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Inability of S100B to Predict Post-Concussion Syndrome in Children who Present to the Emergency Department with Mild Traumatic Brain Injury: A Brief Report

Lynn Babcock, MD, MS [Associate Professor],

Division of Pediatric Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 2008, Cincinnati, OH 45229, (513) 803-2956 (phone), (513) 636-7967 (fax), lynn.babcock@cchmc.org, Formerly at: University of Rochester Medical Center, Department of Emergency Medicine, 601 Elmwood Avenue, Box 655, Rochester, NY 14642

Terri Byczkowski, PhD [Assistant Professor],

Division of Pediatric Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 2008, Cincinnati, OH 45229, (513) 636-0191 (phone), (513) 636-7967 (fax), terri.byczkowski@cchmc.org

Shari L Wade, PhD [Research Professor],

Division of Physical Medicine and Rehabilitation, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 4009, Cincinnati, OH 45229, (513) 636-3370 (phone), 513-636-7360 (fax), shari.wade@cchmc.org

Mona Ho, MS [Senior Research Assistant], and

Division of Pediatric Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 2008, Cincinnati, OH 45229, (513) 803-2637 (phone), (513) 636-7967 (fax), mona.ho@cchmc.org

Jeffrey J Bazarian, MD, MPH [Associate Professor]

Department of Emergency Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Box 655, Rochester, NY 14642, (585) 463-2928 (phone), (585) 463-2969 (fax), jeff_bazarian@urmc.rochester.edu

Introduction

Mild traumatic brain injuries (mTBI) are one of the most common childhood injuries evaluated by clinicians in emergency departments (EDs) within the United States.^{1,2} 10–30% of children who sustain mTBI develop a cluster of cognitive, physical, and emotional symptoms, commonly referred to as post-concussion syndrome (PCS).^{3–7} The duration of symptoms is highly variable; however, the presence of at least 3 symptoms at 3 months is required to meet the diagnostic criteria for PCS outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.⁸ Currently, there is no reliable tool that can be administered at the time of injury to predict development of PCS. ED evaluation for children focuses on symptoms that may predict an abnormal computed tomography (CT)

Corresponding Author: Lynn Babcock, MD, MS, Associate Professor, Division of Pediatric Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML 2008, (513) 803 2956 (phone), (513) 636 7967 (fax), lynn.babcock@cchmc.org.

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scan, yet the cranial CT is normal in the majority of patients with mTBI.⁹ These children are subsequently discharged from the ED without any information about their likelihood of developing PCS. A biomarker that assists with recognition of those at risk of developing PCS would be helpful in discharge planning and follow-up.

Forces that lead to TBI cause axonal stretch which results in axonal microtubule deconstruction, axotomy and loss of neuronal function.¹⁰ Recently, CNS-specific proteins that are released after brain injury, cross the blood-brain barrier (which is temporarily 'leaky' after TBI), and can be measured in the serum have been identified.¹² The most promising of these markers appears to be S100B, a calcium-channel binding protein that is highly expressed in the astroglial cells of brain tissue. It has minimal concentrations in other cells and is metabolized and excreted through the kidneys.¹² S100B has been found to be elevated following mild to severe TBI.^{11–15} Studies in adults have shown that transient serum elevations of these markers after mTBI correlate with abnormal cranial CT with 90%–100% sensitivity and 40–65% specificity.^{11–14} These results have prompted the use of S100B as a screening tool to assist with the decision of acquiring a cranial CT in EDs in Europe. In children with mTBI, S100B there are conflicting reports as to the diagnostic value of S100B and its ability to predict abnormal cranial CT, particularly for those with mTBI.^{15–21} There is little published literature about the prognostic value of S100B to predict outcomes in children with mTBI^{22–24}, and no studies using a measure specific for PCS.

A biomarker of TBI would be useful if it could predict the extent of injury, as well as the development of PCS. Using a convenience sample from a larger cohort study of children enrolled from the ED with mTBI, we explored the ability of the serum marker S100B to predict PCS at 3 months in children following mTBI.

Materials and Methods

This was a secondary analysis of a larger prospective cohort of consecutive TBI patients who participated in a NIH-funded TBI registry study.²⁵ The original cohort was recruited at the University of Rochester Medical Center EDs (Pediatric and Adult) between January, 2003 and September, 2004. Patients were eligible if they met the case definition of mTBI developed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine – a blow to the head or acceleration/deceleration movement of the head resulting in one or more of the following: loss of consciousness (LOC) <30 minutes, amnesia <24 hours or any alteration in mental state and a Glasgow Coma Scale (GCS) of 11–13 measured 30 minutes or more after injury.²⁶ A convenience sample of participants was approached to have blood drawn for serum marker analysis. This study cohort was limited to children who completed follow-up, could verbally communicate (ages 5 to 18 years), and had blood drawn for S100B. The Research Subject Review Board at the University of Rochester approved the parent study and all secondary analyses. The Institutional Review Board at Cincinnati Children's Hospital Medical Center exempted this analysis from review.

Participants were identified by research assistants using information provided by ED staff or extracted from the registration log and chief complaint in the chart. The attending emergency physician confirmed the presence of mTBI. Research assistants collected clinically relevant information from the participants and/or parent/guardian before ED discharge. Data abstracted directly from the patient/parent/guardian included demographics, history of prior TBI, mechanism of injury, and clinical signs and symptoms of TBI (LOC, amnesia, alteration of mental status, nausea/vomiting, headache, Glasgow Coma Scale). It should be noted that patient reported responses for these symptoms were categorical (yes, no, unsure) and the "yes" and "unsure" responses were combined for this analysis. Data abstracted from the chart included results of neuroimaging (if performed), ED medication

administration, receipt of injury specific discharge instructions, referrals and disposition. Severe mechanism of injury was classified using the definition of Kuppermann et al which included any of the following: motor vehicle collision, a pedestrian struck by a motor vehicle, a bicyclist without a helmet or a fall ≥ 3 feet.^{9,27} Other diagnoses were determined by a post-hoc review of billing charts for non-TBI ICD-9 codes. An abnormal cranial CT was defined by the presence of any intracranial injury as well as the presence of skull fractures.

Because S-100B levels peak and then normalize within 6 hours of TBI, participants presenting more than 6 hours after injury were not eligible. Patients with preexisting medical or psychiatric conditions known to be associated with an elevated S-100B level in the absence of TBI were excluded.^{28–30} Among those consenting, four milliliters of venous blood was drawn and centrifuged at 3000 rpm for 10 minutes at room temperature. The resulting serum was held in a freezer at -20°C . After additional funding was secured in the fall of 2007, samples were analyzed for S100B with an enzyme immunoassay test kit (Nanogen, San Diego, CA) using a Microplate Reader Model 550 (Biorad, Hercules, CA). The concentration of S-100B protein in the samples was determined by measuring the absorbance of the samples at 450nm.

Three months after the initial visit, participants or parents/guardians were interviewed by telephone about their PCS symptoms using the Rivermead Postconcussive Questionnaire (RPQ). Interviewers were blinded to the details of the initial ED presentation. The RPQ is a commonly used measure to assess 16 PCS symptoms – headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, and double vision and restlessness.³¹ Participants or their parents/guardians rated the severity of each of 16 symptoms over the past 24 hours on a scale from 0 to 4 relative to its severity prior to injury: absent (0), same (1), mild (2), moderate (3), or severe (4). The total RPQ score is a sum of 16 individual symptom ratings, which reflects the severity of PCS symptoms. We further defined the development of PCS at 3 months as the presence of 3 or more symptoms on the RPQ that rated as worse (scale of 2 or more) than at pre-injury which is in keeping with the DSM-IV definition of PCS.

Data Analysis

Comparisons of variables between those that had S100B levels drawn who followed up and those who did not have S100B levels and/or lost to follow-up were made using chi square tests for categorical data and t-tests for continuous data. Frequencies of all the variables were computed for the cohort of children who had both S100B levels drawn in the ED and completed the follow-up. We defined our outcome of interest, PCS, in two ways: (1) a dichotomized variable – presence of PCS (3 or more symptoms rated 2 or more), and (2) a continuous variable – total RPQ score. Both S100B and total RPQ scores had non-normal distributions. Using the dichotomized outcome, the non-parametric Kruskal-Wallis test was used to assess the differences between the distribution of the S100B values score among patients with and without PCS. In addition, bivariate logistic regression was used to determine the ability of S100B injury to predict PCS. The area under the receiver operating characteristic (ROC) curve for S100B was also used to determine the ability of S100B levels to predict the development of PCS at 3 months. We used non-parametric Spearman's rank-order correlation to assess the relationship between the severity of PCS, assessed as a continuous variable, and initial S100B measured in the ED. An *a priori* significance level of 0.05 was used for all statistical tests. Data analysis was performed in SAS^R 9.22 (Cary, NC).

Results

A total of 481 children > 5 years were enrolled in the ED during the initial cohort study. Of these, 89 children had S100B levels measured and 406 completed the three month follow-up, resulting in 76 children who had both S100B and completed the follow-up. Further details about this initial cohort are reported elsewhere.^{15,32} Characteristics of the cohort of 76 children are presented in Table 1. Comparisons between these 76 children and those who did not complete the follow-up and/or have blood drawn in the ED (n=405) showed that children within this study cohort were more likely to be older (mean 14.0 vs. 13.1 years, $p=0.03$), injured by a severe mechanism of injury (52.6 vs. 37.0%, $p=0.01$), arrive by EMS (73.7 vs. 50.4%, $p<0.01$), present with a lower GCS of 13 or 14 (10.5 vs. 4.0%, $p=0.04$), have other mental status changes (97.4 vs. 90.4%, $p=0.04$), have CT performed in ED (72.4 vs. 51.4, $p<0.01$), have other diagnoses (82.9 vs. 65.4%, $p<0.01$), receive analgesics in the ED (72.4 vs. 53.1%, $p<0.01$), and be admitted to the hospital (23.7 vs. 8.7 %, $p<0.01$). There were no other statistically significant differences in the variables assessed between the two groups.

Of the 76 children, there were 28 (36.8%) who developed PCS. For the children who developed PCS, the mean S100B level was 0.092 $\mu\text{g/L}$ (SD=0.376) and the median was 0.008 $\mu\text{g/L}$ (range of 0 to 2.00). For children who did not develop PCS (n=48), the mean S100B level was 0.022 $\mu\text{g/L}$ (SD=0.3756) and the median was 0.012 $\mu\text{g/L}$ (range of 0 to 0.141). The area under the ROC curve was 0.47 indicating the inability of S100B to discriminate between those who will develop PCS and those that will not. In addition, the non-parametric Kruskal-Wallis and Spearman's rank-order correlation tests did not support an association between S100B and the development of PCS symptoms at 3 months post injury. It should be noted that in the group with PCS there was an S100B value of 2.0, which is an outlier. A repeated analysis without this value provided similar results of not supporting a relationship between S100B and the development of PCS symptoms.

Conclusions

An ideal biomarker for children with mTBI measured in the ED at the time of injury would correlate with the severity of injury and predict those who will have persistent symptoms. In this small convenience sample, S100B, the most widely studied biomarker for TBI, did not predict PCS in children with mTBI who presented to the ED within 6 hours of injury. This adds to the body of conflicting literature about the usefulness of this marker for evaluation of children with mTBI.

Investigators have found that S100B is elevated after TBI and can discriminate between children with TBI and controls.^{33,34} Using 109 children extracted from the larger cohort who had both a cranial CT obtained and serum S100B levels measured, we found that this biomarker did correlate with the severity of TBI. However, we also found that S100B was not useful in predicting intracranial injuries detected on CT in children with mTBI who had a GCS of 15. Similarly, Geyer et al, demonstrated that initial levels of S100B did not discriminate between symptomatic (GCS 13–15 and clinical symptoms) and asymptomatic (contusion only and no clinical symptoms) children who had sustained a blunt trauma to the head.¹⁶ On the other hand, Castellani et al, did find significantly higher S100B levels in children with mTBI who had abnormal cranial CTs as compared to those with normal CT.¹⁷ More importantly, they found an absence of intracranial injuries on cranial CT in children with mTBI who had a normal S100B level (negative predictive value 1.0). Small samples sizes combined with influences of age and extracranial sources on S100B concentrations limit the conclusions about the usefulness of S100B in children with mTBI.²¹ In adults, S100B has been shown to correlate with abnormal CT findings for adults with

mTBI.^{11,12,14,35} As such, investigations are currently underway evaluating the predictive ability of current neuroimaging decision rules in combination with S100B to detect intracranial injuries on CT. Perhaps similar studies in children would further our understanding of the role of S100B in the diagnostic evaluation of children with mTBI.

In children, most of the literature suggests a relationship between higher levels of S100B and poor outcomes for children moderate and severe TBI; however, there is at least one study that did not report any association.^{6,36–39} A few of these studies included children with mTBI, yet none of them addressed the prognostic value of S100B solely in this population, nor did they use a measure designed to detect PCS^{22–24} Furthermore, these studies are limited by small sample sizes, variations in patient selection and time of S100B measurement, as well as differences in outcome measurement. In adults with mTBI, the ability of S100B to predict PCS has not been consistently demonstrated; however, most reports indicate an association.^{36–38} In our study, we failed to find an association between S100B levels and PCS for children with mTBI.

Although this study has the largest reported sample of children with mTBI, S100B levels, and a PCS outcome measurement, it is underpowered to draw conclusions about the clinical utility of S100B in predicting outcome by itself or in combination with other signs and symptom of TBI. A post-hoc power analysis showed that the probability of concluding there is no difference in S100B values between the two groups (with and without PCS symptoms) when, in fact, one exists (false negative) was greater than 70%. However, it is noteworthy that we failed to find any association despite a bias toward children with more severe initial injuries. The lack of association may be due to the calculation of outcome (PCS) with only one tool (RPQ) and at one time-point which does not provide an assessment of other neurocognitive domains affected by mTBI. Recall bias of severity of symptoms prior to injury may have affected scoring on the RPQ. Lastly, despite the use of the RPQ as a measure of PCS in children and over the phone, it has not been validated to be used in this manner.^{31,39,40} It was originally used in adults via in-person administration.^{31,41}

The results highlight the need for further research to uncover a biomarker, or a panel of biomarkers, that can assist with the diagnosis and prognostic modeling for children with mTBI. Further research should also investigate the optimal combination of biomarkers with signs and symptoms on presentation in predicting which children are at greatest risk of poor outcomes following discharge. Risk stratification of this population will help with the selection of those in need of additional interventions after ED evaluation.

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Table 1

Characteristics of the children with mTBI who had S100B measured within 6 hours of injury and completed the 3 month follow-up

Variable	Study Cohort n=76
Demographics	
Age (mean years $\pm$ SD)	14.0 $\pm$ 3.1
Adolescents (11–18 years, %)	86.8
Gender (% male)	60.5
Race (% white)	88.2
Ethnicity (% non - Hispanic)	94.5
Insurance (% public/self)	27.6
Prior TBI (% yes)	31.6
Severe MOI (% yes)	52.6
Mode of Arrival (% EMS)	73.7
Other Diagnoses (% yes)	82.9
ED Variables	
GCS < 15 (% yes)	10.5
LOC (% yes)	59.2
Headache (% yes)	74.7
Amnesia (% yes)	45.3
Nausea/Vomiting (% yes)	42.7
Other MS Changes (% yes)	97.4
CT in ED (% performed)	72.4
Abnormal CT (% abnormal)	4.0
Analgesics in ED (% yes)	72.4
Mild TBI D/C Instructions (% yes)	56.9
Disposition (% admitted)	23.7