International Journal of Children and Adolescents

Brief Communication
IJCA, Vol. 4, No. 1, Feb. 2018.1-6.

The value of serum level of S100B protein in predicting brain edema in children with diabetes ketoacidosis

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Received: 9 Mar 2017 Accepted: 19 Dec 2017

Abstract

Background and Objective: The S100B protein has recently been considered as an important marker for predicting severe brain damage; however, there has been very little evidence of increasing this marker in cerebral edema due to metabolic disorders such as diabetes ketoacidosis (DKA). This study was designed and performed to evaluate the prognostic role of S100B protein in predicting brain edema in children with DKA.

Methods: This case-control study was performed on children aged 22 months to 13 years who suffering moderate to severe DKA that were admitted to intensive care unit. A venous blood sample was taken from the patients during the first 6 hours of admission to the intensive care units. Based on the evidences of brain edema requiring manitol infusion, the patients were divided into 2 groups including the patients with brain edema as the cases and those without this problem as the controls. The serum level of S100B protein was measured by ELISA technique in both groups.

Results: The mean serum level of S100B in the groups with and without brain edema was 1.07±1.15 and 0.67±0.99, respectively with no difference (p= 0.437). Based on the multivariable linear regression modeling, the presence of brain edema was not associated with the level of S100B. According to the ROC curve analysis S100B (AUC= 0.506, P= 0.967) could not predict the occurrence of brain edema children with DKA.

Conclusion: the increase in the serum level of S100B may not predict the likelihood of brain edema in children with DKA.

Keywords: Diabetes ketoacidosis, S100B, Brain edema, Child

Cite this article as: Mirboluk A, Afsharkhas L, Haghighi-Aski B, Moradkhani-Zadeh M, Fattaneh Babaei F. The value of serum level of S100B protein in predicting brain edema in children with diabetes ketoacidosis. *Int J Child Adolescent. 2018*(10 Feb);4(1):1-6.

Background

Diabetes mellitus is an annoying disease caused by insulin dysfunction that causes a reversible or rarely irreversible problem in metabolizing carbohydrates, fat or protein (1). The most common cause of hospitalization for children with type 1 diabetes is diabetic ketoacidosis (DKA), which is also a major cause of death from diabetes (2). Metabolic disorders related to DKA can damage the growing brain of children, and this is shown by electrophysiological studies. There are a number of biochemical markers that indicate neuronal damage and the activation of glial cells in the central nervous system (CNS), and the S100B protein is a component of these molecules (3,4). The S100B protein is a cytokine that is highly found in astrocytes of the CNS (5). This protein increases in several neurological diseases such as head trauma, hypoxia, subarachnoid hemorrhage, cerebral infarction, neurodegenerative disorders and CNS infections (5,6). In epileptic animal models as well as after brain surgery, S100 protein levels rise in brain tissue (7). S100 family proteins are a group of low molecular weight proteins that are found in vertebrates and have two levels of EF-hand bonding to

calcium. There are at least 21 different S100 proteins that are naturally found in nerve stem cells, chondrocytes and adipocytes, macrophage, dendritic cells, and in some cases of epithelial cells of the breast tissue (8). S100 proteins play a role in regulating protein phosphorylation, transcription factor, calcium ion homeostasis, cytoskeleton dynamics, enzymatic activity, growth and cellular differentiation, and inflammatory response (9). A number of S100 members are used as tumor markers of some tumors and found in melanomas (10). The increase in this marker can be revealed in 100% of cases with Schwannoma and Neurofibroma and also in 50% of the peripheral neuronal tumors (11). From the family of such protein, S100B is a protein bound to calcium-binding protein that is found primarily in Astroglial and Schwann cells (12). In some studies, protein S100B has been suggested as a useful marker for predicting post-traumatic brain injury (13). In cases with temporal lobe epilepsy, and partial or idiopathic epilepsies, the serum level of S100B might be considerably increased that can be considered as an important marker for neuronal damages (14). In this regard, few studies have been conducted on the relationship between this protein and brain edema due to DKA in children (15). Hence, the present study aimed to assess the value of S100B in predicting DKA-related brain edema in children and also to determine the compliance of S100B level with clinical and laboratory findings.

Materials and Methods

This case-control study was performed on children aged 22 months to 13 years who suffering moderate to severe DKA that were admitted to intensive care unit in Ali-e-Asghar hospital in Tehran between January 2016 and November 2017. The exclusion criteria were sepsis, meningitis, cerebral hemorrhage, or the presence of proven malignancy. The data needed for the study included age, sex, weight, clinical signs (such as level of consciousness, seizure, etc.), blood glucose levels, venous blood gas, and brain imaging findings (such as brain edema) were extracted from the hospital recorded files and then recorded in the study checklist. A venous blood sample was taken from the patients during the first 6 hours of admission to the PICU and sent to the reference laboratory to determine the level of S100B protein.

No clinical criteria or tests can accurately diagnose cerebral edema in early stages when it is still reversible. Nonetheless, we suggest using the following factors to determine a clinical suspicion and make a treatment decision:

- Minor criteria: (moderately suspicious findings); Headache (especially if this develops or recurs during treatment), Vomiting (if this develops or recurs during treatment), Irritability, lethargy or not easily aroused from (in not readily explained by a history of sleep deprivation), particularly if the onset is after initiation of therapy, Elevated blood pressure (e.g., diastolic BP>90mmHg).
- Major criteria: (very suspicious findings); Abnormal or deteriorating mental status after initiation of therapy, Agitated behavior or fluctuating level of consciousness, Incontinence inappropriate for age, Changes in pupillary response for other clinical nerve pasy-Key steps are to evaluate extraocular movements (cranial nerve [CN] III, IV, VI) and pupillary dilation and reactivity (CN II and III), Inappropriate slowing of heart rate (eg, decline more than 20 beats per minute that is not attributable to improved intravascular volume or sleep state, Rapidly rising serum sodium concentration (suggests a loss of urinary free water as a manifestation of diabetes insipidus, Decreased oxygen saturation, Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneustic breathing).

These major criteria are generally late findings in the course of cerebral edema and suggest neurologic damage that is often irreversible. Treatment should be initiated as soon as cerebral edema is diagnosed or strongly suspected, based on the clinical criteria listed above, rather than relying on findings from computerized tomography (CT) of the head. This is because performing a head CT might delay initiation of therapy, and because the CT results add little to clinical decision-making. Over changes detectable by head CT occur late in the development of cerebral edema, and many children who do not develop clinical cerebral edema may have reduced ventricular volume which returns to normal as the DKA resolves.

Therefore, according to clinical criteria (special changes in mental or neurologic status) the patients were divided into 2 groups including the patients with brain edema (as the case) and those without brain edema (as the controls). Because of the lack of brain CT scanning services in our center, we could not employ this service for confirming brain edema in our participants. The serum level of S100B protein was measured by ELISA technique in both groups.

Results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was an-

alyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann U test. The value of differentiating brain edema from normal condition was assessed by the ROC curve analysis. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In total 20 children suffered from DKA (5 boys and 15 girls, mean age 8.87±3.74 years ranged 22 months to 13 years) were included into the study, according to imaging results, 6 cases (30.0%) had evidences of brain edema needing for mannitol administration. As shown in Table 1, there was no difference between the two groups with and without brain edema in gender, mean age, average weight, clinical manifestations (including nausea and vomiting, abdominal pain, malaise, loss of consciousness, polyuria, polydipsia, sleepiness, and headache), and also laboratory indices (including blood sugar, arterial PH, and HCO3 concentration). No difference was also found in the mean duration of DKA control and also in the frequency of new onset diabetes mellitus. The mean serum level of S100B in the groups with and without brain edema was 1.07±1.15 and 0.67±0.99 respectively with no difference (p= 0.437). There was also no meaningful difference in the serum level of IL-6 marker across the two groups (6.78±5.96 versus 9.14±6.40, p= 0.834). Based on the multivariable linear regression modeling with the presence of baseline variables (Tables 2 and 3), the presence of brain edema was not associated with the level of S100B or with the concentration of serum IL-6. According to the ROC curve analysis (Figure 1 and 2), neither S100B (AUC= 0.506, P= 0.967) nor IL-6 (AUC= 0.655, P= 0.284) could predict the occurrence of brain edema children with DKA.

Discussion

As already mentioned, the S100B protein has recently been considered as an important marker for predicting severe brain damage. The S100B protein is released by damaged astrocytes. After passing through the blood-brain barrier, this molecule will be detectable in circulation. Various studies have indicated the potential role of this substance as a peripheral biomarker of neurological damage including reactive gliosis, astrocytic death, or dysfunction of the blood-brain barrier. The increase in serum or cerebrospinal fluid levels of this protein in acute or chronic severe neurological damages such as in traumatic brain injury, tonic colonic seizures, stroke, Alzheimer's disease, schizophrenia; myopathies and SLE are quite predictable. But so far, there has been very little evidence of increasing this marker in other neurological disorders such as cerebral edema. This study was designed and performed to evaluate the prognostic role of this marker in predicting cerebral edema in children with DKA. In this regard, serum levels of S100B and the same level of inflammatory factor IL-6

Table 1. Baseline characteristics in children with and without brain edema due to DKA

Item	With brain edema	Without brain edema	P value
Male gender	33.3%	21.4%	0.613
Mean age, year	10.00 ± 3.52	8.39 ± 3.85	0.393
Mean weight, kg	26.67 ± 11.24	31.57 ± 16.69	0.802
Clinical symptoms			
Nausea, vomiting	66.7%	57.1%	0.999
Abdominal pain	16.7%	42.9%	0.354
Malaise	33.3%	28.6%	0.999
Loss of consciousness	16.7%	0.0%	0.300
Polyuria	33.3%	35.7%	0.999
Polydipsia	33.3%	50.0%	0.642
Sleepiness	16.7%	0.0%	0.300
Headache	16.7%	14.3%	0.999
Laboratory indices			
Blood sugar	423.33 ± 130.64	474.93 ± 98.81	0.343
PH	6.96 ± 0.13	7.06 ± 0.10	0.099
HCO3	5.28 ± 2.60	5.65 ± 2.31	0.757
Duration of DKA control, month	22.00 ± 6.33	21.07 ± 10.85	0.848
New onset diabetes mellitus	50.0%	50.0%	1.000

simultaneously were measured and compared in two groups of children with DKA with and without cerebral edema. The first point was that a significant number of children (including one third of children) with DKA suffered brain edema. According to numerous studies, the general incidence of brain edema among children with DKA is about 1%, which is far lower than the incidence obtained in our study. The reason for the significant increase in our study was that our community was mainly focused on children with DKA who needed hospitalization and management in specialized care units. However, in some studies, high incidence of cerebrospinal edema in children with DKA was reported. In a study by Tiwari et al (16), children with a mean age of 5.6 years were evaluated with an incidence of 26% for brain that was close to our study. In another study by Lawrence et al (17), the prevalence of cerebral edema associated with DKA was shown to be 19%. In the study of Jayashree et al (18), the incidence of cerebral edema was 13.2%.

Another finding in our study was that there was no difference between the two groups with and without cerebral edema in terms of early indices such as gender, age, laboratory indices and duration of DKA control. In the study of Tiwari et al (16), The sex, gender, or weight of patients did not predict the occurrence of cerebral edema that was consistent with our study. In Glaser et al study (19), the two factors related to the incidence of cerebral edema included PCO2 and serum BUN levels, but gender, age, or weight of children had not been found to reveal any relationship with cerebral edema. In the study by Lawrence et al (17), the occurrence of brain edema was associated with an increase in BUN or HCO3 levels. First, it can be concluded that the incidence of cerebrospinal edema is quite different based on the severity of the DKA disease or its initial control, and can be as high as 30% or even more. Second, the most important risk factors for cerebral edema in children with DKA include increase in serum urea and PCO2 and possibly HCO3 disturbances and therefore, demographic or anthropometric properties will not play a role in the incidence of cerebral edema.

But the important point in our study was the lack of correlation between the two S100B and IL-6 indices with the occurrence of brain edema in children with DKA. In other words, the assessment of the above-mentioned two markers was not able to predict cerebral edema. Few studies have been conducted on the relationship between the level of S100B and the incidence of cerebral edema in such patients. In the study of Glaser et al in 2015 (19), compared with normal or hyperglycemic mice, serum levels of S100B during DKA periods were significantly reduced. After DKA, the S100B gradually increased and returned to the hyperglycemic level within 72 hours. In the study of Kaya et al (20), in 2015, the S100B value in diabetic patients with DKA was significantly higher than that of the control group, but before the treatment, there was no difference between the two groups in terms of S100B. In a study by Wolf et al 2015 (21), S100B

Table 2. Multivariable linear regression analysis to assess relation between S100B level and brain edema

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
Constant	-12.017	21.332		-.563	.585
Brain edema	-.320	.771	-.146	-.415	.686
Sex	.446	.613	.192	.727	.482
Age	.055	.147	.199	.373	.716
weight	-.031	.037	-.447	-.824	.427
BE	-.002	.003	-.181	-.551	.592
PH	2.150	3.135	.247	.686	.507
HCO3	-.268	.156	-.608	-1.715	.114
Time control	.009	.030	.083	.299	.771

Table 3. Multivariable linear regression analysis to assess relation between IL-6 level and brain edema

	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
Constant	-647.879	391.428		-1.655	.126
Brain edema	-17.648	14.147	-.376	-1.248	.238
Sex	-6.066	11.252	-.122	-.539	.601
Age	-4.445	2.697	-.753	-1.648	.127
weight	.662	.684	.449	.968	.354
BE	.095	.057	.468	1.665	.124
PH	103.822	57.528	.555	1.805	.099
HCO3	-8.217	2.864	-.870	-2.869	.015
Time control	-.573	.548	-.248	-1.045	.318

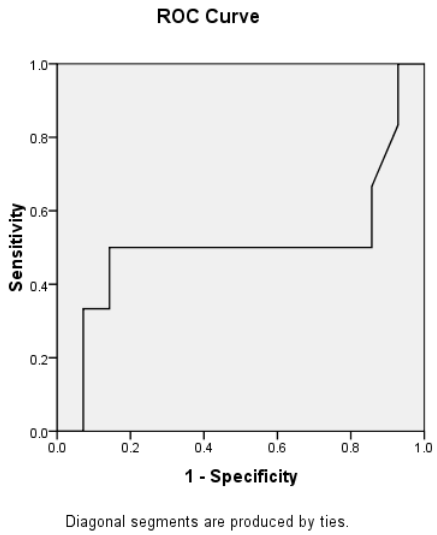

Figure 1. The ROC curve analysis to determine the predictive role of S100B for brain edema

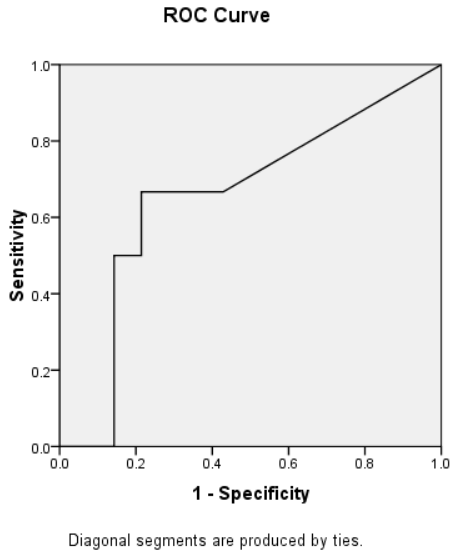

Figure 2. The ROC curve analysis to determine the predictive role of IL-6 for brain edema

levels were significantly different between patients with brain edema. This increase was higher in older people than in younger ones. In a study by Tanaka et al (22), a transient increase in serum level of S100B was found within 6 hours after intracranial hemorrhage in mice. The serum level of S100B was directly related to the induction of intracranial hemorrhage during the first 6 hours as well as with faster formation of brain edema and also with the volume of hematoma. By comparing our results with other studies, the most important issue in assessing the level of S100B in patients at risk for cerebral edema is the measurement time of this index so that no significant is in the level of S100B in the early stages of the disorder or after treatment compared to patients with non-edema. In our study, the S100B level was evaluated early in the onset of the disorder or after initiation of treatment with mannitol, suggesting no difference in S100B levels between the two groups with and without brain edema.

Conclusion

In this study, brain edema was seen in about one-third of children with DKA that was significantly more than literature reports. In our study, serum S100B levels in patients with brain edema was higher than control group but p value did not show significant difference and it may be due to small sample size. Consequently, it is recommended to implement further studies with larger sample sizes and multiple sampling for detection of serum S100B during treatment.

Conflicts of interest: None declared.

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