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The Use of Biomarkers After Inflicted Traumatic Brain Injury: Insight into Etiology, Pathophysiology, and Biochemistry

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Inflicted traumatic brain injury (iTBI) is the most common cause of severe brain injury in infants. Proper diagnosis is difficult even for experienced emergency department physicians. Misdiagnosis is common and can have catastrophic consequences for patients and society. After iTBI, biochemical markers are released from brain tissue and pass into the cerebrospinal fluid and serum. Measuring the concentrations of these markers may help to identify brain injury that could otherwise be missed. Biomarkers may also be able to help differentiate noninflicted TBI from iTBI, assist in the timing of iTBI, improve our understanding of the pathophysiology of iTBI, and predict outcome after iTBI.
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Inflicted traumatic brain injury (iTBI) is a leading cause of death and disability in children less than 2 years of age; nearly one quarter of all pediatric hospital admissions for TBI [1] and two thirds of all infant homicides are the result of iTBI [2]. The incidence of severe or fatal iTBI in children less than 1 year of age is approximately 1 in 3300 [3]. Therefore, pediatric emergency department (ED) physicians are likely to encounter many children with iTBI during the course of their careers.

Compared with victims of noninflicted TBI (nTBI), victims of iTBI are younger and often have evidence of prior (and therefore repetitive) TBI. Outcome after iTBI is dismal; up to one third of infants die from their injury, and most of the survivors have significant long-term disabilities [4,5]. When compared with children with nTBI, children with iTBI have a worse outcome when adjusting for age and severity of injury [5,6].

Proper diagnosis of iTBI is difficult even for experienced ED physicians. Often, there is difficulty in recognizing that an infant or young child has been a victim of trauma. The presentation of iTBI can be subtle, and important historical data are often lacking. At other times, a difficulty facing the ED physician is determining whether a given TBI is the result of an inflicted or noninflicted event. Whereas most young victims of nTBI present for medical care with a clear and consistent history of a major head injury event (eg, a motor vehicle collision), many children with iTBI present with an absent, changing, or inconsistent history of a minor head injury event, such as a short distance fall [7-9]. Although a denial of any trauma in the presence of intracranial injury is suspicious for abuse, it is often difficult to determine the etiology when the history of trauma seems plausible and possibly compatible with the injuries sustained. The importance of early recognition that an injury might be the result of abuse cannot be overemphasized; if not recognized, a child may be discharged

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from an ED or inhospital setting and returned to a violent environment only to be reinjured or killed.

Many infants with iTBI do not present with specific signs of brain dysfunction such as a seizure or loss of consciousness. Instead, they present with mild, nonspecific clinical signs such as irritability, recurrent vomiting, fever, or loss of appetite [9,10]. In addition to the lack of a clear history of trauma or symptoms of brain injury, almost half of children with iTBI present without any evidence of external trauma [11,12]. Others present with only subtle indications of trauma such as a scalp or facial bruise, which can easily be overlooked [9,13].

For all these reasons, even a high index of clinical suspicion is often not enough to properly identify children with iTBI. Misdiagnosis of iTBI is therefore common and can have catastrophic medical consequences for patients and significant financial consequences for society [9,14].

The frequency with which iTBI is misdiagnosed and the resulting morbidity and mortality are compounded by the fact that there is currently no well-established screening test to help physicians differentiate between iTBI and nTBI or identify children with nonspecific symptoms who might benefit from additional evaluation with cranial computed tomography (CT). Although having a low threshold for neuroimaging in young children is clearly important, it is not possible to obtain a head CT on all children with vomiting, fussiness, or irritability. The 2 currently available screening tools for abuse—skeletal survey and/or dilated eye examination—are not sensitive enough to be used as a screening tool for iTBI [15,16] and require physicians experienced in those evaluations [17]. Physicians clearly need a new tool for identifying unsuspected iTBI and for differentiating between iTBI and nTBI.

Biomarkers of Brain Injury: Background

Serum biomarkers are currently used clinically to quantitatively assess and define injury in virtually every organ system other than the brain (Table 1). The most widely accepted serum biomarkers in adults are creatine kinase isoenzyme MB and troponin, which have surpassed the electrocardiogram as the gold standard for diagnosis of myocardial infarction [18].

The use of biomarkers to assess brain injury has been an area of research since the late 1970s and early 1980s [19,20]. Development of a useful biomarker of brain injury has proven to be more difficult than development of biomarkers for other organ systems for several reasons. Perhaps, most importantly, the brain is a more complex and less homogenous organ, and different types of injury can occur to different types of brain cells with variable degrees of severity. In addition, the presence of a blood-brain barrier limits the amount and size of the markers that can be detected in blood.

Table 1 The use of biochemical markers of injury in various organ systems.

Organ	Marker
Heart	Troponin, creatine phosphokinase–MB
Liver	Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase
Pancreas	Lipase, amylase
Muscle	Creatine phosphokinase–MM
Kidney	Blood urea nitrogen, creatinine
Brain	???

Extensive adult studies have shown that the presence of biochemical markers in the serum and cerebrospinal fluid (CSF) after TBI is a sensitive and specific indicator of brain injury [21-25]. As a result, there is extensive literature exploring the use of brain biomarkers for a wide variety of clinical scenarios, including understanding the pathophysiology of injury, predicting intracranial injury after concussion, and predicting outcome. The majority of this research has been in adults. There are several potential additional uses of biomarkers unique to iTBI: identifying unsuspected TBI, timing injury in cases of known iTBI, and distinguishing iTBI from nTBI. The primary focus of this review will be on the role of biomarkers as a screening tool for unsuspected iTBI. The role of biomarkers in each of these other clinical scenarios will also be discussed, as well as the emerging technology of proteomics and its possible role in identification of new biomarkers unique to iTBI.

Using Serum Biomarkers to Identify Unsuspected iTBI

Emergency department physicians currently have only clinical suspicion as a way to decide which infants with nonspecific signs and symptoms and a normal physical examination should undergo neuroimaging. Recent research suggests that serum biomarkers could be used as a screening tool to identify brain injury in these infants [26]. Although CSF could, in theory, be used as a screening tool as well, serum has several advantages over CSF. The most important is ready access to blood, which provides the ability to more easily integrate measurement into routine care even in nontrauma centers and/or those hospitals where ED physicians are not comfortable obtaining CSF from young children. The serum bio-

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