Serum Neuron-specific Enolase as a Predictor of Short-term Outcome in Children with Closed Traumatic Brain Injury

Subhankar Bandyopadhyay, MD, Halim Hennes, MD, MS, Marc H. Gorelick, MD, MSCE, Robert G. Wells, MD, Christine M. Walsh-Kelly, MD

Abstract

Background: Closed traumatic brain injury (cTBI) is a significant cause of mortality and morbidity in children. The natural course and extent of recovery from cTBI in children are poorly understood. Neuron-specific enolase (NSE), an enzyme detected in serum following structural damage of neuronal brain cells, appears to be a good marker for intracranial injury. However, to the best of the authors’ knowledge, the usefulness of NSE as a predictor of disability in children with cTBI has not been reported.

Objectives: To examine the association between posttraumatic serum NSE level and short-term physical disability in children with cTBI.

Methods: This was a retrospective analysis of a prospectively enrolled cohort of children aged 0–18 years with isolated cTBI presenting to the emergency department (ED) within 24 hours of injury, and having a cranial computed tomography (CT) scan as part of the evaluation. The NSE level was obtained at the time of ED evaluation. Physical disability was measured using the Glasgow Outcome Scale (GOS). The GOS score was assigned retrospectively for enrolled patients by a single investigator blinded to NSE level. Patient outcomes were categorized as good (GOS = 5) or poor (GOS < 5). A single radiologist reviewed all cranial CT scans. Results: Ninety eligible subjects with NSE levels were identified; 86 met the enrollment criteria. Seven subjects (8%) had poor outcome. There was a significant difference in NSE levels between the poor and good outcome groups, even within high-risk subgroups. The area under the curve (AUC) for NSE prediction of poor vs. good outcome was 0.83. A serum NSE level of 21.2 ng/dL was 86% sensitive and 74% specific in predicting poor outcome.

Conclusions: It appears that the serum NSE level can be used as a predictor of global short-term physical disability in children following cTBI.

Key words: neuron-specific enolase; enolase; prediction; pediatrics; children; disability; outcomes. ACADEMIC EMERGENCY MEDICINE 2005; 12:732–738.

Closed traumatic brain injury (cTBI) is a significant cause of morbidity and mortality in children.1,2 Most studies on disability following TBI in children and youth are based on case series from selected hospitals or rehabilitation facilities. The difficulty of measuring the effects of the injury in the context of naturally occurring developmental changes contributes to the challenge of assessing outcomes of TBI in children.

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Received October 28, 2004; revision received February 1, 2005; accepted February 15, 2005.

Presented at the Pediatric Academic Society annual meeting, San Francisco, CA, May 2004; and as a poster at the SAEM annual meeting, Orlando, FL, May 2004.

Supported by a grant from the Medical College of Wisconsin Clinical Research Center (Grant # 627).

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doi:10.1197/j.aem.2005.02.017

Approximately 85% to 95% of all cTBIs are classified as mild to moderate.3,4 Traditionally, emergency department (ED) management has focused on stabilization, establishing the diagnosis, preventing secondary injury, and referral/disposition of children with TBI. Over the past two decades, researchers have focused on improving our ability to predict the need for imaging studies, hospital admission, cost of care, and other proximal outcome measures.5–13 However, even with mild TBI, 5% to 15% may develop lasting sequelae, generating interest in understanding long-term functional and neurocognitive outcomes in head-injured children.6,7,10,12

There is a paucity of literature addressing our ability to predict long-term outcome in areas of neurocognitive and physical functioning, or the impact of ED management on these outcomes, in children with cTBI. Early predictors of long-term morbidity in children with cTBI could potentially play an important role in identifying children at risk for lasting sequelae, and in targeting costly surveillance efforts and preventive intervention strategies to enhance functional recovery in these children.

The brain tissue contains a unique form of a glycolytic protein, “neuron-specific enolase” (NSE),
which is found only in neurons of brain and other central nervous system tissues. Structural damage of neuronal brain cells causes leakage of NSE into the extracellular compartment and the bloodstream. NSE can be detected in the serum following neuronal cell death secondary to traumatic injury or a catastrophic vascular event. Several studies in adult patients, and one pediatric study, have already established NSE as a marker of intracranial injury.14–26 Because NSE can be detected in the serum within six hours of TBI, this enzyme may be a useful early predictor of neurocognitive and/or global functional deficits following cTBI in children. To our knowledge, no studies in the pediatric literature have examined the NSE level as a potential predictor of long- or short-term functional, neurocognitive, or behavioral outcomes in children with cTBI. The objective of this study was to examine the association between posttraumatic serum NSE level and the short-term outcome of physical disability measured by the Glasgow Outcome Scale (GOS), in children with cTBI.

METHODS

Study Design. This was a retrospective analysis of children who had been prospectively enrolled in a separate study. The institutional review board of the hospital approved this study.

Study Setting and Population. The study cohort was obtained from an academic children’s hospital emergency department (ED) head trauma study database with enrollment between December 1997 and November 2000. This ED is located in the Children’s Hospital of Wisconsin, in Milwaukee, and has an annual census of 44,000. It is the only freestanding children’s hospital in the state, and is actively serviced by an out-of-hospital emergency medical services system and an in-hospital transport team with access to both air and ground transport. An annual average of 500 patients with cTBI are seen, with approximately 5% to 10% having moderate to severe cTBI.

Study Protocol. Subjects between 0 and 18 years of age, evaluated within 24 hours of sustaining cTBI, and requiring a cranial computed tomography (CT) scan in accordance with the written ED protocol were enrolled. Blood for serum NSE assay was drawn at the time of ED evaluation. Subjects were excluded if they had penetrating TBIs, intentional head trauma, multisystem injuries, pelvic or lower extremity fractures, spinal cord injuries, or bleeding disorders. Patients who sustained injury more than 24 hours prior to presentation or with a history of cerebral palsy, mental retardation, developmental delay, or ventricular shunts were also excluded.

Measurements. The primary outcome variable was GOS score at the time of hospital discharge. The GOS is a validated five-point ordinal scale of global physical disability following cTBI, with the lower score indicating worse outcome (Table 1).27–30 The GOS at the time of discharge from the hospital, from either the ED or the inpatient service, was assigned retrospectively for all enrolled patients by a single investigator blinded to the NSE level. Subjects’ GOS scores were categorized as good (GOS = 5) or poor (GOS < 5) outcome.

Data collected include demographics, mechanisms of injury, symptoms, vital signs, and physical examination findings. The interval from time of injury to obtaining the blood sample for NSE determination was recorded. The NSE assays for the cohort were done by standard radioimmunoassay (RIA) technique by Specialty Laboratories (Santa Monica, CA) using stored frozen serum (–70°C) of centrifuged 5 mL patient blood. NSE level ≥ 15 ng/mL was considered abnormal as per the test reference range of the processing laboratory. A single radiologist reviewed all cranial CT scans. An abnormal CT scan was defined as a CT scan with cerebral contusions, cerebral edema, or parenchymal, subarachnoidal, subdural, or epidural bleeding. Presence of skull fracture alone was not sufficient to classify a CT as abnormal.

TABLE 1. The Glasgow Outcome Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>1</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Persistent vegetative state: Unresponsive and speechless; after 2–3 weeks, may open eyes and may have sleep/wake cycle</td>
</tr>
<tr>
<td>3</td>
<td>Severe disability: Conscious but disabled; dependent for daily activities; may or may not be institutionalized</td>
</tr>
<tr>
<td>4</td>
<td>Moderate disability: disabled but independent; can work in a structured setting</td>
</tr>
<tr>
<td>5</td>
<td>Good recovery: resumption of normal life despite minor deficits</td>
</tr>
</tbody>
</table>
RESULTS
Among 90 previously enrolled subjects in the head trauma study database, 86 met enrollment criteria for the present study. Among four ineligible subjects, two subjects were diagnosed as having intentional head trauma and the rest had lower extremity (pelvic and femur) fractures. The mean (±SD) age was 8.2 ± 5.5 years (range 11 months to 18 years). Approximately two thirds were male and white. Among 86 enrolled subjects, ten had Glasgow Coma Scale (GCS) scores < 13 (moderate and severe cTBI). The distribution of subjects based on GCS scores obtained in the ED is shown in Table 2. Injury Severity Scale (ISS) score was not recorded for the study because enrollment was strictly restricted to subjects with isolated cTBI. From the ED, 67% of the study population were admitted to the hospital because of either the injury itself or its complications. The mean time interval from the time of reported injury and the time blood was drawn for NSE measurement was 3.8 hours (range 0.4 to 14.8).

Seven patients (8%) had poor outcome according to the preset criteria of GOS < 5. The mean (±SD) NSE level was significantly higher in the subjects with poor outcome (46.4 ± 12.7 ng/mL) than those with good outcome (19.5 ± 1.4 ng/mL) (Table 3). Distribution of NSE levels in our patient population is shown in Figure 1. Among patients with good outcome (GOS = 5), the admitted patients had higher mean (±SD) NSE levels (22.4 ± 2.0; 95% CI = 16.8 to 22.3 ng/mL) than the patients who were discharged from the ED (14.4 ± 0.9; 95% CI = 12.6 to 16.2 ng/mL). The mean (±SD) NSE levels were also significantly higher in patients who presented with abnormal GCS scores or had abnormal cranial CT scans (Table 4).

To determine whether the NSE level adds independent predictive information, we compared NSE levels between poor and good outcome within certain subgroups at higher risk of poor outcome: those who were admitted in the hospital (n = 58), those with intracranial hemorrhage (n = 32), and those with moderate to severe cTBI (GCS < 13, n = 10) (Table 5). Even within each of these high-risk subgroups, the NSE level was significantly higher among patients with poor outcome.

The overall ability of the NSE level to discriminate poor versus good outcome was good, with an area under the ROC curve (c statistic) of 0.83 (Figure 2). The NSE level at a cutoff value of 21.2 ng/mL was 86% sensitive and 74% specific in predicting poor outcome in our patients with cTBI. In contrast, the NSE level was a relatively poor predictor of abnormal CT scan, with a c statistic of 0.66.

DISCUSSION
Results from our study clearly indicate that a plausible association exists between cTBI outcome and the serum level of NSE, a marker for cTBI. Previous adult and pediatric studies have suggested a clear rise in serum NSE level following cTBI, and our findings suggest that this rise in posttraumatic serum NSE titer is associated with short-term outcome. NSE levels are significantly higher among children with poor outcome, even within various high-risk subgroups, suggesting that the NSE level may serve as an independent and useful early predictor of disability in children following cTBI.

Several biochemical markers have been associated with ischemic or traumatic insults to the brain. The association of such biochemical markers with hypoxemia, ischemia, stroke, and hypothermia is already established in studies of adult patients. Only in the last several years, interest has grown to explore the association of these markers with TBI in children. Berger et al. reported increased titers of NSE and S100B in the cerebrospinal fluid (CSF) following both intentional and unintentional cTBI in children. Peak CSF NSE concentration was reached as early as five hours (median 11, range 5 to 20) following cTBI. A recent study in adult patients suggested that determination of serum levels of glial and neuronal proteins may add to the clinical assessment of the primary damage and prediction of outcome after severe TBI.

However, we know of no prior studies in children with cTBI that have tried to correlate poor outcome with biochemical markers. Our results show that children with poor outcomes following cTBI (GOS < 5) had nearly threefold higher NSE concentrations following cTBI than children with good outcomes (GOS = 5). Although there was an overlap in NSE

## Table 2. Distribution of the Subjects Based on Initial Glasgow Coma Scale (GCS) Score on Presentation to the Emergency Department

<table>
<thead>
<tr>
<th>GCS Score</th>
<th>Frequency (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
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<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>46</td>
</tr>
</tbody>
</table>

## Table 3. Neuron-specific Enolase (NSE) Levels in the Poor and Good Outcome Groups

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>NSE Level (ng/mL; mean ± SE)</th>
<th>95% CI (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (GOS &lt; 5) (n = 7)</td>
<td>46.4 ± 12.7</td>
<td>15, 77</td>
</tr>
<tr>
<td>Good (GOS = 5) (n = 79)</td>
<td>19.5 ± 1.4</td>
<td>17, 22</td>
</tr>
</tbody>
</table>

*GOS = Glasgow Outcome Scale score.
levels between the poor and good outcome groups (Figure 1), none of the subjects in the good outcome group had an NSE level higher than the acceptable upper limit of reference range (>15 ng/mL). The differences in the NSE levels were also significant between the poor and good outcome groups, even in patients who are considered to be at higher risk of having poor outcome (with intracranial hemorrhage, GCS ≤ 12, etc.). According to our results, the NSE level for predicting poor outcome in our study population had a sensitivity and a specificity of 86% and 74%, respectively, which may be acceptable as an early screening test for identifying children at risk of developing significant physical disability. Our results must be interpreted with caution, however, since we relied on single-point NSE analysis rather than serial estimation, and therefore may have been unsuccessful in catching peak NSE levels in some of our patients. However, this would not have influenced our results, as the majority of our patients with good outcomes had NSE levels ranging between 17 and 22 ng/mL, and it is highly unlikely that they sustained any further secondary brain injury, which would influence their NSE titers. On the other hand, patients who had a poor outcome, but whose NSE titers were determined early (18–25 ng/mL), might have not yet reached their peak.

Predicting neurologic, physical, and cognitive disability following cTBI becomes challenging in the context of naturally occurring developmental changes in the pediatric population. The patient’s age, the mechanism of injury, the prior history of developmental or cognitive disability, any social or language barrier, and genetic predisposition, along with the extent of progression of TBI itself, all play significant roles in the recovery after cTBI. Researchers have not yet been able to identify a single factor that is directly attributable to either deficit or complete recovery following cTBI. Injury severity based on GCS alone is limited in predicting outcome in children with cTBI. Neuropsychological outcomes following cTBI are not significantly different in children who had low GCS scores (3–5) compared with children who had GCS scores of 6 or higher. Subsequent studies have established that multiple injury indices (ISS, head-abbreviated ISS, and GCS at several time points), along with GCS and physiologic reflex (oculocephalic), are suitable predictors of outcome following cTBI, but none of these parameters has been singled out as the most important prognostic factor. Our study results show NSE, when added to the higher

TABLE 4. Association of the Neuron-specific Enolase (NSE) Level with Glasgow Coma Scale (GCS) Score and Computed Tomography (CT) Scan

<table>
<thead>
<tr>
<th>NSE Levels (ng/mL; mean ± SE) (95% CI)</th>
<th>Normal</th>
<th>Abnormal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>16.8 ± 1.1 (14.6, 19)</td>
<td>26.9 ± 3.0 (20.8, 33)</td>
<td>0.003</td>
</tr>
<tr>
<td>GCS score*</td>
<td>16.7 ± 1.2 (14.3, 19.1)</td>
<td>31.1 ± 3.6 (23.5, 38.7)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Abnormal GCS score = GCS < 15.
risk category (low GCS, intracranial bleed), clearly distinguished subjects having poor and good outcomes based on the GOS score at the time of discharge. Further prospective studies are needed to explore the strength of the association of these biochemical markers with outcome following cTBI in children.

An ideal outcome scale that examines all of the domains in daily life is nonexistent. The GOS is a simple scale that has been used widely but has a very limited scope. The GOS measures acceptable and unacceptable outcomes. Furthermore, it has an excellent track record of being used retrospectively, and its interrater reliability is also excellent. Although the GOS was initially developed to assess outcome in adult stroke patients, Fisher validated its utility across all pediatric ages when he developed the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales based on the GOS.49 We have converted the GOS into a dichotomous outcome variable by grouping scores of 1–4 as “poor” versus a score of 5 corresponding to a “good recovery,” for the purpose of broad classification of poor and good outcomes only. There is previously documented use of the GOS as a dichotomous variable in children with severe cTBI,50 as we did in our study. We were, however, limited to the documentation of the GOS at the time of discharge, and were unable to correlate a three- or six-month post-injury outcome score with NSE. Furthermore, we assigned a GOS score of 5 to any patients discharged from the ED who did not have a physical/occupational or rehabilitation service consult on their chart, and did not have any recorded limitation of activity.

**LIMITATIONS**

The major limitation of our study is the paucity of subjects with poor outcomes. We believe the overlap in NSE concentrations seen between the poor and good

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**TABLE 5. Neuron-specific Enolase (NSE) Levels in High-risk Subgroups of Closed Traumatic Brain Injury (cTBI)**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>NSE Level in Poor Outcome (ng/mL)</th>
<th>NSE Level in Good Outcome (ng/mL)</th>
<th>Mean Difference Δ in NSE Level (ng/mL)</th>
<th>95% CI of Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>Admitted (n = 58)</td>
<td>46.4 ± 12.7</td>
<td>22.4 ± 1.9</td>
<td>24.0 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>Abnormal CT scan (n = 43)</td>
<td>50.4 ± 14.2</td>
<td>23.1 ± 2.9</td>
<td>27.2 ± 8.4</td>
</tr>
<tr>
<td></td>
<td>Intracranial hemorrhage (n = 32)</td>
<td>53.7 ± 19.2</td>
<td>23.2 ± 3.0</td>
<td>30.5 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>GCS* &lt; 13 (n = 10)</td>
<td>57.2 ± 15.3</td>
<td>18.4 ± 2.0</td>
<td>38.7 ± 15.4</td>
</tr>
</tbody>
</table>

*GCS = Glasgow Coma Scale score.
outcome groups could have been addressed in depth with a larger sample size. The retrospective nature of our data abstraction from medical records with regard to the GOS also has its own limitations. We dichotomized the GOS into good vs. poor outcome because of the limited number of subjects with poor outcomes.

CONCLUSIONS

Neuron-specific enolase can be used as a predictor of poor functional outcome in children with closed TBI. Future studies are needed to explore the association between other biochemical markers of brain injury and areas of longer-term cognitive, behavioral, physical, and social functioning following cTBI in children.

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