

Neuron-Specific Enolase and S100B in Cerebrospinal Fluid After Severe Traumatic Brain Injury in Infants and Children

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ABSTRACT. *Background.* Traumatic brain injury (TBI) is a leading cause of death and disability in children. Considerable insight into the mechanisms involved in secondary injury after TBI has resulted from analysis of ventricular cerebrospinal fluid (CSF) obtained in children with severe noninflicted and inflicted TBI (nTBI and iTBI, respectively). Neuron-specific enolase (NSE) is a glycolytic enzyme that is localized primarily to the neuronal cytoplasm. S100B is a calcium-binding protein localized to astroglial cells. In adults, CSF and serum concentrations of NSE and S100B have served as markers of neuronal damage after TBI. Neither NSE nor S100B has previously been studied in CSF after TBI in infants or children.

Objective. To compare the time course and magnitude of neuronal and astroglial death after nTBI and iTBI by measuring CSF concentrations of NSE and S100B using a rapid enzyme-linked immunosorbent assay.

Methods. Severe nTBI and iTBI were defined by strict clinical criteria. Serial ventricular CSF samples ($n = 35$) were obtained from children 1.5 to 9 years with severe nTBI ($n = 5$) and children 0.2 to 1.5 years ($n = 5$) with severe iTBI. Lumbar CSF samples from 5 children 0.1 to 2.3 years evaluated for meningitis were used as a comparison group. CSF NSE and S100B concentrations were quantified by an enzyme-linked immunosorbent assay (SynX Pharma Inc, Ontario, Canada).

Results. There was no difference in age between patients with iTBI (median [range]: 0.2 years [0.2–1.8]), nTBI (2.0 years [1.5–9]), and the comparison group (0.2 years [0.2–1.8]). The initial Glasgow Coma Scale score was higher in the iTBI group (9 [4–14]) versus the nTBI group (3 [3–7]). NSE was increased in TBI versus the comparison group in 34 of 35 samples. Mean NSE was markedly increased (mean \pm SEM, 117.1 ± 12.0 ng/mL vs 3.5 ± 1.4 ng/mL). After nTBI, a transient peak in NSE was seen at a median of 11 hours after injury (range: 5–20 hours). After iTBI, an increase in admission NSE was followed by a sustained and delayed peak at a median of 63 hours after injury (range: 7–94). The magnitude of peak NSE

was similar in nTBI and iTBI. S100B was increased versus the comparison group in 35 of 35 samples. Mean S100B was markedly increased in TBI versus the comparison group (1.67 ± 0.2 ng/mL vs 0.02 ± 0.0 ng/mL). S100B showed a single peak at 27 hours (range: 5–63 hours) after both nTBI and iTBI. The mean S100B concentration, peak S100B concentration, and the time to peak were not associated with mechanism of injury.

Conclusions. Markers of neuronal and astroglial death are markedly increased in CSF after severe nTBI and iTBI. iTBI produces a unique time course of NSE, characterized by both an early and late peak, presumably representing 2 waves of neuronal death, the second of which may represent apoptosis. Delayed neuronal death may represent an important therapeutic target in iTBI. NSE and S100B may also be useful as markers to identify occult iTBI, help differentiate nTBI and iTBI, and assist in determining the time of injury in cases of iTBI. *Pediatrics* 2002;109(2). URL: <http://www.pediatrics.org/cgi/content/full/109/2/e31>; head trauma, child abuse, apoptosis, delayed neuronal death, abusive head trauma.

ABBREVIATIONS. TBI, traumatic brain injury; nTBI, noninflicted traumatic brain injury; iTBI, inflicted traumatic brain injury; CSF, cerebrospinal fluid; NSE, neuron-specific enolase; GCS, Glasgow Coma Scale; ELISA, enzyme-linked immunosorbent assay; ICP, intracerebral pressure.

Trauma is the leading cause of death and disability in children. Traumatic brain injury (TBI) accounts for half of the mortality from trauma.¹ TBI can be divided into 2 subgroups—noninflicted (nTBI) and inflicted (iTBI). iTBI is the leading cause of death from TBI in infants and may be the cause of up to 95% of severe TBI in this age group.²

TBI is characterized by a primary injury that produces immediate cell death in severely disrupted brain regions and secondary damage that evolves as part of a cascade of injury mechanisms such as ischemia, brain swelling, inflammation, axonal degeneration, and programmed cell death.

Considerable insight into the mechanisms involved in secondary injury after TBI has resulted from analysis of ventricular cerebrospinal fluid (CSF) obtained in children with severe TBI.³ A number of mediators of secondary damage are increased in CSF after severe TBI in children; these include excitatory amino acids (glutamate, quinolinic acid),^{4,5} cytokines (interleukins 6, 8, and 10),^{6,7} and markers of delayed neuronal death (nucleosomes, cytochrome-C).^{8,9}

iTBI is characterized by a number of unique fea-

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tures. The mechanism of iTBI—violent shaking often followed by impact with a hard surface—is unlike any of the mechanisms of nTBI and is particularly deleterious to the brain.¹⁰ In addition, there is often marked neuronal hypoxia and ischemia resulting from a combination of delayed presentation, delay in diagnosis by health care professionals,¹¹ seizures, and/or apnea. A history of repeated insults may also magnify the severity of the injury.¹²

The biochemical response to iTBI is also unique and characterized by extremely high levels of mediators of secondary damage, but very low levels of endogenous neuroprotectants. Ruppel et al⁴ reported that CSF levels of glutamate were massively increased for a prolonged period of time in patients with iTBI compared with patients with nTBI. Janesko et al⁹ recently observed that increases in the apoptosis trigger cytochrome-C were associated with iTBI and mortality. Furthermore, patients with iTBI exhibit remarkably low levels of the antiapoptotic gene product Bcl-2.⁸

Neuron-specific enolase (NSE) is a glycolytic enzyme that is localized primarily to the neuronal cytoplasm. In adults, CSF concentrations of NSE have served as markers of neuronal damage in patients with a variety of neurologic conditions including status epilepticus,¹³ Creutzfeldt-Jakob disease,¹⁴ and metastatic lung cancer.¹⁵ NSE is also found in the CSF^{16–19} and serum¹⁷ of adults after TBI.

S100B is a calcium-binding protein localized to astroglial cells. Its physiologic function is not entirely understood, but its levels are increased in the presence of central nervous system lesions.²⁰ Neither the neuronal marker NSE nor the astroglial cell marker S100B has previously been studied in CSF after TBI in infants or children. Unlike the other markers of brain injury that have been studied in children, NSE and S100B are brain-specific, and their presence in the serum is specific for neuronal and astroglial cell death, respectively.

We hypothesized that NSE and S100B levels would be increased in the CSF of infants and children after severe TBI versus a comparison group. Using serial analysis of CSF after severe TBI in infants and children, we sought to delineate the extent of increase as well as the time course of increases in these CSF markers after severe TBI and their relationship to Glasgow Coma Scale (GCS) and mechanism of injury.

We hypothesized that there might be a difference in time course that was dependent on the mechanism of injury.

METHODS

Participants

Using a protocol approved by the hospital's institutional review board, we retrospectively studied 10 children admitted to the Children's Hospital of Pittsburgh pediatric intensive care unit with severe TBI (GCS <8) who had an intraventricular catheter placed for intracranial pressure measurement and CSF drainage and had their CSF collected and stored at the time of injury. The children ranged in age from 2 months to 9 years; patients <4 years old were preferentially selected to minimize the confounding effect of age in this comparison of nTBI and iTBI. For half the children the mechanism of injury was iTBI; this diagnosis was made either by confession of the perpetrator or based on accepted clinical criteria.¹⁰ CSF was collected at the time of catheter placement and then intermittently until catheter removal. All patients received standard neurointensive care at the time of injury. For children with iTBI in whom the time of injury was not known, the time used for all calculations was the latest possible time at which the injury could have been inflicted.

CSF was available from a comparison group of 5 children 0.1 to 2.3 years of age who were evaluated for meningitis with lumbar puncture and subsequently found to have no CSF pleocytosis (<6 white blood cells/mL³) and negative bacterial cultures. CSF was stored initially at -20°C and then transferred to -70°C until analysis.

Measurements

CSF NSE and S100B concentrations were quantified by an enzyme-linked immunosorbent assay (ELISA; SynX Pharma Inc, Ontario, Canada) according to the manufacturer's instructions. Samples were analyzed in duplicate and compared with known concentrations of NSE and S100B. The lower limits of detection of the ELISA are 1.00 ng/mL for NSE and 0.01 ng/mL for S100B.

Data Analysis

Data are expressed either as mean ± 1 standard error or as median values. A generalized linear regression model, controlling for the within-subject variation, was used to determine whether there was a difference in the CSF NSE and S100B concentrations among cases and controls. Restricting the sample to cases, a generalized linear model controlling for the within-subject variation was used to determine whether there were associations between the CSF NSE/S100B concentrations and initial GCS score or mechanism of injury. Initial GCS and injury mechanism were included in a linear regression model to determine whether they were associated with peak concentrations of either CSF NSE or S100B. Kaplan-Meier curves were used to assess differences in the time to the peak concentration of CSF NSE and S100B between patients with nTBI and iTBI. A log-rank statistic was used to test for differences in the time to peak concentration. A *P* < .05 was considered statistically significant.

TABLE 1. Demographic and Outcome Data

Patient Number	Age (Years)	Injury Mechanism	Initial GCS Score	Outcome
1	1.5	Fall	7	G
2	3.0	Go-cart rollover	3	MD
3	2.0	MVC	3	D
4	9.0	MVC	3	MD
5	1.8	MVC	3	MD
6	0.2	Abuse	14	SD
7	0.2	Abuse	9	MD
8	0.2	Abuse	4	SD
9	0.4	Abuse	12	SD
10	1.8	Abuse	7	SD

MVC indicates motor vehicle crash; G, good; MD, moderate disability; SD, severe disability; D, dead.

RESULTS

Patient demographics are shown in Table 1. Three children with iTBI had initial GCS scores greater than 8. Patients 6 and 9 deteriorated to GCS scores of <8 within 24 hours of their admission, at which time they received an intraventricular drain. Patient 7 presented with a GCS of 9 and a bulging anterior fontanel; an intraventricular drain was therefore placed on admission. There was no difference in age between patients with iTBI (median [range] 0.2 years [0.2–1.8]), nTBI (2.0 years [1.5–9]) and the comparison group (0.2 years [0.2–1.8]; $P = .11$ between iTBI and nTBI). The initial GCS score was higher in the iTBI group (9 [4–14]) versus the nTBI group (3 [3–7]; $P = .04$). A total of 35 CSF samples (18 samples from patients with nTBI, 17 from patients with iTBI, an average of 3.5 samples per patient) were analyzed. There was 1 death, in a patient with nTBI. The remaining 4 patients with nTBI survived with good outcome (1 patient), moderate disability (2 patients), or severe disability (1 patient) 3 months after injury. There were no deaths in the iTBI group. Four of 5 patients with iTBI had severe disability and 1 had moderate disability 3 months after injury.

CSF NSE After TBI

CSF NSE concentrations were increased versus the median value of controls in 34 of 35 determinations. The mean NSE concentration in patients with TBI was 117.07 ± 12.02 ng/mL versus 3.50 ± 1.42 ng/mL in controls ($P < .0001$; standardized β weight 8.77; Fig 1). Neither initial nor mean NSE concentration was associated with GCS or mechanism of injury.

Patients with iTBI had an initial peak in NSE concentration on day 1 after injury followed by a second, higher peak that was sustained for up to 8 days. For 2 of the 5 patients with iTBI, the concentration of NSE was still increasing at the last sampling time. In contrast, for all 5 patients with nTBI, the initial concentration was the peak concentration. The presence of this second, delayed peak in patients with iTBI

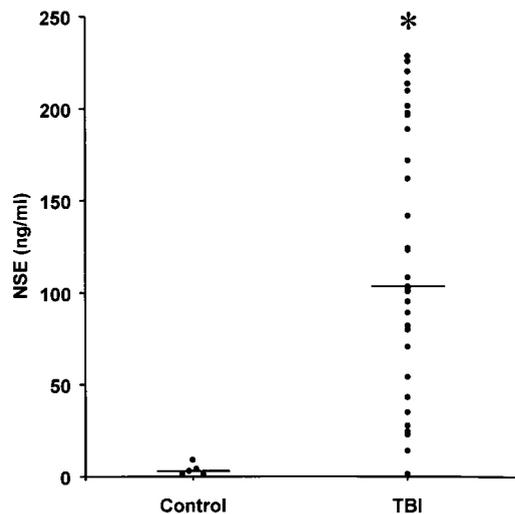


Fig 1. NSE concentration in CSF from children with severe TBI and controls. * $P < .0001$ versus comparison group. Median values shown.

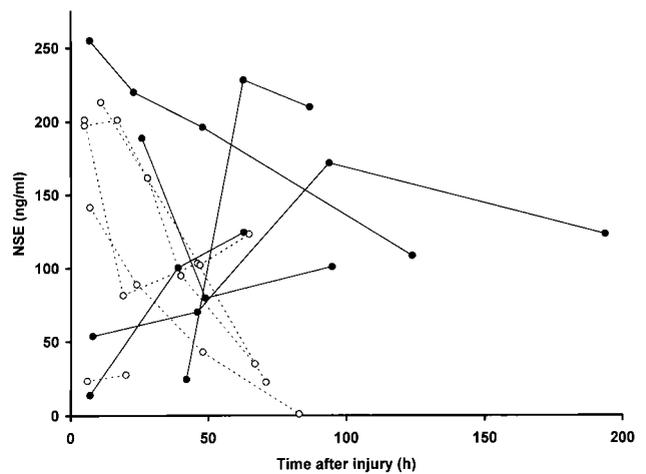


Fig 2. NSE concentrations in CSF versus time after injury in children severe TBI. Open circles/dotted lines represent children with nTBI. Solid circles/solid lines represent children with iTBI.

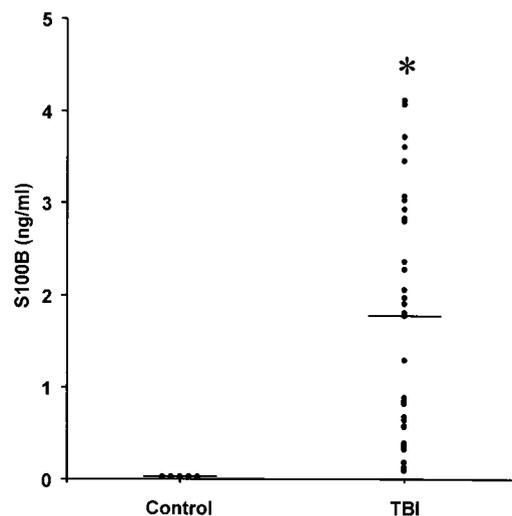


Fig 3. S100B concentration in CSF from children with severe TBI and controls. * $P < .004$ versus controls. Median values shown.

was best quantified by calculating the number of hours from the time of injury to the time of the peak NSE concentration. In victims of iTBI the median peak was 63 hours after injury (range: 7–94) versus 11 hours after injury (range: 5–20) in nTBI ($P = .02$; Fig 2).

CSF S100B After TBI

CSF S100B concentrations were increased versus control in all determinations. The mean S100B (SEM) concentration after TBI was 1.67 ng/mL (0.22 ng/mL) versus 0.02 ng/mL (0.00 ng/mL) in controls ($P = .004$; standardized β weight: 8.77) and occurred at a median of 27 hours (range: 5–63 hours) after injury (Fig 3). The mean S100B concentration, peak S100B concentration, and the time to peak were not associated with mechanism of injury. Mean S100B concentration was associated with GCS; S100B concentrations were higher in patients with GCS >4 than in patients with GCS <4 ($P = .01$).

DISCUSSION

CSF NSE After TBI

This is the first study, to our knowledge, to examine NSE concentrations in the CSF of infants and children after TBI. The concentrations of NSE after severe TBI are several times higher and more consistently increased versus the comparison group than reported in adults.²¹ This may reflect increased susceptibility of the developing brain to cell death after traumatic injury. This is supported by Bittigau et al²² who demonstrated increased apoptotic neuronal death after experimental TBI in immature rats and by Levin et al²³ who reported a particularly poor outcome after TBI in young children. The consistent increase in our patients could also be related to the ELISA used in our study, which is more sensitive than previous assays. It may also reflect greater injury severity in this patient population, particularly in children with iTBI. It is unlikely to be attributable to an age-dependent difference in the concentration of NSE in neurons in children versus adults; previous studies of CSF NSE concentrations in patients without neurologic disease suggest that NSE concentrations increase, rather than decrease, with age.^{24,25}

The second peak in NSE concentration in patients with iTBI is remarkable, and may reflect delayed neuronal death. This finding is consistent with previous research in both experimental animal models of TBI and recent clinical studies showing increases in markers of delayed neuronal death in abuse victims.^{4,8,9} Specifically, the increased delayed neuronal death may be related to a relative lack of anti-apoptotic neuroprotectants such as Bcl-2, in combination with a relative excess of apoptosis triggers such as cytochrome-C.^{8,9} This lack of balance between proapoptotic and anti-apoptotic factors would favor delayed neuronal death. The possibility that an apoptotic mechanism is an important contributor to the sustained increase in CSF NSE is supported by our finding that the time course of S100B in CSF did not vary based on the mechanism of injury. Neurons are much more sensitive to hypoxic damage and have a lower injury threshold to undergo apoptosis than do astrocytes.

We considered the possibility that the second peak was related not to primary injury, but to poor in-hospital control of intracerebral pressures (ICP). To assess this, clinical data from nine of ten patients were available and were carefully analyzed. Except for patient 5 (nTBI) and 8 (iTBI), all patients consistently had a mean ICP <20. These data suggest that poor in-hospital control of ICP was not the cause of the difference between the time course of NSE concentrations in nTBI and iTBI.

CSF S100B After TBI

This is the first study, to our knowledge, to show that S100B is increased in CSF after severe TBI in children. As with NSE, the concentrations of S100B we observed after TBI are severalfold higher and more consistently increased versus control than that seen in adults with TBI,²⁰ whereas our control concentrations are lower than most previously reported

CSF S100B concentrations.^{26,27} The possible reasons for this consistent increase mirror the reasons with NSE, namely increased susceptibility of the developing brain to traumatic injury, greater injury severity, or the high sensitivity of our ELISA which is approximately twofold greater than the sensitivity with the monoclonal immunoradiographic assay used in previous studies.^{28–30} In 8 of 10 patients, S100B concentrations had a single peak with a rapid decline. Presumably, these early increases in S100B concentrations correlate with primary brain injury at or near the time of impact.

The inverse relationship between GCS and S100B was unexpected. Other studies of CSF markers of brain injury have either shown a positive correlation or a lack of any correlation between peak concentrations and initial GCS score.^{4,7,31} Because of the small sample size in this study, the inverse relationship observed between S100B concentrations and GCS is most likely the result of a type I error.

Limitations of the Study

There are several limitations to our study. It may be argued that the group of patients with iTBI is not homogeneous and that it is therefore difficult to draw conclusions about the role of these markers in these patients. Patients with iTBI are a heterogeneous group; they have TBI from unknown mechanisms of injury and with unknown times of injury. However, despite this heterogeneity, the patterns of S100B and NSE accumulation are remarkably consistent suggesting that these patients can be analyzed as a group. This has also been consistent across other CSF markers.^{3–5,8,9}

It is possible that ventricular CSF concentrations of S100B and NSE may not reflect lumbar concentrations. Because it would be unethical to perform simultaneous lumbar and ventricular sampling in the patients in this study, it is not possible to answer this question directly. However, there are 3 studies in the literature in which concurrent sampling was performed.^{32–34} In all 3 studies, lumbar samples were more sensitive for detection of malignancy³² and infection,^{33,34} Based on these results, we would hypothesize that lumbar CSF from our control patients would be more sensitive to the presence of S100B and NSE, and thus an appropriate control group. In addition, ventriculostomies are generally placed for ventriculo-peritoneal shunt revision in the setting of infection or shunt failure or for brain tumor management. These conditions represent a poor comparison group.

Finally, there is the possibility that placement of the ventriculostomy results in increased S100B and NSE concentrations. Although ventriculostomy placement may cause a transient increase in the concentrations of either of these markers, it is unlikely to cause the magnitude of increase seen in our patients and would certainly not account for the secondary peak of NSE in patients with iTBI. The more likely scenario is that the immediate increase in S100B and NSE concentration is the result of primary brain injury rather than ventriculostomy placement. This is supported by recent data from our laboratory that

shows increased serum concentrations of S100B³⁵ and NSE immediately after mild and moderate TBI. These patients do not have a ventriculostomy in place.

CONCLUSION

This study demonstrates that NSE and S100B concentrations are markedly increased in the CSF of children after TBI. In addition, there is a secondary peak in CSF NSE concentration in children with ITBI that may result from delayed neuronal death.

NSE and S100B may have the potential to be used as quantitative measures of the success of therapy for TBI. Similarly, CSF NSE and S100B quantified early after injury might serve as an objective marker of the severity of injury—particularly important in light of the poor performance of GCS in children. The use of NSE and S100B as markers of injury severity has been studied in adults, where serum S100B and NSE concentrations are also increased after TBI.^{17,26,30,36,37} In these patients, there is a highly significant, direct correlation between the amount of these proteins in the serum and patient outcome.³⁷ A recently published study of almost 800 adults with mild, moderate, and severe TBI found that increased serum S100B was an excellent predictor of computed tomography scan abnormalities, raising the possibility that S100B could also be used as a screening test for diagnosis of intracranial injury.³⁸ A pilot study in children shows an increase in serum NSE after TBI,³⁹ and preliminary studies in our lab show an increase in both serum NSE and S100B.³⁵

Future research in our laboratory will focus on the possibility of using CSF and/or serum concentrations of NSE and S100B as markers of injury severity and as screening tests for unsuspected TBI in the emergency department or clinic setting. We also plan to assess the possibility of using serial measurements of NSE to help discriminate iTBI from nTBI and to help pinpoint the time of injury in cases of iTBI. Because serum is much more accessible than CSF, measurement of serum S100B and NSE concentrations may represent a relatively noninvasive means to help screen for intracranial injury after trauma, and perhaps identify occult iTBI by screening of high-risk patients.

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Neuron-Specific Enolase and S100B in Cerebrospinal Fluid After Severe Traumatic Brain Injury in Infants and Children

Rachel Pardes Berger, Mary Clyde Pierce, Stephen R. Wisniewski, P. David Adelson,
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