Acute S100B in serum is associated with cognitive symptoms and memory performance four months after paediatric mild traumatic brain injury

Key words: paediatric mild traumatic brain injury, biomarker S100B serum, post-concussive symptoms, neuropsychological outcome

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Abstract

Objective: This study explored whether acute serum marker S100B is related with post-concussive symptoms (PCS) and neuropsychological performance four months after paediatric mild traumatic brain injury (mTBI).

Research Design and methods: In a prospective short-term longitudinal study, we investigated children (age 6-16 years) with mTBI (n=36, 16 males) and children with orthopaedic injuries (OI, n=27, 18 males) as control group. S100B in serum was measured during the acute phase and was correlated with parent-rated PCS and neuropsychological performance four months after the injury.

Main outcomes and results: Our results revealed no between-group difference regarding acute S100B serum concentration. In children after mTBI, we found group-specific significant Spearman correlations between S100B and post-acute cognitive PCS (r=.54, p=.001) as well as S100B and verbal memory performance (r=-.47, p=.006). In children after OI, there were insignificant positive relations between S100B and post-acute somatic PCS. In addition, we found insignificant positive correlations between neuropsychological outcome and S100B in children after OI.

Conclusions: S100B was not specific for mild brain injuries and may also be elevated after OI. The group-specific association between S100B and ongoing cognitive PCS in children after mTBI should motivate to examine further the role of S100B as a diagnostic biomarker in paediatric mTBI.

Introduction

Traumatic brain injury (TBI) is the leading cause of long-term disability in children and thus a worldwide public health problem. With an estimated annual incidence rate of 200-500 per 100,000 children, TBI is the most common injury consequence in childhood[1]. In 80-90% of all paediatric TBI cases, the TBI is mild in its severity. Although most of the children after a mild TBI (mTBI) recover completely within the first days and weeks, evidence exists that about 10% of children do not recover as expected, with ongoing post-concussive symptoms (PCS) even weeks following the injury[2]. While somatic symptoms often recede within the first days, a small percentage of children exhibit cognitive PCS in terms of attention and memory problems, which may impede return to school and daily activities[3]. Considering the high incidence rate of paediatric mTBI and possible cognitive long-term impairments, children with an elevated risk of a protracted recovery should be detected as early as possible.

To date, the main goal of mTBI treatment in the general paediatric Emergency Department (ED) is to identify structural damage or complications like secondary hemorrhage. Little attempt is made at this early time-point to recognize children with the risk of a protracted recovery with persistent PCS. Due to the high incidence of mTBI, there is a need for an easy to administer, cost efficient diagnostic tool to identify as early as possible at-risk children who are prone to develop persistent PCS[4]. During the past several years, biomarkers have been tested as possible diagnostic tools and one of the most widely studied biomarkers is the neuroprotein S100B[5]. S100B, which can be measured in serum, is a calcium channel binding protein that is mainly expressed in the astrocytes and may be increased after an mTBI[4]. However, S100B is also present in peripheral, non-central nervous cell types (e.g. adipocytes, chondrocytes, bone marrow cells)[6]. Since soft-tissue damage and bone fractures in non-head trauma also result in increased S100B serum concentrations, S100B serum level seems not to be specific for brain injuries[7].

Although research regarding TBI biomarkers has increased dramatically over the last decades[5], only few studies investigated the association between S100B in serum and ongoing PCS after paediatric mTBI. In adult samples, controversial findings exist regarding the association between acute S100B serum level and the presence of PCS, with some studies reporting an association[8,9,10], while other studies did not find any association between S100B in serum and general PCS[11] or cognitive PCS[12]. In children, to the best of our knowledge, only one study investigated the association between S100B in serum and PCS, measured with the Rivermead Postconcussion Questionnaire[13] three months after the injury[14]. Babcock et al. investigated children in the age range of 5-18 years and did not find any association between acute S100B in serum and overall PCS.

Regarding the association between S100B and neuropsychological outcome, even less research was conducted in mTBI samples so far, without any study in children. There is evidence that mTBI patients with elevated S100B in serum reveal a trend toward impaired neuropsychological performance three months after the injury, with specific deficits in memory and attention, compared to those mTBI patients without detectable levels[15]. However, there exist also studies in which no influence of S100B on neuropsychological performance in adult mTBI samples was found[11].

Thus, the aim of our study was to examine the association between the acute biomarker S100B and post-acute clinical outcome, measured with PCS questionnaires as well as neuropsychological performance four months after the injury. We hypothesized that the neuroprotein S100B will be detectable in children after mTBI and in children after an orthopaedic injury (OI), but that the amount of S100B serum level will be higher in children after mTBI, compared to children after OI. Second, we explored the association between S100B in serum and PCS. Since there is evidence that somatic and cognitive PCS represent separable symptom dimensions[16], with different recovery trajectories in the post-acute period[3], we aimed to examine the association between S100B and somatic, cognitive as well

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as general PCS. Third, we analysed the relation between S100B in serum and post-acute neuropsychological outcome and focused hereby on memory and attention performance as the cognitive domains most often reported to be affected after mTBI[3].

Methods

Study design and setting

The authors performed a prospective short-term longitudinal study of children with an mTBI presenting to the Emergency Department (ED) of the University Children's Hospital and compared the outcome to children with an orthopaedic injury (OI). The protocol of this study was approved by the ethics committee. All caregivers provided informed written consent prior to participation, consistent with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Participants

From a larger inpatient sample described previously[17], we included 36 children (16 males) after mTBI and 27 children after OI (18 males), with all of them having an acute measurement of S100B in serum (T0) as well as a post-acute PCS and neuropsychological assessment four months after the injury (T1). According to our power analysis (G*Power 3[18]), we had to include 26 patients in each group (effect size d=0.8, α-error=.05, β-error=.8). Recruiting was conducted between February 2012 and April 2013 in the ED. Inclusion criteria were a) the diagnosis of an mTBI, confirmed by a physician and defined according to the American Congress of Rehabilitation Medicine (1999)[19] (Initial Glasgow Coma Scale of 13-15, loss of consciousness (<30 minutes), duration of post-traumatic amnesia (PTA) (<24 hours), alteration in mental state at the time of the accident, with possible focal deficits that were transient), b) without any pre-existing psychiatric or neurodevelopmental disease (except ADHD which is known to be more common in children sustaining a (mild) TBI[20]). Inclusion

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Criteria for the OI were a) fractures of the non-dominant upper extremity or of the lower extremity below the knee or soft wound tissue wounds requiring surgical intervention, b) no head involvement as well as no injury of the dominant upper extremity and c) the absence of pre-existing psychiatric or neurodevelopmental disease (except ADHD, for the same reason as above[20]). Between hospitalization and T1, one child in each group declined further participation.

Measures:

S100B analysis

Venous blood samples were taken acutely (in both groups) as well as 12 and 24 hours after the injury (only mTBI group). S100B was routinely measured on a Roche Modular E170 platform, using the S100 electrochemiluminescence sandwich immunoassay reagents with the associated S100 CalSet calibrators. As a cut-off point, we used the upper S100B serum reference level of .16 µg/l (95th percentile, detected in a large sample of healthy children, aged 3-18 years)[21].

Outcome measures

Post-concussive symptoms were measured using a translated and slightly adapted version of the Post-concussion symptom inventory (PCSI[22]). Our questionnaire consisted of 29 items that had to be rated on a Likert scale (0-3, never/seldom/sometimes/often), covering physical, cognitive, sleep-related and emotional symptoms. To attain more information on cognitive items, we added the following cognitive items from the Health and Behaviour Inventory (HBI[16]): "easily distracted" / "forgetful" / "difficulties to complete a task" / "difficulties to stay focused on a task". PCS were rated by parents at T0 and T1. For this study, we have taken the overall PCS sum for the factor "*general PCS*". Furthermore, we aggregated the sum of the somatic items *(headache, nausea, vomiting, balance problems, dizziness, visual*

problems *(blurry, double vision), sensitivity to light or noise, numbness or tingling feeling, appearing in a clumsy manner)* into the score *"somatic PCS"* and the sum of the cognitive items *(answering questions slowly, appearing slowed down, concentration problems, difficulty remembering, easily distracted, difficulties to complete a task, difficulties to execute an order, difficulties to stay focused on a task, forgetting, sluggish cognitive tempo)* into the score *"cognitive PCS"*. Internal consistency was at both time-points acceptable to strong for the total scale (α=.89/.91) as well as for the subscales somatic PCS (α=.77/.70) and cognitive PCS (α=.89/.91).

Verbal learning and memory performance of single words was assessed with the German version of the Rey Auditory Verbal Learning Test[23]. The dependent variables were verbal learning (the sum of the recalled words over the five learning trials) and verbal memory (delayed recall). Raw scores were transformed into age-corrected percentiles (PR).

Selective attention was measured with the Conner's Continuous Performance Test (CPT-II)[24], with using the errors of omission as a proxy for inattention and the errors of commission as a proxy for impulsivity. Raw scores were transformed into age-corrected percentiles (PR).

The highest level of parental education (from the mother or the father – whichever was higher) was used as a proxy for *socio-economic status (SES)* and was coded using the following scale: 1=obligatory schooling, 2=high school/on the job training, 3=college degree, 4=university/graduate degree.

Statistical analyses

For the statistical analyses we used the Statistical Package for Social Sciences software for Windows, version 21 (SPSS IBM, New York, USA). Demographic characteristics were compared using two-tailed independent sample t-tests (age at injury) and nonparametric Chi-square test (χ^2, for gender and SES). Mann-Whitney U-Tests as well as two-sample t-tests

were computed for group differences and two-sided partial Spearman correlations (controlled for age at injury) were computed for correlations between S100B and PCS or neuropsychological outcome. Since S100B levels peak and normalize within 6 hours[21], we analysed S100B serum values for the whole sample as well as separately for children who had the S100B serum measurement within 6 hours of injury. Statistical significance was set by *p*<.05, however, when conducting multiple comparisons, we applied a Bonferroni corrected significance threshold. Effect size (ES) is reported as *Cramer V* or *Pearson r* and according to[25], an ES of 0.2 is of "practical significance"; ES≥0.5 indicate moderate effects and ES≥0.8 indicate strong effects.

Results

A total of 92 children (46 children per group) were recruited for this study. Overall, dropout rate was described previously[17] and comparable to other studies (e.g.[26]). Descriptive and injury-related characteristics of both groups are shown in table 1. Injury severity of our mTBI group was very mild, with a mean GCS of 14.8 and only a third of participants presenting with a short duration of unconsciousness (<5 min). Statistical analyses revealed that demographic variables concerning age at injury, SES, gender and the amount of previous mTBI were comparable between the TBI and OI groups. One child in the mTBI group had an intracranial injury (epidural hematoma). Although the presence of intracranial lesions is related with worse neurobehavioral outcome[27], we included this child because he was an eligible patient. Additionally, our results did not change when excluding this case.

---Insert table 1 about here---

S100B serum measurement

As illustrated in figure 1, there were no between-group differences regarding acute S100B in serum. However, there was a higher variability of S100B values with four outliers in children after mTBI, compared to children after OI. These four outliers (0.252 µg/l; 0.267 µg/l; 0.285 µg/l; 1.05 µg/l) all had additional body injuries such as a sprained big toe or contusions (shoulder, nose, knee). In the group of children after OI, there were two outliers (0.292 µg/l; 0.333 µg/l); neither of them had additional injuries. Our main findings will not change when excluding the outliers. Regarding the amount of time between the injury and the first S100B serum sample, there was a group difference (U=323.5, p=.02, r=.28) pointing to the fact that blood samples were taken later after the injury in children after OI (Mdn=384 min, IQR=222-780 min), compared to children after mTBI (Mdn=268.50 min, IQR=217.8-350 min). Eight children after mTBI (22%) and 14 children after OI (52%) had S100B serum measurement later than 6 hours after the injury. When only considering children who had S100B serum measurement within 6 hours after the injury, there was no between-group difference regarding S100B serum level (mTBI: Mdn=.13, IQR=.09-.17; OI: Mdn=.12, IQR=.08-.17). In each group, eight children (mTBI: 22%; OI: 30%) had an acute S100B serum level above the cut-off score of 0.16 µg/l[21]. Taking only values above the cut-off score, there was no between-group difference in S100B serum level (mTBI: Mdn=.24, IQR=.18-.28; OI: Mdn=.18, IQR=.17-.27).

To test the time course of the S100B serum level in children after mTBI, we took a second and third S100B serum measurement at a mean of 11.88 hours (SD=1.02) and 23.82 hours (SD=0.55) after the injury. The median values of the second measurement (Mdn=.10, IQR=.07-.13) and third measurement (Mdn=.08, IQR=.07-.11) were lower compared to the first measurement. The three S100B serum measurements in children after mTBI correlated among themselves (controlled for age at injury): First and second measurement: r_s=.69, p<.001; second and third measurement: r_s=.80, p<.001 and first and third measurement: r_s=.64, p<.001.

---Insert figure 1 about here---

Parent-rated PCS at T0 and T1 and neuropsychological outcome at T1

The amount of parent-rated PCS at T0 and T1 is shown in figure 2. Cross-sectional between-group comparisons revealed that parents of children after mTBI observed in the acute phase (T0) more general PCS (U=247.5, z=-3.31, p=.00, r=.42), more somatic PCS (U=250.5, z=-3.29 , p=.00 , r=.41) and more cognitive PCS (U=262, z=-3.13, p=.00, r=.39), compared to parents of children after OI. Four months after the injury (T1), there were no significant between-group differences in parent-rated PCS outcome observable. Regarding neuropsychological outcome, there were no between-group differences concerning verbal learning (mTBI: M=57.15, SD=34.47; OI: M=50.96, SD=33.74), verbal memory (mTBI: M=55.15, SD=30.69; OI: M=63.58, SD=28.01), inattention (mTBI: M=52.26, SD=26.91; OI: M=48.56, SD=26.27) and impulsivity (mTBI: M=40.29, SD=31.18; OI: M=54.46, SD=33.62) four months after the injury.

---Insert figure 2 about here---

Associations between S100B in serum and clinical outcome measures at T0 and T1

Group-specific Spearman Correlations between S100B and PCS are presented in table 2. At T0, there were generally insignificant correlations between S100B serum level and parent-rated PCS in both groups, with one exception concerning the association between acute somatic PCS and S100B serum level (r_s=.34, p=.05) in children after OI. At T1, there were again insignificant correlations between S100B and general PCS in both groups. However, in children after mTBI, but not OI, we found a significant association between S100B serum and cognitive PCS (r_s=.54, p=.001). A post-hoc analysis revealed that especially attention specific

items (concentration problems, easily distracted, difficulties to execute an order, difficulties to complete a task, difficulties to stay focused on a task) of the cognitive subscale correlated moderately with S100B in serum (r_s=.53, p<.01) in children after mTBI.

Further, as indicated in table 2, we found a group-specific significant correlation between S100B and memory performance (r_s=-.47, p=.006) in children after mTBI, but not in children after OI. In both groups, we did not find any significant association between S100B and the computer-based selective attention performance regarding inattention and impulsivity in the CPT-II task. In children after mTBI, even stronger associations between S100B and cognitive outcome emerged when we only considered children who had their S100B measurement within 6 hours after the injury.

---Insert table 2 about here---

Discussion

In contrast to our first hypothesis, acute S100B in serum did not differ between children after mTBI and OI, neither when considering all children nor when only including children who had the S100B measurement within 6 hours after the injury. Thus, the neuroprotein S100B seems not to be specific for neural injuries[10], because it might be released by sources other than brain tissue, such as fat tissue, bone marrow or cartilage[6]. Furthermore, in our mTBI sample, the release of S100B is insignificant and below the defined reference cut-off score of 0.16 µg/l[21].

Similar to earlier studies, there were only cross-sectional between-group differences regarding acute PCS[28]. Four months after the injury, the amount of parent-rated PCS as well as neuropsychological outcome was comparable between children after mTBI and OI, without any difference. Despite the lack of between-group differences regarding S100B level as well as the amount of post-acute PCS, we found positive, group-specific associations between

S100B and cognitive or somatic PCS four months after the injury: While S100B was significantly related with cognitive PCS in children after mTBI, S100B was associated with somatic symptoms in children after OI. In addition, these correlation patterns got stronger when we only included children who had the S100B measurement within 6 hours after the injury. Thus, the higher the acute S100B level in serum, the more cognitive or somatic symptoms were observed by parents in the post-acute phase after the injury.

Interestingly and according to recent studies[11,14], our general PCS value, covering various symptoms, did not correlate significantly with S100B in serum. Hence, our findings indicate not that the general overall PCS as the highest score is associated with S100B in serum, but that symptom- and group-specific associations between PCS and S100B may exist. In contrast to an earlier study, where no association between S100B and three cognitive items of the Rivermead Postconcussion Questionnaire[13] was found[12], our data revealed a relation between S100B and cognitive post-acute symptoms, possibly due to our broader cognitive subscale that covers 10 items. Thus, our cognitive scale could have been more sensitive to detect cognitive symptoms in everyday life, indicating that it might be promising for future research to focus on symptom-specific measures instead of overall values such as general PCS.

Besides the correlations between acute S100B and post-acute PCS, we found negative associations between S100B and neuropsychological outcome, particularly regarding memory performance in children after mTBI: Children with higher S100B in serum showed a worse memory performance four months after their injury. These findings correspond with the above reported relation between S100B and parent-rated cognitive PCS, supporting the idea that acute S100B is related with post-acute cognitive outcome in children after mTBI. Interestingly, in children after OI, we found as well meaningful, but insignificant and positive correlations between S100B and memory outcome. Since S100B was not released by a head injury in children after OI, we do not expect any association between S100B and

neuropsychological outcome. Thus, additional studies are needed to enhance our understanding regarding the association between acute S100B and post-acute neuropsychological outcome in head and non-head-injured paediatric samples to evaluate further the role of S100B as a possible diagnostic tool after an acquired brain injury. Similar to a recent study[8] in which a combination of acute clinical, imaging, and biomarker outcome was predictive regarding the development of post-acute PCS in adult patients after mTBI, we think that future paediatric outcome studies should include as well several acute outcome measures and to relate them with the PCS trajectory in children after mTBI.

The following limitations should be mentioned: First, our sample was relatively small, making it difficult to detect possible between-group-differences regarding the level of S100B in serum. Nevertheless, despite our restricted sample size, especially in the separate correlational analysis, we observed meaningful to moderate effect sizes. Second, only few children in the OI group had the first S100B serum measurement within 6 hours after the injury, pointing to the possibility that the mean S100B serum level in children after OI might be an underestimation. Third, we have used a translated, slightly adapted version of the PCSI[22], without deriving the somatic and cognitive factors from factor analytic approaches. However, basic psychometric standards for the application of the PCSI were given since internal consistency was acceptable for the total scale as well as for the subscales somatic and cognitive PCS (α=.70-.89).

To conclude, our data revealed group-specific correlation patterns between S100B in serum and post-acute PCS four months after the injury: While there was a significant relation between S100B in serum and cognitive symptoms in children after mTBI, S100B was associated with somatic symptoms in children after OI. In addition, these correlation patterns got stronger when we only included children who had the S100B measurement within 6 hours after the injury, pointing to an important time window to measure S100B as prognostic variable. To the best of our knowledge, this study is the first reporting symptom- and group-

specific associations between S100B and clinical outcome after paediatric mTBI. Our findings indicate that future research should explore further the role of S100B as a possible diagnostic biomarker in children after mTBI.

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Tables:

Table 1: Demographic and injury characteristics

Table 2: Two-sided partial Spearman correlations (controlled for age at injury) between S100B in serum, PCS and neuropsychological outcome

Figure Legends:

Fig 1: Boxplots illustrating the acute level of S100B in serum

Fig 2: Mean number (SD) of general, somatic and cognitive post-concussive symptoms measured in the acute phase (T0) as well as four months after the injury (T1)