Traumatic brain injury is one of the leading causes of death and morbidity in children.\textsuperscript{1,4,8,20} Patients with mild TBI demonstrate heterogeneity in clinical presentation with or without loss of consciousness or posttraumatic amnesia and with GCS scores ranging from 13 to 15.\textsuperscript{23} The different age groups and communication difficulties in pediatric patients may sometimes present further obstacles in obtaining a detailed injury history and identifying TBI symptoms in an accurate and timely manner. The neurological examination in pediatric patients, especially in the very young ones, may be quite challenging, and the patient’s initial clinical picture and injury history may frequently be unreliable. Their evaluation requires time and patience, which unfortunately can be difficult to find in a chaotic and busy emergency room. In addition, pediatric cases of mild TBI can impose a diagnostic dilemma on the managing physician, since the decision for a hospital admission to obtain imaging studies is not easy and significantly raises the cost of treatment. The physician’s experience is the key factor dictating the management plan given that there are currently no guidelines for the treatment of mild TBI in children.\textsuperscript{1,4,8,20}

The above considerations in pediatric cases of mild TBI create a need to design a diagnostic tool that would combine diagnostic performance, ease of use, minimal invasiveness, cost effectiveness, and outcome prediction in a timely and efficient manner.\textsuperscript{6,20} For years, imaging studies have been used as supplemental tools in diagnosing and managing pediatric TBI cases. However, these studies are not always feasible because of their prohibitive use due to high costs, time requirements, and difficult application. The necessity of finding an optimal biomarker from the blood or CSF that could establish a TBI diagnosis, accurately measure its severity, and predict its outcome is more than apparent.\textsuperscript{6,20} Protein S100B, neuron-specific enolase, and glial fibrillary acidic protein

Role of the S100B serum biomarker in the treatment of children suffering from mild traumatic brain injury

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\textbf{Object.} The aim of this study was to provide a systematic update of the current literature regarding the clinical role of the S100B serum biomarker in the initial evaluation of children who have sustained a mild traumatic brain injury (TBI).

\textbf{Methods.} Searches in MEDLINE were defined with the keywords “mild TBI children S100,” “mild TBI pediatric S100,” and “children S100 brain injury.” From the pool of obtained studies, those that had the inclusion criteria of mild TBI only or mixed types of TBI but including detailed information about groups of children with mild TBI were used.

\textbf{Results.} Few studies were identified and fewer included more than 100 cases. The prospective studies showed that the S100B biomarker levels could be influenced by patient age and the time frame between head injury and blood sampling. Moreover, extracranial sources of S100B or additional injuries could influence the measured levels of this biomarker. A normal value of S100B in children with mild TBI could rule out injury-associated abnormalities on CT scans in the majority of reported cases.

\textbf{Conclusions.} The vulnerability of S100B serum levels to the influences of patient age, blood sampling time, and extracranial S100B release limits the biomarker’s role in the initial evaluation of children with mild TBI. The application of S100B in pediatric mild TBI cases has an elusive role, although it could help in selected cases to avoid unnecessary head CT scans. (DOI: 10.3171/2010.8.FOCUS10185)

\textbf{Key Words} • biomarker • children • mild traumatic brain injury • S100B biomarker

Abbreviations used in this paper: GCS = Glasgow Coma Scale; TBI = traumatic brain injury.
are the most commonly studied biomarkers, while protein S100B has been studied the most in the field of pediatric TBI.1,3,7,14,18,20

The aim of our study was to assess the role of S100B as a clinical biomarker in pediatric cases of mild TBI and to systematically review the pertinent literature.

Methods

We accessed the MEDLINE database to gather the required data and information for this review article. Our search strategy involved 3 different search sessions using the keywords “mild TBI children S100,” “mild TBI pediatric S100,” and “children S100 brain injury.” We included only those articles published in the English language. After obtaining the first pool of studies, a second filter procedure followed. The inclusion criteria isolated studies with pediatric cases of mild TBI only. Whenever studies with mixed types of TBI or mixed populations (adult and pediatric) were encountered, we tried to extract information specific to pediatric cases of mild TBI.

Results

Profile of S100B

The S100 calcium binding protein B, or S100B, belongs to the S-100 protein family and is characterized by 2 calcium-binding sites of the helix-loop-helix conformation. The S100 proteins are located in the cytoplasm and nucleus of a wide range of cells and are involved in the regulation of a number of cellular processes, such as cell cycle progression and differentiation. Specifically, S100B regulates cellular homeostasis and enzyme activity and inhibits protein kinase C phosphorylation of growth-associated protein 43, which is involved in axonal growth and synaptogenesis during development, synaptic remodeling, and long-term potentiation.15 It also plays a significant role in the stabilization of tau and microtubule-associated protein 2 (MAP-2).26 The S100 genes include at least 13 members, which are located as a cluster on chromosome 1q21. There are at least 21 different types of S100 proteins.27 The name of this protein group derives from its solubility in ammonium sulfate, which is 100% at a neutral pH.

The S100B protein was first identified in 1965 by Moore.28 It is a low-molecular-weight protein (10–12 kD) composed of 2 subunits, alpha and beta, with the alpha subtype found mostly in striated muscles, heart, and kidneys; the beta subtype, in glial cells; and the beta subtype, in high concentrations in astroglia.9 The S100 proteins and especially S100B can act as a cancer biomarker in malignant melanoma. It has a serum half-life of 60–120 minutes and is eliminated by renal clearance.11,12 Although S100B is glial-specific and expressed primarily by astrocytes and Schwann cells, it is also found in several non–nervous system cells, such as adipocytes (white and brown fat), chondrocytes, skin, and glioblastoma and melanoma cells.27 However, it is not expressed by all astrocytes. It has been shown that S100B is only expressed by a subtype of mature astrocytes, which are in proximity to blood vessels, and also by NG2-expressing cells.25 It can be found in very low levels in human CSF and serum, and normal levels of this protein have been strongly correlated with the absence of any intracranial injuries.21 Low basal levels of S100B in human serum suggest that sharp increases in the concentrations of this protein are sensitive indicators of brain injury. Cerebral lesions cause immediate leaking of S100B from damaged glial cells into the blood or CSF.19 The precise mechanism of the increased serum concentration of S100B in cases of TBI remains uncertain. The S100B could be directly released by damaged cells, but it is also secreted into the extracellular space by activated glial cells. It may enter the serum through a transient disruption of the blood-brain barrier or via the CSF circulation.20 It has been shown that serum S100B levels correlate well with a patient’s clinical condition and imaging findings as well as their outcome scores in cases of TBI. It has been postulated that S100B protein is the most promising marker for evaluating the severity of TBI in patients suffering from mild injuries.20 It has also been shown that in patients with severe TBI, serum S100B concentrations higher than 1.13 ng/ml are associated with increased death and morbidity.24 Thus, this protein has been proposed as a potential biomarker indicating the severity of neuronal injury and the disruption of the blood-brain barrier and predicting a patient’s outcome.22 On the other hand, it has been demonstrated that there is a poor correlation between CSF and serum S100B levels; this is because the intact blood-brain barrier is not permeable to S100B. It has been postulated that an increase in serum concentration may be indicative of blood-brain barrier disruption rather than irreversible neuronal damage.6 Furthermore, increased S100B serum levels have been described in cases of melanoma and hepatic, renal, and/or intestinal ischemia, probably due to the presence of S100B in other nonglial cells.17 In addition, the use of S100B as a neuronal injury biomarker has been questioned because its concentration was increased in trauma patients with no head injuries.2

Clinical Studies of S100B in Children With Mild TBI

Most of the clinical studies concerning mild TBI and S100B serum levels in children included a limited number of patients, and thus no statistically powerful conclusions can be extracted. Interestingly, very few studies included more than 100 patients. Geyer et al.3 conducted a prospective clinical study involving 148 children with mild TBI. The biomarkers S100B and neuron-specific enolase were measured within 6 hours of injury. Two diagnostic groups were studied. The first one, called the “mild TBI group” included children with GCS scores of 13–15 and signs of concussion. The second one, called the “head contusion group,” included children with a GCS score of 15 and no signs or symptoms of concussion. The authors found that patient age and the time frame between injury and blood withdrawal significantly influence the serum S100B concentrations. The levels of S100B in the mild TBI and head contusion groups did not significantly differ. Moreover, there was no significant difference between the levels of S100B in patients with GCS Scores 15 or 14. These authors concluded that S100B demonstrates low sensitivity in mild TBI cases in children (Table 1).

A. S. Filippidis et al.
In a prospective study, Castellani et al. tried to reveal whether S100B levels in 109 children with mild TBI (GCS Scores 13–15 at admission and clinical symptomatology present) were related to their CT findings. The inclusion criteria were as follows: 1) children who required a CT scan during hospitalization and 2) whose S100B levels had been determined within 6 hours of the traumatic event. Blood sampling had also occurred within 6 hours after the injury event. An interesting finding was the increased serum S100B levels in patients with an abnormal CT scan as compared with levels in children with non-diagnostic findings on CT, and this difference was statistically significant. However, no statistically significant difference in the serum S100B concentrations was found between the different GCS subgroups (patients with GCS scores of 13 vs 14 vs 15), after the adjustment of p values for pairwise analysis. When CT findings were used as a factor to assess serum S100B marker performance, sensitivity was 1.00, specificity 0.42, positive predictive value 0.46, and negative predictive value 1.00 with an area under the curve of 0.68. All children with normal serum S100B values had no injury-related abnormalities on head CT scans. This finding can be used in routine clinical practice to avoid unnecessary CT scans in children with normal S100B levels. It should be noted that children with head and other systemic injuries had higher mean S100B values. It should be noted that children with concomitant injuries had consistently higher S100B serum concentrations than the children with head injury only (Table 1). 

Akhtar et al. tried to assess the significance of serum S100B levels in 17 children who had sustained a TBI and had been screened with brain MR imaging. All children in their study had a negative CT scan. Unfortunately, there were no details regarding the admitting GCS scores. The S100B biomarker did not efficiently identify TBI patients with positive or negative MR imaging studies. Moreover, additional systemic injuries affected the serum levels of S100B, so that children with concomitant injuries had consistently higher S100B serum concentrations than the children with head injury only (Table 1).

Berger et al. reported their experience with 12 children who had sustained TBIs, with admitting GCS scores of 15, normal head CT scans, and no clinical evidence of concussion. In that cohort, 67% of the children demonstrated increased serum levels of S100B. The authors concluded that S100B could be a more sensitive biomarker than CT or MR imaging in cases of pediatric TBI. The high levels of S100B could potentially reflect CNS damage that was undetected with imaging modalities (Table 1).

### Discussion

The application of serum S100B protein as a clinical biomarker and outcome-predicting factor in pediatric cases of mild TBI meets several obstacles given that numerous factors can influence baseline serum S100B concentrations and many pathological conditions other than TBI can cause elevated S100B levels. Patient age is one of the most influential factors in determining normal baseline serum levels of S100B. The effect is significant in the pediatric population, which expresses highly varying growth factors at different developmental stages and produces a variety of proteins to meet everyday growth demands. This observation has been confirmed by Geyer et al. in their pediatric study of mild TBI as well as in other clinical studies. Gazzolo et al. evaluated the normal levels of S100B in serum in 1004 children to create a reference curve and found that there are 2 peaks, 1 in children younger than 1 year of age and another occurring in adolescents. The changes in S100B reference levels in children of different ages were also confirmed in the study by Castellani et al. All of these studies show that S100B is definitely an age-dependent protein, and any future S100B TBI studies should use reference levels for specific age groups.

Another source of variability in the S100B levels in cases of TBI is the presence of additional injuries. Although S100B can be found at high levels in astrogial and neurons, the lack of specificity of this biomarker for the CNS may create a distorted image in cases of mild TBI associated with multiple injuries. Concomitant systemic injuries, such as long bone fractures and extensive skin injuries, adipose tissue injuries, and muscle or joint injuries, can become a source of additional S100B release in the serum and thus perplex its diagnostic accuracy in TBI cases.

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**TABLE 1: Literature review of studies on pediatric patients with mild TBI**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geyer et al., 2009</th>
<th>Castellani et al., 2009</th>
<th>Morochovic et al., 2009</th>
<th>Akhtar et al., 2003</th>
<th>Berger et al., 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample size</td>
<td>148</td>
<td>109</td>
<td>102</td>
<td>17</td>
<td>12†</td>
</tr>
<tr>
<td>type of population</td>
<td>pediatric</td>
<td>pediatric</td>
<td>pediatric &amp; adult ‡</td>
<td>pediatric</td>
<td>pediatric</td>
</tr>
<tr>
<td>% males</td>
<td>57.4</td>
<td>67</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>age range</td>
<td>6 mos–15 yrs</td>
<td>5 mos–17.5 yrs</td>
<td>12–84 yrs</td>
<td>6–15 yrs</td>
<td>ND</td>
</tr>
<tr>
<td>GCS score</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>&gt;12</td>
<td>$</td>
<td>15</td>
</tr>
<tr>
<td>time point of S100B sampling (hrs)</td>
<td>≤6</td>
<td>≤6</td>
<td>≤6</td>
<td>≤6, ≤12 ¶</td>
<td>≤12</td>
</tr>
<tr>
<td>imaging modality</td>
<td>none</td>
<td>CT</td>
<td>CT</td>
<td>CT &amp; MRI</td>
<td>CT</td>
</tr>
</tbody>
</table>

* No outcome measurements (Glasgow Outcome Scale or neuropsychological tests) were used in any of the studies. Abbreviation: ND = no data.
† Extracted data of 12 patients with mild TBI (from a total of 168).
‡ Extracted pediatric data used in the paper.
¶ First sample, second sample.

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The sampling time of S100B in relation to the time of head injury is also an important factor that may influence its serum concentrations and thus make the interpretation of any S100B increases inconclusive in TBI cases. Delayed serum measurements of S100B following a head injury may lead to erroneous conclusions regarding the severity and extent of neuronal damage, because of the relatively short half-life of the S100B protein. Geyer et al. emphasized the importance of the time span between injury and S100B blood sampling in the accurate measurement of S100B serum levels. It cannot be overemphasized that exact knowledge of blood sampling is mandatory for interpreting serum S100B levels and evaluating their association with the severity and prognosis of the underlying head injury.

The role of S100B as a biomarker in children suffering from mild TBI meets strong criticism in the literature. Studies by Geyer et al., Berger et al., and Akhtar et al. demonstrated a low sensitivity for S100B in pediatric cases of mild TBI. In all of these series, serum levels of S100B failed to efficiently identify children with intracranial pathology on imaging studies. These findings agree with those in the mild TBI study by Morochovic et al., which showed that S100B is an unreliable screening tool for detecting intracranial pathology in adults and children. On the other hand, the study by Castellani et al. identified a role for S100B in the initial evaluation of children with mild TBI. These authors found that S100B had 100% sensitivity in identifying children with no intracranial pathology on obtained head CT scans. The authors clearly stated that selection biases could probably affect their study, since the decision to perform a CT scan was not blinded and only children with a progressively worsening clinical picture underwent CT scanning. Nonetheless, their findings were promising, and the potential role of S100B in the triage of children with mild TBI should be explored in a large-scale, prospective clinical trial.

Conclusions

In summary, the role of the S100B biomarker in the initial evaluation of children with mild TBI is still controversial and remains to be defined. Many factors—including a patient’s age, the serum sampling time, and the presence of multiple extracranial injuries—can influence the levels of S100B, yielding inadequate or even confusing results. The identification of a more specific biomarker for CNS injuries, the use of paired biomarkers in pediatric studies of mild TBI, and the design and performance of large-scale, prospective clinical studies could provide more data and shed more light on the ambiguous role of biomarkers in the evaluation of children with mild closed-head injuries.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Filippidis. Acquisition of data: Filippidis. Analysis and interpretation of data: Filippidis, Kapsalaki. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Fountas.

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