seizures and S100B concentrations (P = 0.605, rho: −0.085). When the children were divided into two groups according to the duration of F5 (seizure duration 5 min or shorter versus seizure duration longer than 5 min), the serum S100B concentrations between the groups were similar (31.9 ± 8.6 pg/ml and 32.1 ± 1.7 pg/ml, respectively). Finally, S100B concentrations were not correlated with age and sex.

4. Discussion

S100B is a cytokine produced and released predominantly by astrocytes in the CNS.5 In previous studies, elevated S100B concentrations were associated with various neurological diseases, such as minor and severe head injury, subarachnoid hemorrhage, cerebral infarction, neurodegenerative processes and CNS infections.9,13,14 In addition, animal models of epilepsy and postsurgery brain specimens from epileptic patients also showed elevated brain tissue S100B concentrations.15,16 However, there are only a limited number of studies examining serum S100B concentrations in patients with epilepsy. For example, Portela et al found normal serum S100B levels in patients with focal epilepsy,15 while Lu et al. reported elevated plasma S100B concentrations in patients with TLE when compared with controls.11 In our study, we found no significant elevation of serum S100B concentrations in patients with SFS.

The association between febrile seizures and TLE is a controversial topic. Some retrospective studies confirm such a link between febrile seizures and TLE,6 while other studies indicate that no link exists between the diseases.17 For example, Lu et al. showed elevated serum S100B concentrations in twenty-eight TLE patients when compared to healthy controls. However, febrile seizure history data was not analyzed in this study. Therefore, prospective studies that investigate serum S100B concentrations in TLE patients with or without febrile seizures may help interpret these findings.

The peak S100B levels have been reported within the first 24 h in hypoxic brain damage after traumatic brain injury.9 In the present study, we measured S100B concentrations at 0–1 h to serve as a baseline and at 6–24 h to detect a possible delayed posts-eizure elevation.

Neuron-specific enolase is another biochemical marker of neuronal damage. Elevated rates of NSE have been demonstrated in different neurologic insults such as anoxia, stroke and epilepsy.
In a study, an increase in NSE (serum and CSF) values at different time points after FS have not been shown. However, Tanabe et al. found that both the NSE level in the CSF and the ratio of the CSF to serum NSE levels showed strong correlations with seizure duration in patients with complex febrile seizures. To our knowledge, the present study is the first detailed study examining serum S100B concentrations after onset of febrile seizures.

In prior studies, it was shown that the blood–CSF barrier does not affect the passage of S100B from the CSF to serum. While plasma S100B levels reflect CSF S100B levels, we did not measure CSF S100B levels due to ethical reasons in the present study.

Although S100B is highly brain specific and the highest concentrations of S100B are found in astroglia and Schwann cells, low concentrations can be found in neuroectodermal and mesodermal tissues outside the CNS. Routsi et al. found increased levels of serum S100B in critically ill patients without brain injury. In addition to healthy volunteers, our study included patients with fever who served as a control group in order to exclude the possibility of effect of fever on release of S100B from CNS or other tissues.

One limitation of our study is the lack of inclusion regarding the patients with complex febrile seizures and febrile status. de Oliveira et al. showed elevated CSF S100B levels 24 h after pilocarpine-induced status epilepticus in rats. In addition, complex febrile seizures have shown to be a risk factor for developing epilepsy, and patients with prolonged febrile seizures and febrile status are included in most of the studies which examine the effect of febrile seizures on the hippocampus. Our study found similar serum S100B levels in children who had seizures 5 min or less versus longer than 5 min, and these results suggest that the seizure duration does not affect the S100B levels in SFS.

In conclusion, the present results show that SFS is not associated with elevated serum S100B concentration. This finding suggests that SFS does not cause astroglial activation; however, no other studies have measured serum S100B in patients with febrile seizures. Therefore, further studies on this subject are required to assess S100B levels comparing simple and complex febrile seizures.

References