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Identification of Inflicted Traumatic Brain Injury in Well-Appearing Infants Using Serum and Cerebrospinal Markers: A Possible Screening Tool

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ABSTRACT

OBJECTIVE. Inflicted traumatic brain injury (iTBI) is the leading cause of death from TBI in infants. Misdiagnosis of iTBI is common and results in increased morbidity and mortality. Biomarkers may be able to assist in screening infants who are at high risk for iTBI and whose injury might otherwise be missed. We investigated whether serum and/or cerebrospinal fluid (CSF) concentrations of neuron-specific enolase (NSE), S100B, and myelin-basic protein (MBP) are sensitive and specific for iTBI in high-risk infants.

METHODS. A prospective case-control study was conducted of 98 well-appearing infants who presented with nonspecific symptoms and no history of trauma. Serum or CSF was collected. NSE, S100B, and MBP concentrations were measured by enzyme-linked immunosorbent assay. Abnormal marker concentrations were defined a priori. Patients were followed for 12 months to assess for subsequent abuse.

RESULTS. Fourteen patients received a clinical diagnosis of iTBI. Using preestablished cutoffs, NSE was 77% sensitive and 66% specific and MBP was 36% sensitive and 100% specific for iTBI. S100B was neither sensitive nor specific for iTBI. Five patients who were not identified with iTBI at enrollment were identified at follow-up as being possible victims of abuse; 4 had an increased NSE concentration at enrollment.

CONCLUSIONS. Serum and/or CSF concentrations of NSE and MBP may be useful as a screening test to identify infants who are at increased risk for iTBI and may benefit from additional evaluation with a head computed tomography scan. S100B is neither sensitive nor specific for iTBI in this study population. The ability to identify iTBI that might otherwise be missed has important implications for decreasing the morbidity and the mortality from iTBI.
INFLECTED TRAUMATIC BRAIN injury (iTBI) is a leading cause of death from TBI in infants.\textsuperscript{1,2} Population studies from Scotland,\textsuperscript{3} Wales,\textsuperscript{4} and the United States\textsuperscript{5,6} all have demonstrated a similar incidence of iTBI; the study in Scotland showed an annual incidence of iTBI of 1 in 4056 children who were younger than 1 year, whereas the study of severe and fatal iTBI in the United States showed an incidence of 1 in 3367.

Proper diagnosis of iTBI is often difficult even for experienced and astute physicians because caregivers rarely provide a history of trauma,\textsuperscript{2,6} children present with nonspecific symptoms such as vomiting or fussiness,\textsuperscript{7} and the physical examination is sometimes normal.\textsuperscript{8,9} As a result, misdiagnosis is common and can have catastrophic medical consequences.\textsuperscript{10,11} In a study by Jenny et al,\textsuperscript{10} 31% (54 of 173) of children who received a diagnosis of iTBI had been evaluated previously by a physician for nonspecific clinical symptoms that were compatible with head trauma. More than 40% of these children experienced medical complications related to the missed diagnosis; of the 5 deaths among the children with missed iTBI, 4 might have been prevented by earlier recognition of abuse. The importance of timely, accurate diagnosis of iTBI cannot be overemphasized: when not recognized, child abuse is a progressive and escalating form of trauma that often ends in death or permanent disability.\textsuperscript{12}

The frequency with which iTBI is misdiagnosed and the morbidity and the mortality that result from misdiagnosis are compounded by the fact that there is currently no well-established screening test to help physicians identify children who have nonspecific symptoms and might benefit from additional evaluation with cranial computed tomography (CT). The 2 currently available screening tools for abuse, skeletal survey and dilated eye examination, are not sensitive enough to be used as a screening tool for iTBI\textsuperscript{13} and require physicians who are experienced in evaluation of infant eyes and/or pediatric radiographs.

We previously reported on the possible use of serum and cerebrospinal fluid (CSF) biochemical markers as potential screening tools to evaluate infants who are at increased risk for iTBI.\textsuperscript{14,15} Many of these children have serum and/or CSF collected as part of routine care; therefore, a screening tool using these fluids could be added to current practice guidelines without a significant change in practice. In a previous study,\textsuperscript{14} we measured serum concentrations of 3 biochemical markers of injury (neuron-specific enolase [NSE], S100B, and myelin-basic protein [MBP]) in children with noninflicted TBI and iTBI. Cutoffs for NSE, S100B, and MBP were defined using receiver operator curves (ROC). At cutoffs of 11.77 ng/mL for NSE, 0.017 ng/mL for S100B, and 0.30 ng/mL for MBP, the sensitivity and the specificity of these markers were 71% and 64% (NSE), 77% and 72% (S100B), and 44% and 96% (MBP).\textsuperscript{14} A limitation of that study was that the ROC cutoff values were determined post hoc and the majority of the patients with iTBI presented either with a history of trauma or with severe symptoms. As a result, these were infants who were unlikely to receive a misdiagnosis.

The current study, therefore, was undertaken to determine whether the cutoff concentrations for serum NSE, S100B, and MBP determined in the previous study could be applied prospectively. The goal was to identify iTBI in what would be a target population for these screening tests: well-appearing infants who present without a history of trauma and with nonspecific symptoms.

METHODS

Patients

The protocol was approved by the Children’s Hospital of Pittsburgh (CHP) Institutional Review Board, and informed consent was obtained from the parents of all patients. Children were eligible when they were younger than 1 year and presented to the CHP emergency department (ED) with a temperature <38.3°C and 1 of the following symptoms: (1) apparent life-threatening event (ALTE), defined by the National Institutes of Health\textsuperscript{16}; (2) >4 episodes of vomiting without diarrhea in the previous 24 hours; (3) seizures or seizure-like activity; or (4) any other nonspecific neurologic sign or symptom not described above, such as lethargy or fussiness. We chose these symptoms because infants with any of these symptoms are at an increased risk for having iTBI.\textsuperscript{10} Enrollment was not consecutive and was based on availability of the investigators.

Measures

At the Time of Presentation

History of the present illness, medical history, physical examination findings, clinical diagnosis, and results of any laboratory and/or radiologic testing were collected. Specific laboratory and radiologic studies including lumbar puncture, venipuncture, and head CT were not performed as part of the study protocol but were done at the discretion of the treating physician. No data about socioeconomic status or social history were collected. Study personnel were not part of the treating team for any patient in the ED and therefore were not involved in any decisions about evaluation and treatment of potentially eligible patients.

A maximum of 2 mL of serum and/or 1 mL of CSF was collected at the time of the medical evaluation. To be eligible, patients were required to have blood or CSF collected as part of routine care; no patient underwent phlebotomy or lumbar puncture specifically for the study. Samples were centrifuged and frozen at –70°C until analysis. NSE, S100B, and MBP concentrations were quantified by enzyme-linked immunosorbent as-
say (Nanogen Corp, San Diego, CA) and analyzed in
duplicate. NSE was measured only in nonhemolyzed
samples because hemolysis interferes with the NSE as-
say. When a given patient had insufficient serum or CSF
to analyze all 3 biomarkers, NSE was measured prefer-
entially followed by S100B and then MBP. In cases in
which there was insufficient serum and a hemolyzed
sample, S100B was measured preferentially. Abnormal
biomarker concentrations were defined by cutoff values
that were established in a previous study.14

Follow-up
To assist in the determination of the sensitivity and the
specificity of the biomarkers, patients who were not
clinically identified as having iTBI at the time of enroll-
ment were tracked for subsequent evidence of possible
child abuse or exposure to domestic violence. Follow-up
occurred 6 and 12 months after enrollment and included
review of the child’s CHP medical record and telephone
contact. Tracking stopped after 12 months, because after
1 year of age, the risk for iTBI decreases significantly.1

Classification of Patients
Clinical Classification of Patients
On the basis of the clinical diagnosis and follow-up in-
formation, patients were classified into 1 of 4 categories:

iTBI, no brain injury (NBI), indeterminate, or brain in-
jury not caused by iTBI (Fig 1). Patients with iTBI re-
ceived their clinical diagnosis by consensus of the CHP
Child Protection Team, which was consulted on all cases
of possible abuse. Patients with NBI had no clinical evi-

dence of iTBI at presentation or follow-up. Indetermi-
nate patients did not receive a clinical diagnosis of iTBI at
enrollment but had evidence of possible child abuse or
exposure to domestic violence at follow-up. Patients
who received a diagnosis of a brain injury that was not
caused by iTBI did not have biomarker concentrations
measured and were not included in data analysis. These
patients are discussed further below.

Biomarker Classification of Patients
Patients were classified as true-positives, false-positives,
true-negative, and false-negatives on the basis of
whether biomarker concentrations were in agreement
with clinical diagnosis.

Statistical Analysis
Statistical tests were conducted by using SPSS 10.02
(SPSS Inc, Chicago, IL). All P values are 2-sided, and P <
.05 was considered statistically significant. Categorical
variables were compared by using Pearson’s χ². Nor-
mally distributed continuous variables were compared
by using t tests; skewed data were compared using
Mann-Whitney. Correlations among markers were per-
formed by using the Spearman’s ρ. Data are presented as
mean (SD) when normally distributed and median
when not normally distributed.

ROCs were constructed for each biomarker and an
area under the curve (AUC) was calculated. For the
purpose of the ROC curve, we compared 2 groups: iTBI
and NBI. Indeterminate patients were not included in
the ROC curves. Logistic regression was used to examine
the effect of NSE, S100B, and MBP on predicting brain
injury status (iTBI vs NBI). On the basis of the cutoffs
calculated by the ROC curve, sensitivity and specificity
were calculated for each biomarker.

RESULTS
Ninety-eight patients were enrolled from March 2002 to
July 2004. The demographics and presenting symptoms
for the iTBI and NBI groups are compared in Table 1.
Overall, there were no differences in age, gender, or
presenting symptoms of the iTBI and NBI groups. Care-
givers of patients with ITBIs waited significantly longer

FIGURE 1
Classification of patients on the basis of clinical
diagnosis and follow-up information. IND indi-
cates indeterminate.
after the start of symptoms to bring their children to medical attention compared with caregivers of patients with NBI (median [range]: 49.9 hours [1.5–1585.0 hours] vs 7.0 hours [0.8–671.4 hours]; \( P = .001 \), Mann-Whitney). As part of routine care, 100% of patients with iTBI and 28% (22 of 79) of patients with NBI had a head CT scan performed at enrollment. The most common clinical diagnoses for patients with NBI were ALTE/ap-"yrm (18%), gastroesophageal reflux disease (15%), infantile spasms (11%), and myoclonus (5%). Additional diagnoses included vomiting of unknown cause, fever, leth-argy, thrush, gastroenteritis, dehydration, pyloric steno-sis, and noncranial injury as a result of abuse.

**Follow-up**

We reviewed the medical records for 100% of patients 6 months after enrollment and for 75% of patients 12 months after enrollment. Forty-three percent of families were contacted by telephone. Forty-eight percent of families had no additional contact with CHP after the time of diagnosis. There were no cases in which a family provided information about significant medical problems that were not identified by chart review. No deaths occurred during the follow-up period.

Medical record review and telephone follow-up identified 5 patients who had subsequent evidence of possible child abuse or exposure to domestic violence. These patients were reclassified as indeterminate; their pre-senting symptoms, follow-up information, and biomarker concentrations are summarized in Table 2. In this group of 5, 4 (80%) had an increased NSE concentration at the time of enrollment.

**Group Classification**

On the basis of the discharge diagnoses and the follow-up information described above, 76% (74 of 98) of patients were classified as having NBI, 14% (14 of 98) as having iTBI, 5% (5 of 98) as indeterminate, and 5% (9 of 98) were classified as having brain injury not caused by iTBI. The diagnoses among patients with brain injury not caused by iTBI were arteriovenous malformation, cerebral edema from hypernatremia, intraventricular hemorrhage from prematurity, obstructive hydrocephalus, and birth trauma. Among the 14 patient with iTBI, 12 had a subdural hematoma (SDH), 2 had both chronic and acute SDH, 2 had chronic SDH only, and 8 had an acute SDH only. Five patients also had cerebral edema. Of the 2 patients with iTBI without an SDH, 1 had an isolated skull fracture and the other had a normal CT scan but a clinical diagnosis of iTBI on the basis of retinal hemorrhages, an abnormal mental status, and a perpe-trator confession.

**Sensitivity and Specificity of Biomarkers**

Sixty-one (66%) patients had serum available and 32 (34%) had CSF available for biomarker analysis; each patient had a single CSF or serum sample available for analysis. Among patients with serum available, 59% (36 of 61) had a sufficient volume of nonhemolyzed sample available for analysis of all 3 biomarkers. Among patients with CSF available, 75% (24 of 32) had sufficient sample available for analysis of all 3 biomarkers.

Using the cutoffs for abnormal biomarker concentra-tions established in a previous study of children with TBI, NSE was 76% sensitive and 66% specific and MBP was 36% sensitive and 100% specific for iTBI. S100B was increased in 90% of patient with NBI and therefore was not specific for iTBI in this population.

To determine whether the ROC curves from the pre-vious study could be used in the current population, ROC curves that evaluated the ability of each marker to predict iTBI were recalculated by using all available sam-ples. An ROC that evaluated the ability of NSE to iden-tify iTBI shows an AUC of 0.70 with 69% sensitivity and 70% specificity at an NSE concentration of 11.77 ng/mL (vs 11.36 ng/mL calculated in the previous study). An ROC that evaluated the ability of MBP shows as AUC of 0.67 with 36% sensitivity and 100% specificity for iTBI. S100B was increased in 90% of patient with NBI and therefore was not specific for iTBI in this population.

To determine whether serum or CSF was more sen-sitive and/or specific for identification of iTBI, we cre-ated separate ROC curves for NSE and S100B for serum and CSF. An ROC for CSF NSE showed an AUC of 0.83 and was 75% sensitive and 83% specific for iTBI at a cutoff of 11.66 ng/mL. However, because only 4 of the patients with iTBI had CSF available for analysis, addi-tional patients are needed to confirm the high sensitivity

| TABLE 1 - Characteristics of Patients in the iTBI and NBI Groups |
|-----------------|-----------------|-----|
| iTBI (n = 14)   | NBI (n = 74)    | P   |
| % Male          | 43              | 55  | NS  |
| Mean (SD) age, mo | 4.5 (2.6)      | 2.8 (2.7) | NS  |
| Ethnicity, %    |                 |     |
| White           | 67              | 71  | NS  |
| Black           | 17              | 15  |    |
| Biracial        | 0               | 11  |    |
| Other           | 17              | 3   |    |
| Presenting symptoms, % |     |     |
| Vomiting/fussiness | 57            | 44  | NS  |
| Seizure         | 21              | 19  |    |
| ALTE            | 21              | 38  |    |
| Median (range) time from onset of symptoms to presentation, h | 49.9 (2.53–1585.0) | 7.0 (0.8–671.4) | .001 |
of CSF for iTBI. An ROC for S100B showed an AUC < 0.5 for both serum and CSF.

The evaluate the effect of not having complete biomarker data for all patients, we compared the ROCs using data from only patients with all 3 biomarkers measured with the ROCs using data from all available samples (data reported above). ROCs using samples only from patients with all 3 biomarkers (n = 60) showed NSE with an AUC of 0.75, MBP with an AUC of 0.62, and S100B with an AUC of 0.45. The corresponding statistical test was significant only for NSE. As described above, the ROCs using all available samples showed NSE (n = 74) with an AUC of 0.70, MBP (n = 71) with an AUC of 0.67, and S100B (n = 89) with an AUC of 0.52. In this case, the corresponding statistical test was significant with both NSE and MBP, although the AUC for MBP was virtually the same in both cases. This suggests that the larger sample size was the reason for the statistical significance of MBP. In addition, the significance of both NSE and MBP was supported by the logistic-regression analysis below.

Logistic-regression analysis was performed in 2 steps to assess the effect of each marker on the ability to predict iTBI status. NSE and MBP were used in step 1, resulting in a χ² = 0.001, suggesting a good model fit. Addition of S100B at step 2 did not increase the model fit. Hosmer and Lemeshow tests were not significant at both steps; neither measure was improved by the addition of S100B. When both MBP and NSE were used to predict iTBI status, 1 patient with NBI was classified incorrectly as having iTBI, whereas 6 patient with iTBI were classified incorrectly as not having iTBI; overall, 84% (74 of 88) of patients were classified accurately using the logistic-regression model. However, because only patients with measurements of all 3 biomarkers could be put into the model, the sample size was limited.

DISCUSSION
Our results suggest that serum and CSF concentrations of NSE and MBP have the potential to be used as screening tests for iTBI in well-appearing infants who present without a history of trauma and with nonspecific symptoms, such as vomiting or fussiness. The ability to identify even a subset of well-appearing children with un-

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Clinical Data and Biomarker Concentrations for Indeterminate Patients</th>
</tr>
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<tbody>
<tr>
<td>Presenting Symptom</td>
<td>Biomarker Concentrations, ng/mL*</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Fussiness</td>
<td>NSE 15.91 MBP 0.22</td>
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<td></td>
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<tr>
<td>Fussiness</td>
<td>NSE 17.01 MBP ND b</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Fussiness</td>
<td>NSE 21.6 MBP 0.19</td>
</tr>
<tr>
<td>Vomiting</td>
<td>NSE 16.93 MBP ND b</td>
</tr>
<tr>
<td>Vomiting</td>
<td>NSE 8.21 MBP 0.13</td>
</tr>
</tbody>
</table>

ND indicates not done.

* Cutoff values: NSE, 11.36 ng/mL; MBP, 0.30 ng/mL.

b ND indicates not done due to secondary to inadequate sample volume and/or hemolyzed sample.

c To assess better the cause of the fluid seen on CT, the radiologist recommended an MRI; the family failed to appear for a subsequent appointment with the neurosurgeon and was lost to follow-up.
suspected iTBI has important implications for child protection because of the high risk for repeat injury or death when an abused infant is misdiagnosed and returned to the same violent environment in which the abuse occurred. Seventy-nine percent (11 of 14) of the patients with iTBI in this study had an increased NSE or MBP concentration; although none of them had a history of trauma, all were described as well-appearing by the ED physician who examined them, and all presented with nonspecific symptoms that could easily be misdiagnosed as other, more common childhood conditions, such as colic or gastroesophageal reflux. Five additional infants were identified clinically as possibly having had missed iTBI; 4 (80%) had had an increased NSE concentration at the time of enrollment. That 6.8% (5 of 74) of the patients in this study represented with possible child abuse within 6 months of enrollment emphasizes the high rate of abuse in this population. Importantly, all 5 of these patients initially presented with vomiting and/or fussiness. These were also the presenting symptoms for 57% (8 of 14) of the patients with iTBI, suggesting that these infants may be the ones at highest risk for missed iTBI. The significant delay in seeking medical care among patients who have been clinically identified with iTBI compared with those without iTBI is consistent with previous literature that supports a delay in seeking medical care after iTBI.17

The sensitivity and the specificity of NSE and MBP for the detection of iTBI in our population are similar to the sensitivity and the specificity of the triple screen in obstetrics, which is used universally to identify fetuses who are at high risk for neural tube defects and chromosomal abnormalities.18 As with the triple screen, increases in serum and/or CSF NSE and MBP might be useful as a screening test, not a diagnostic test, to identify infants who would benefit from additional evaluation with a head CT.

Serum Versus CSF
The established cutoff values for NSE, S100B, and MBP were derived from data from serum samples. In the current study, however, almost one third of patients had CSF but not serum available for analysis. On the basis of the preliminary ROC curve created with CSF alone, we believe that the sensitivity and the specificity of CSF may be higher than that of serum; because CSF is anatomically coupled to the brain, peripheral sources of the markers and difficulty crossing the blood-brain barrier (BBB) are not confounding factors. To determine whether different cutoff values are needed for serum and CSF, it will be important to increase the sample size of patients who have iTBI and have CSF samples available for analysis.

S100B Does Not Improve Prediction of iTBI
The literature supports the sensitivity of S100B as a marker of brain injury.15,19,20 In our sample, however, S100B was increased in 90% of patients using the predetermined cutoff. In addition, an ROC showed an AUC < 0.5, and binary logistic regression showed that S100B did not improve the ability to predict brain injury in this population. There was no statistically significant correlation between age and S100B concentration. As a result, S100B is unlikely to be a useful screening test for iTBI. We hypothesize that because S100B is synthesized primarily by the end foot processes of the astrocytes, an integral part of the BBB, differences in the BBB in infants and older children may be responsible for the wide variability of S100B concentrations in otherwise healthy children without evidence of iTBI. Previous research in adults supports S100B as a marker of BBB permeability and suggests that NSE is a marker of parenchymal damage.21,22 Recent literature in rats, mice, and snails suggests an additional role of S100B as a possible modulator of synaptic transmission and plasticity.23–25 We hypothesize that differences in synaptic plasticity and transmission in infants may also play a role in the wide variability of S100B in this age group.

Limitations
There are several limitations to this study. First, not all patients had a cranial CT to evaluate for iTBI. As a result, in >70% of cases, classification of a patient as NBI was based on clinical judgment and follow-up data. Thus, the false-negative and false-positive rates of the markers may be different from calculated. Although CT is currently the gold standard for diagnosis of iTBI, we believed that the risks to patients (radiation exposure and possible sedation) were not justified. Although MRI may be more sensitive and specific for iTBI than CT and eliminates radiation risk, we did not perform MRI primarily because infants almost always require sedation for an MRI, a risk that we did not believe was justified. Almost 30% of patient with NBI, however, did have a CT performed as part of routine evaluation. This is higher than anticipated and may have several explanations. CT scans were performed almost exclusively in patients with seizures and ALTE, children in whom the possibility of abuse may be more frequently considered. Importantly, the largest number of iTBI cases and all 5 of the indeterminate cases presented with vomiting and/or fussiness, the patient group least likely to have a CT scan performed. The study itself also may have affected physicians’ practice. In most cases, the treating physician obtained the consent to contact to allow investigators to approach families and therefore was aware that the study was designed to evaluate markers of brain injury. This may have prompted the treating physician to consider iTBI in the differential diagnosis and order a head CT.
A second limitation is that patients were part of a convenience sample. During the study period, many other children with the same symptoms were evaluated in the CHP ED and were not approached for enrollment because (1) they did not have serum or CSF collected as part of routine care, (2) they had serum or CSF collected but did not have any leftover that could be used for study purposes, (3) the treating team did not realize that the child might be eligible for the study and therefore did not obtain consent for study personnel to approach the family for consent, or (4) the treating team approached the family but the family refused consent to contact. Because of confidentiality issues, it is not possible to know how many patients fit into the above categories. However, among patients who were approached by study personnel, >95% consented to enrollment. It is also possible that patients in whom serum or CSF samples were obtained as part of routine care had more significant symptoms (eg, more episodes of vomiting) than those who did not have samples obtained.

Finally, because the prevalence of iTBI in the general population is lower than in the study population, the positive predictive values of these tests will be low despite acceptable sensitivity and specificity. Although the prevalence of iTBI in the group of infants who were eligible for the current study is not known, it is likely much higher than the incidence of 1 in 3367 that was seen among all children who were younger than 1 year and observed in a recent population-based study in United States. That study included only children with severe or fatal iTBI; in cases of noninflicted TBI, the severe or fatal cases make up only 10% of the total number of patients with TBI.\(^1\) The limitation introduced by a low positive predictive value must be addressed in future studies to select the most appropriate target populations for screening. The results of our study suggest that the subgroup of infants with vomiting and/or fussiness may be a subgroup in which screening is most justified. Additional analysis is also necessary to evaluate the cost-effectiveness of biomarker screening and the risk-benefit ratio of screening with biomarkers given the morbidity and the mortality of missed cases of iTBI and the complications and cost of follow-up testing with CT scan.

CONCLUSIONS

This study demonstrates that serum and CSF concentrations of NSE and MBP may have potential as screening tests to identify children who are at high risk for iTBI and would benefit from additional evaluation with head CT. To our knowledge, this is the first test that would easily allow physicians to screen high-risk infants for iTBI. The ability to identify infants who have iTBI and might otherwise have received a misdiagnosis would allow health care providers to limit medical complications as a result of delayed diagnosis, minimize reinjury to infants by preventing them from returning to an unsafe environment, and protect siblings who may be living in the same violent environment. Future research is necessary to compare the sensitivity and the specificity of serum and CSF concentrations of NSE and MBP in a larger group of at-risk infants, determine the group of infants who should be targeting for screening, and evaluate the cost-effectiveness of biomarker screening.

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