Patterns of Osteopontin Expression in Abusive Head Trauma Compared with Other Causes of Pediatric Traumatic Brain Injury

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Objective To examine levels of plasma osteopontin (OPN), a recently described neuroinflammatory biomarker, in children with abusive head trauma (AHT) compared with children with other types of traumatic brain injury (TBI).

Study design The study cohort comprised children aged <4 years diagnosed with TBI and seen in the intensive care unit in a tertiary children's hospital. Patients were classified as having confirmed or suspected AHT or TBI by other mechanisms (eg, motor vehicle accidents), as identified by a Child Protection Team clinician. Serial blood samples were collected at admission and at 24, 48, and 72 hours after admission. Levels of OPN were compared across groups.

Results Of 77 patients identified, 24 had confirmed AHT, 12 had suspected AHT, and 41 had TBI. There were no differences in the Glasgow Coma Scale score between the patients with confirmed AHT and those with suspected AHT and those with TBI (median score, 4.5 vs 4 and 7; $P = .39$). At admission to the emergency department, OPN levels were significantly higher in children with confirmed AHT compared with the other 2 groups (mean confirmed AHT, 471.5 ng/mL; median suspected AHT, 322.3 ng/mL; mean TBI, 278.0 ng/mL; $P = .03$). Furthermore, the adjusted mean trajectory levels of OPN were significantly higher in the confirmed AHT group compared with the other 2 groups across all subsequent time points ($P = <.01$).

Conclusions OPN is significantly elevated in children with confirmed AHT compared with those with suspected AHT and those with other types of TBI. OPN expression may help identify children with suspected AHT to aid resource stratification and triage of appropriate interventions for children who are potential victims of abuse. *(J Pediatr 2020;227:170-5)*.

See editorial, p 15 and related article, p 176

According to the US Centers for Disease Control and Prevention, abusive head trauma (AHT) accounts for approximately one-third of fatalities related to child maltreatment and resulted in the deaths of nearly 2250 US children from 1999 to 2014.[1] The estimated incidence of AHT in the first year of life is 35 cases per 100 000 infants.[2] For those who survive AHT, its consequences are significant, with lifelong physical and cognitive effects, along with a substantial burden for caregivers.[3-5]

Children with AHT present with a myriad of features that are subjects of ongoing controversy and debate.[6,7] Studies have shown that several clinical features are more consistent with abusive injury, including apnea, retinal hemorrhage, and specific bruising patterns.[2,6,7] With regard to intracranial injury, certain findings in combination, such as subdural hemorrhage, cerebral ischemia, cerebral edema, and skull fractures, are more common in AHT compared with other mechanisms.[8] This pattern is particularly prominent when these features are observed within the context of inconsistent caregiver history and younger patient age.[6]

Although blood biomarkers hold promise for identifying children who may have more severe head injuries, none are in widespread clinical use and none have been shown to identify those at higher risk for AHT.[9-12] Similar to screens for other diseases, an ideal traumatic brain injury (TBI)-related biomarker should easy to assay expeditiously at the point of care, cost-effective, minimally invasive, and of high sensitivity and specificity. We have previously reported that osteopontin (OPN), an inflammatory cytokine expressed by activated microglia, is a putative biomarker for pediatric TBI.[13] OPN has many attributes that make it an intriguing candidate biomarker, including low background plasma levels in healthy conditions, high stability in biofluid, and integrin-mediated brain-to-blood transport.[14-18]

AHT	Abusive head trauma
cAHT	Confirmed abusive head trauma
CPT	Child Protection Team
GCS	Glasgow Coma Scale
OPN	Osteopontin
sAHT	Suspected abusive head trauma
TBI	Traumatic brain injury

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The aim of the present study was to expand on our previous work examining the use of OPN in treating pediatric head injuries and to determine whether there are differences in OPN expression between children who sustain AHT compared with children with other causes of TBI. To accomplish this objective, we used a prospective cohort of children admitted to the hospital with TBI. We hypothesized that plasma OPN levels would be markedly elevated at all time points in children diagnosed with AHT compared with children who sustained TBI due to other mechanisms.

Methods

Study Sample

The study was approved by the Children's Healthcare of Atlanta Institutional Review Board and used blood samples collected as part of previously approved protocols between 2013 and 2019. Children were eligible as cases if they were aged ≤4 years, had a diagnosed TBI, and had a Glasgow Coma Scale (GCS) score of 3-12, or 13-15 with positive neuroimaging findings. Exclusion criteria included penetrating trauma (eg, gunshot wound), GCS score of 13-15 without positive neuroimaging findings, age >4 years, transfer from another hospital, and nontraumatic head injury or other medical illness.

The participants were divided into the categories of confirmed AHT (cAHT), suspected AHT (sAHT), and TBI not including AHT. Cases of abuse were identified based on the conclusion of a Child Protection Team (CPT) consensus. Specifically, the CPT provided an in-depth summary of presenting clinical and medical symptoms and concluded, based on their assessment, whether the child's injuries were the result of suspected abuse. Furthermore, we classified the children as cAHT when an alleged abuser was arrested. Clinical and demographic variables were collected from patient electronic medical records.

Sample Collection

Blood samples were collected on admission to the emergency department within 6 hours of reported injury, as well as 3 follow-up collections at 24, 48, and 72 hours after the time of the initial draw or until the patient was discharged. Blood was prepared and processed according to the TBI Common Data Elements Biospecimens and Biomarkers Working Group guidelines.[19] Samples were centrifuged, aliquoted, and frozen at −80°C for future batch processing.

Human plasma samples were analyzed in duplicate using commercial ELISA kits (R&D Systems, Minneapolis, Minnesota). According to the manufacturer's protocol, the human plasma samples were diluted 50 times with the dilution buffer provided in the kit. If the ELISA readouts of diluted samples were higher than the assay range, these samples were further diluted until covered by the calibration range.

Statistical Analysis

Descriptive statistics for the study were reported as median and interquartile range (IQR; 25th-75th percentiles) for continuous data and counts and percentages for categorical data. The normality of continuous data was assessed using the Shapiro-Wilk test. Given the 3 groups of interest (c AHT, sAHT, and TBI), comparisons of continuous data were performed using the Kruskal-Wallis test for nonnormally distributed data and ANOVA for normally distributed data. Categorical data were compared using the χ^2 test or Fisher exact test for cell counts <5. Post hoc comparisons across groups of interest were conducted using Tukey-adjusted pairwise comparisons for continuous data and the χ^2/Fisher exact test with Bonferroni correction ($P < .0167$ for the 3 comparison groups) for categorical data. Generalized linear models with an interaction term for group × time were analyzed to assess differences in OPN trends between the cAHT and TBI groups. Race and age were adjusted for in the models, and adjusted least squares means were reported. All other statistical tests were assessed at the .05 significance level. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Patient Demographics

Between June 2013 and March 2019, a total of 347 participants (127 of whom were aged <4 years) were enrolled in 2 separate TBI studies. Forty-eight of these 127 patients were excluded due to missing or unusable samples (eg, clotting). The patients' demographic and clinical characteristics are presented in **Tables I** and **II**. The final sample comprised 77 patients ranging in age from 0 to <4 years (median age, 1.7 years). The cAHT group was significantly younger (0.7 years) compared with the sAHT group (2.7 years) and the TBI group (2.2 years). Significant differences were also noted between height and weight, with the cAHT group being significantly smaller. Males were overrepresented in the cAHT and sAHT groups when compared with the TBI group. Blacks were also overrepresented compared with other racial categories in the cAHT and sAHT groups as opposed to the TBI group. Additional differences between groups included duration of acute hospitalization and number of days spent on a ventilator (**Table II**).

OPN Level

Plasma levels of OPN differed significantly among the groups on admission to the emergency department ($P = .03$; **Table II** and **Figure 1**). The cAHT group had significantly higher levels of OPN at admission (median, 471.5 ng/mL) compared with the other 2 groups. Comparing the trajectory of OPN over time (**Figure 2**), the cAHT group showed a steady increase in levels across the 4 time points, with significantly higher OPN levels at 72 hours compared with the TBI group ($P = .0285$), even after adjusting for age and race. Although the OPN levels in the cAHT group remained higher compared with the other groups across all time points (interaction for group × time, $P = .0523$), no statistically significant differences among the 3 groups were observed at the 24-, 48-, or 72-hour time points.

Table I. Patient demographic characteristics

Characteristics	N	All (N = 77)*	cAHT (N = 24)	sAHT (N = 12)	Accidental TBI (N = 41)	*P* value
Age, y, median (IQR)	77	1.7 (0.7-3.5)	0.7 (0.3-1.5)[a]	2.7 (1.4-3.7)[b]	2.2 (0.9-3.6)[b]	**.001**
Height, cm, median (IQR)	70	84 (68.5-98)	69.3 (54.0-81.5)[a]	95.0 (74.0-102.0)[b]	88.0 (80.0-101.0)[b]	**.001**
Weight, kg, median (IQR)	76	12 (8.8-16)	9 (6.625-11.38)[a]	14.4 (8.8-16)[b]	13.4 (10.4-16.8)[b]	**<.001**
Female sex, n (%)	77	32 (41.6)	8 (33.3)	2 (16.7)	22 (53.7)	**.045**
Race, n (%)	77					**.044**
White		32 (41.6)	5 (20.8)[a]	4 (33.3)	23 (56.1)[b]	
Black or African American		38 (49.4)	17 (70.8)[a]	8 (66.7)	13 (31.7)[b]	
Asian		4 (5.2)	1 (4.2)	0 (0.00)	3 (7.3)	
Mixed race (white/black)		2 (2.6)	1 (4.2)	0 (0.00)	1 (2.4)	
Declined to answer		1 (1.3)	0 (0.00)	0 (0.00)	1 (2.4)	
Race, n (%)	77					**.003**
Black or African American vs not/declined)		40 (51.9)	18 (75.0)[a]	8 (66.7)	14 (34.1)[b]	
Ethnicity, n (%)	77					.704
Hispanic or Latino		13 (16.9)	3 (12.5)	2 (16.7)	8 (19.5)	
Non-Hispanic or Latino		63 (81.8)	20 (83.3)	10 (83.3)	33 (80.5)	
Declined to answer		1 (1.3)	1 (4.2)	0 (0.00)	0 (0.00)	

P value: Kruskal-Wallis test (nonnormal) or ANOVA (normal) tests for continuous variables or the χ^2 test (if cell count <5, Fisher exact test) for categorical variables. Different superscript letters indicate significant differences between groups (Tukey-adjusted multiple pairwise comparisons or χ^2/exact test with Bonferroni correction). Statistical significance assessed at the .05 level; $P < .05$ shown in bold type.
*Some values are missing. Refer to column 2 for total N available for each variable.

Discussion

This preliminary study examined the utility of OPN as a new candidate blood biomarker for differentiating AHT from other causes of TBI in children. We found higher OPN plasma levels at admission to the emergency department in patients with confirmed AHT compared with patients with other causes of TBI. Furthermore, the trajectory of OPN appeared to differ among the groups, with a continual increase in OPN seen across the 72-hour period in children with AHT. In addition, our findings support previously reported evidence indicating worse outcomes that children with AHT compared with children with TBI.[20,21] Specifically, patients with AHT had a longer length of stay, more days on a ventilator, and a higher mortality rate.

An inflammatory response following TBI is well documented, with activation of both the central nervous system and peripheral immune system, with peripheral cells entering the central nervous system via blood-brain barrier disruption.[22] In a study examining the cerebrospinal fluid of 66 pediatric patients following severe TBI, Newell et al found elevated markers of macrophage/microglial activation (sCD163 and ferritin). In addition, they found that high ferritin levels in the cerebrospinal fluid was associated with younger age, lower GCS score, AHT, and unfavorable outcomes.[22] These findings suggest an exaggerated neuroinflammation in patients with AHT specifically.

We have demonstrated that OPN, a neuroinflammatory marker, is predictive of the severity of TBI in both preclinical and clinical studies.[13] OPN has biological characteristics that

Table II. Patient clinical characteristics

Characteristics	N	All (N = 77)*	cAHT (N = 24)	sAHT (N = 12)	Accidental TBI (N = 41)	*P* value
GCS score, median (IQR)	77	5 (3-8)	4.5 (3-6.5)	4 (3-7)	7 (3-9)	.389
Deceased, n (%)	77	17 (22.1)	9 (37.5)	1 (8.3)	7 (17.1)	.073
Severity, n (%)	77					.214
Mild complicated		12 (15.6)	5 (20.8)	1 (8.3)	6 (14.6)	
Moderate		6 (7.8)	0 (0.00)	0 (0.00)	6 (14.6)	
Severe		59 (76.6)	19 (79.2)	11 (91.7)	29 (70.7)	
Length of stay, d, median (IQR)	77	8 (3-14)	11.0 (6.0-20.0)[a]	8.5 (5.5-12)	4 (2-13)[b]	**.023**
Vent days, median (IQR)	77	4 (1-10)	8 (3-11.5)[a]	5.5 (2-10.5)	2 (1-6)[b]	**.020**
Craniotomy, n (%)	77	22 (28.6)	8 (33.3)	4 (33.3)	10 (24.4)	.687
Skull fracture, n (%)	77	45 (59.2)	10 (41.7)	8 (66.7)	27 (67.5)	.107
Rehabilitation, n (%)	77	32 (41.6)	11 (45.8)	7 (58.3)	14 (34.1)	.287
Intubated, n (%)	77	65 (84.4)	21 (87.5)	12 (100.0)	32 (78.0)	.196
Sedated, n (%)	77	36 (46.8)	9 (37.5)	7 (58.3)	20 (48.8)	.463
External ventricular drain, n (%)	77	31 (40.3)	12 (50.0)	2 (16.7)	17 (41.5)	.153
OPN, ng/mL, median (IQR)						
At admission	76	320.9 (237.7-610)	471.5 (332.3-637.8)[a]	322.3 (268.9-599.2)	278.0 (191.0-504.7)[b]	**.033**
24 h	35	534.8 (404.4-697)	633.5 (433.0-791.0)	422.5 (333.8-476.9)	517.6 (404.35-697)	.270
48 h	27	613 (273.5-778.7)	720.0 (616.0-893.0)	336.1 (57.0-650.4)	462.0 (273.5-778.7)	.167
72 h	18	697.5 (522.2-1283)	1114.5 (1002.2-1717.0)	412.9 (218.9-606.9)	622.8 (412.4-768.4)	.079

P value: Kruskal-Wallis test (nonnormal) or ANOVA (normal) for continuous variables or χ^2 test (if cell count <5, Fisher exact test) for categorical variables. Different superscript letters indicate significant differences between groups (Tukey-adjusted multiple pairwise comparisons or χ^2/exact tests with Bonferroni correction).Statistical significance assessed at the 0.05 level. $P < .05$ shown in bold type.
*Some values are missing. Refer to column 2 for total N available for each variable.

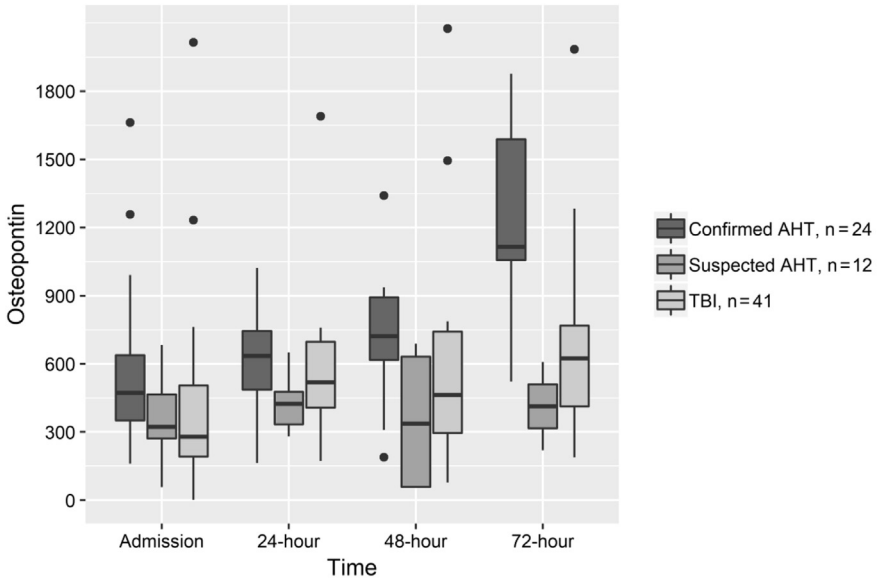

Figure 1. OPN levels in the 3 patient groups at hospital admission and 24 hours, 48 hours, and 72 hours after admission. In the boxplot graph, outliers (*black dots*) are values falling outside of the ±1.5*IQR range from the 25th or 75th percentile. The *black center line* indicates the median.

make it a potential candidate biomarker for identifying children with AHT. It is released from microglia as a result of brain injury and can be detected easily via plasma due to its ability to cross the blood-brain barrier. In addition, it is a biologically stable molecule, and point-of-care measurement is feasible.[23] We speculate that OPN is up-regulated in children with AHT compared with those with other mechanisms of TBI, for several reasons. First, the enhanced systemic inflammation associated with a chronic stressful environment is likely present in this population.[24] It is well known that chronic childhood stress can lead to a prolonged inflammatory response as well as a diminished immune response.[25-27] Second, it is plausible that these children exhibit an enhanced inflammatory response related to probable repeated injury that may have occurred before admission.[28,29] In many cases of AHT, there is clinical and radiographic evidence of multiple injuries of differing ages.[7,8] Repeated TBI is associated with an aberrant or more exaggerated inflammatory response than a single episode of TBI.[22,30] Third, studies have shown a higher incidence of hypoxic-ischemic encephalopathy in children with abusive head trauma, a diagnosis that has also been associated with an up-regulation in OPN.[6,14,31] Associated hypoxic-ischemic encephalopathy may contribute to the higher levels of OPN seen in AHT compared with TBI alone.

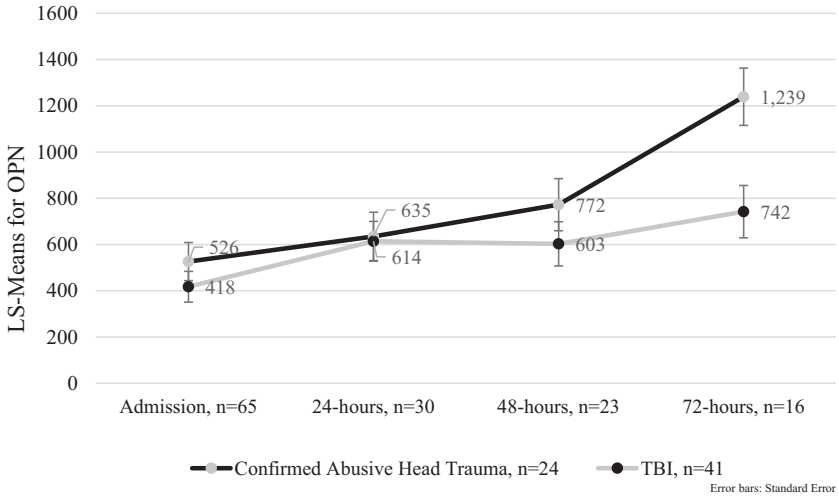

Figure 2. Trajectory of least squares mean OPN level in children with AHT vs those with TBI at hospital admission and 24 hours, 48 hours, and 72 hours after admission. The *dark line* represents confirmed AHT; *gray line*, TBI. Error bars represent the standard error.

The relationship between age and OPN levels requires further study. Baseline data on OPN levels at various ages is lacking. In a study examining OPN in healthy children, no relationship was found between OPN level and age; however, that sample included older children and did not assess infants and toddlers.[32] It is also possible that an elevated OPN level is a reflection of a different, possibly enhanced inflammatory response in infants following severe head trauma, irrespective of etiology. In this series, we were able to adjust statistically for age as an influence on OPN levels. Although we found higher OPN levels in children with AHT independent of age, we cannot exclude the possibility that age alone is a driving factor of the observed OPN levels, and this requires additional investigation.

This study is not without limitations. Although there was a sufficient sample size at admission, issues with consent occurred at later time points owing to a variety of factors, including death, and removal of caregiver rights, resulting in a smaller sample size at 24, 48, and 72 hours. Controversies also exist regarding the diagnosis of AHT and have been well described.[6,33] Without a reliable witness or direct evidence, the diagnosis is made with varying and incomplete degrees of certainty. We defined cases of confirmed AHT based on the conclusion of our hospitals' CPT consensus, which has been considered satisfactory in previous studies.[11,34,35] In addition, although the literature reports minimal OPN levels in normal children, OPN levels were not measured in our patients before the trauma.[32] It is possible that children suffering from abuse unrelated to head injury also could have elevated OPN levels due to the stressful environment, and the biomarker may be unrelated to TBI.[28,29] Finally, our cohort included only children with mild complicated to severe head injury. No inference can be made about those children who present with mild TBI and negative neuroimaging findings, which arguably could be a more meaningful patient population to screen for AHT.

In summary, given the significant repercussions of inaccurate diagnosis of AHT, there remains that need for an objective biomarker to aid in the identification of AHT. Our data provide evidence for OPN as a potential diagnostic tool in pediatric TBI which may help distinguish children with AHT. These findings need to be replicated in larger independent cohorts before incorporation into clinical algorithms might be considered. The use of serum OPN level to identify AHT alone or in in combination with other clinical or laboratory biomarkers warrants further investigation. ■

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50 Years Ago in *The Journal of Pediatrics*

From Toxicity to Specificity, an Overview on Acute Lymphocytic Leukemia Treatment

Pinkel D. Treatment of childhood acute lymphocytic leukemia. J Pediatr 1970;77:1089-91.

Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood and the most curable disease in pediatric oncology. In the 1960s, ALL was an almost uniformly fatal disease, but due to new therapies and breakthroughs in the last 50 years, the current 5-year survival rate has improved to 89% in children and 61% in young adults.[1]

The essence of ALL treatment remains the same and continues to be grouped in the following phases: induction, consolidation, and a prolonged maintenance. One of the most significant changes is the individualization of each patient, classifying them according to risk stratification, predictive biomarkers, molecular prognosis, and monitoring of minimal residual disease, aiming to reduce complications and mortality of chemotherapy itself. Another major shift includes central nervous system prophylaxis, an essential part of ALL management and a prerequisite for successful treatment.[2]

Fifty years ago, "complete remission" was based on Bisel morphologic criteria, which Pinkel considered insufficient, as it excluded central nervous system involvement. Today, analytic minimal residual disease testing using flow cytometry is a strong prognostic indicator in all leukemia subtypes.[3]

The last decade has seen significant advances in treatment; thanks to molecular biology, Paul Ehrlich's "magic bullet" concept is reaching its full realization. Today, we are in the era of monoclonal antibody therapy with new drugs such as blinatumomab, inotuzumab, and chimeric antigen receptor T cells, which target specific abnormal molecules and pathways of cancer cells.[2]

These new therapies came with new complications and adverse effects, so the imperative to improve supportive care, comfort, and quality of life remains. However, they pave the way to a future in which treatment toxicity for patients is minimized. The challenges of 50 years ago are being today addressed with the goal to completely phase out conventional chemotherapy.

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