

Hypoxic-Ischemic Injury Complicates Inflicted and Accidental Traumatic Brain Injury in Young Children: The Role of Diffusion-Weighted Imaging

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ABSTRACT

We evaluated the relationship between clinical features and hypoxic-ischemic injury (HII) shown by diffusion-weighted MRI (DWI) in young children with head trauma, comparing inflicted trauma (IT) to accidental trauma (AT). This single-center consecutive cohort study included children age birth to 36 months admitted for head injury July 2001 to December 2004 with brain magnetic resonance imaging (MRI) obtained ≤ 1 week, identified from prospectively maintained registries of children with trauma. Clinical and radiological data during the hospital stay were extracted from medical records. MRIs were analyzed by study examiners blinded to clinical status and scored by type, severity and location of lesions attributable to traumatic, hypoxic-ischemic, or mixed injury patterns. 30 IT patients and 22 AT patients met inclusion criteria. IT cases were younger than AT, 3.0 versus 8.5 months. Mean time to MRI in IT (2.1 days) was similar to AT (1.9 days). HII was more common in IT (11 of 30) than AT (2/22, $p = 0.03$). Children with HII more commonly had seizures, needed intubation at presentation, and needed neurosurgical intervention compared to those without HII. Most patients with HII (10/14) required in-patient rehabilitation compared to those without HII (4/38). Our study is the first to characterize HII using diffusion-weighted MRI in young children, comparing IT and AT. The higher rate of HII on DWI-MRI in IT than in AT is likely multifactorial, involving respiratory insufficiency, seizures, and intracranial mass-occupying lesions requiring neurosurgical intervention. HII predicted need for in-patient rehabilitation in a large majority of children.

Key words: infants; inflicted trauma; MRI; traumatic brain injury

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) is the most common cause of death among children in the United States, with an annual incidence of 63 hospitalizations and 4.5

deaths per 100,000 children, ages 0–14 years (Langlois et al., 2005). Head injury among children less than 2 years of age has been attributed to inflicted trauma (IT) in 24–32% of cases (Duhaime et al., 1992; Dashti et al., 1999). However, up to 80% of deaths from TBI in this

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age group have been attributed to inflicted trauma (IT) (Bruce and Zimmerman et al., 1989). Outcome among young victims of IT is poor, with a majority of survivors suffering permanent morbidity (Duhaime et al., 1996).

The mechanisms responsible for neurologic injury due to IT in infants and young children are incompletely understood and are a source of on-going debate (Shannon and Becker et al., 2001; Geddes et al., 2000). While direct mechanical mechanisms such as contusion and shearing are important in IT, there are indications that secondary injury from a multitude of factors play a significant role, including hypoxia-ischemia, excitotoxicity, and inflammation. The contribution of hypoxia-ischemia in particular has been emphasized in autopsy studies of children with IT (Geddes et al., 2001a,b). The advent of widely available diffusion-weighted magnetic resonance (MR) imaging (DWI) and high-quality noninvasive vascular imaging techniques provide new opportunities for evaluating the role of hypoxic-ischemic injury (HII) in TBI. However, there is a paucity of published research in well-defined prospective clinical cohorts systematically evaluated with DWI. While Suh et al. (2001) reported a high incidence of possible HII in a cohort of infants with presumed IT, there are no studies of DWI findings comparing children with accidental trauma (AT) to those with IT.

The purpose of this study was to characterize the frequency and anatomic distribution of HII as demonstrated by DWI abnormalities among infants and young children with head trauma, comparing children with inflicted trauma (IT) to those with accidental trauma (AT). We aimed to evaluate the association between HII and clinical features at initial presentation, and discharge status. We tested the hypotheses that (1) the presence of HII detected by DWI during the first week after TBI is associated with more severe acute clinical encephalopathy as measured by Glasgow Coma Scale on admission, and (2) more severe HII on imaging is associated with greater likelihood of discharge to in-patient rehabilitation as compared to discharge to home, and (3) HII is more common in patients with IT than with AT.

METHODS

Subjects

In this consecutive cohort study, admitted patients who met the following inclusion criteria were identified and enrolled between July 2001 and December 2004: age from newborn to 36 months, a diagnosis of head trauma, and completion of a brain MRI within the first week after injury. Exclusion criteria were pre-existing or ac-

quired coagulopathy, penetrating head injury, burns, known high cervical cord injury, and circulatory arrest requiring >5 min of chest compressions. Cases of IT were identified from an institutional registry of children with inflicted trauma, which is a prospectively enrolled cohort of children referred to the Child Abuse team for suspected inflicted trauma. Cases of AT were identified from the Children's Hospital of Philadelphia (CHOP) Trauma Registry, which is a prospectively accrued database of all children admitted to the hospital with an injury diagnosis. Cases were classified as IT according to a previously published validated algorithm (Duhaime et al., 1992). The algorithm was applied rigorously for purposes of inclusion in this study. Children whose injuries did not fully meet criteria for presumptive abuse were excluded from this study. Cases were classified as AT only if there was a well-documented history of a witnessed accidental head injury.

This study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

Clinical Data

Clinical data was extracted from the registry database and by review of the medical record, and included age, gender, admission Glasgow Coma Scale (GCS) score, trauma score, injury severity score, occurrence of seizures at presentation and/or during the first week, need for neurosurgical intervention and/or intracranial pressure monitoring, length of acute hospital stay (LOS), and discharge status. Status at discharge was classified as discharged to home (or foster care) or transferred to in-patient rehabilitation. Trauma score (TS) is a brief bedside scale assessing physiologic status of major organ function and ranges from 3 to 16, with lower scores indicating poorer function. It includes five domains (GCS, respiratory effort, respiratory rate, systolic blood pressure, capillary refill), each of which is scored from 0 to 5, with lower scores indicating worse organ function. Injury severity score (ISS) represents an anatomically derived survey of injury, ranging from 0 to 73, with higher scores indicating greater injury (Baker et al., 1974). TS and ISS provide complimentary prognostic information in trauma populations (Kaufmann et al., 1990; Massagli et al., 1996).

Magnetic Resonance Imaging

MRI was obtained for clinical indications at the discretion of the primary treating physicians. There was no uniformly established protocol concerning criteria for obtaining a brain MRI in children with head trauma. MRI was performed using conventional anatomical image acquisition protocols using a 1.5-Tesla system to obtain

TABLE 1. SCHEME FOR CLASSIFYING HYPOXIC-ISCHEMIC INJURY (HII) ON BRAIN MAGNETIC RESONANCE IMAGING

<i>Lesion type</i>	<i>Location</i>
T2 hyperintensity with restricted diffusion in vascular borderzone regions	ACA/MCA MCA/PCA Hippocampus Cerebellum Basal ganglia Thalamus Brainstem
T2 hyperintensity with restricted diffusion in bilateral subcortical gray matter regions	ACA MCA PCA Vertebro-basilar arteries
T2 hyperintensity with restricted diffusion in distribution of a focal/unilateral arterial occlusive infarct	Cerebral cortex Supratentorial only Supratentorial and infratentorial
T1 cortical laminar necrosis	
T2 hyperintensity with restricted diffusion in diffuse or global patterns (translaminar, gray and white matter)	

ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

sagittal T1, axial T2, fluid attenuated inversion recovery (FLAIR), gradient echo, and diffusion sequences with apparent diffusion coefficient (ADC) maps.

Magnetic Resonance Imaging Interpretation and Scoring System

MRIs were analyzed by a study neuroradiologist or neurologist (A.P. or R.I.) blinded to clinical status of the patient, using a semi-quantitative scoring system to grade the nature, location, and severity of lesions due to presumed and suspected HII, and those lesions due to presumed or suspected traumatic injury. Lesions were classified as definite HII by one of the following findings: (a) increased T2 signal with concomitant diffusion restriction in a vascular distribution or (b) increased T1 signal indicative of cortical laminar necrosis in a vascular distribution. Injury patterns attributed to vascular distributions are detailed in Table 1, and include arterial watershed territories, large vessel arterial occlusive infarcts, symmetric deep gray nuclei injury (basal ganglia, thalamus), or diffuse cerebral edema. Lesions were classified as suspect HII by findings of areas of increased T2 signal with concomitant diffusion restriction in a distribu-

tion that did not conform to a typical vascular pattern as described for definite HII. Traumatic injury was defined by the presence of hemorrhage (extra-axial, intraventricular, or parenchymal), contusions, or white matter shearing injuries (Table 2). Severity of HII and traumatic MRI abnormalities was graded by assigning a score from 1 to 4 to each type of lesion, as follows: 1 for small unilateral lesions; 2 for large unilateral lesions; 3 for small bilateral lesions; and 4 for large bilateral lesions. A total HII severity score and total brain trauma severity score (bTS) were obtained by summing the subscores for each type of lesion. Inter-rater reliability of this image analysis method was assessed in a subset of 14 cases scored by both examiners, each blinded to the results of the other. There was good agreement between examiners, as shown by a correlation coefficient (R^2) of 0.94 for HII scores, and 0.88 for bTS scores ($p < 0.001$ for both scores by linear regression analysis).

Statistical Analysis

Data are expressed as mean and standard deviation. Relationships between variables were evaluated by *t*-test, Mann-Whitney rank sums test, or bivariate analyses with chi square or Fisher exact test.

RESULTS

Patient Characteristics

A total of 22 patients with IT and 30 patients with AT met inclusion criteria during the period of study. Patient characteristics are detailed in Table 3. Age ranged from 2 weeks to 35 months. Infants with IT were younger than

TABLE 2. SCHEME FOR CLASSIFYING TRAUMATIC LESIONS ON MAGNETIC RESONANCE IMAGING

Extra-axial hemorrhage: includes subdural, epidural, subarachnoid, and intraventricular hemorrhages
Cortical contusion
White matter shear injury
White matter hemorrhage
Parenchymal hemorrhage

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TABLE 3. PATIENT CHARACTERISTICS

<i>Group</i>	<i>Accidental trauma</i>	<i>Inflicted trauma</i>	<i>p</i>
Number	22	30	
Age, months: mean (SD)	8.5 (8.6)	3.2 (3.0) ^a	0.01
Gender			
Male	10	19	0.27
Female	12	11	
Mechanism of injury in accidental trauma cases			
Fall	18		
Motor vehicle crash	4		

^aDiffers from accidental trauma group by Mann-Whitney rank sums test.

those with AT, with a mean age of 3.2 ± 3.0 and 8.5 ± 8.6 months, respectively ($p = 0.01$, Mann-Whitney rank sums test). Infants with IT were particularly young, with 21 of 30 cases ≤ 3 months. The groups did not differ in gender composition, with 29 males among the 52 patients in the two groups combined. The injury mechanism in the 22 AT cases was a fall in 18 cases and motor vehicle crash in four cases.

Clinical Characteristics

Clinical encephalopathy was mild in most patients as measured by admission Glasgow Coma Scale (GCS) scores (Table 4). Admission GCS was similar in AT and IT groups, with a mean of 12 in both groups. Frequency of coma or obtundation at initial presentation as shown

by a GCS of ≤ 9 was similar in both groups, affecting eight of 30 (26%) children with IT and five of 22 (23%) children with AT. Injury severity was similar in both groups, as measured by similar mean trauma scores (14 ± 3 in both groups) and injury severity scores (19 ± 8 in both groups). There was a trend for a greater frequency of intubation in children with IT than those with AT, affecting 14 of 30 (46%) in IT and five of 22 (23%) in IT, $p = 0.09$. Three IT patients with GCS >13 required intubation because of apnea associated with repetitive seizures. Seizures at presentation or during the first 24 h occurred more commonly in IT, affecting 11 of 30 (37%) in IT and two of 22 (9%) in AT, $p = 0.03$. Seizures were the primary presenting complaint only in children with IT, whereas the traumatic injury per se was the presenting complaint for those with AT. Seizures were most

TABLE 4. INJURY CHARACTERISTICS AND HOSPITAL COURSE

<i>Group</i>	<i>AT (n = 22)</i>	<i>IT (n = 30)</i>	<i>p</i>
Admission GCS			
Mean (SD)	12 (4.6)	12 (3.9)	n.s.
Number ≤ 9	5	8	
Trauma score			
Mean \pm SD	14 \pm 3	14 \pm 3	n.s.
Number ≤ 9	3	4	
Injury severity score			
Mean \pm SD	19 \pm 8	19 \pm 8	n.s.
Number > 5	16	24	
Number intubated at presentation	5	14	0.09
Number of patients with seizures on presentation or within first 24 h	2	11	0.04
Hospital length of stay:	5.9 \pm 5.8	12.4 \pm 10.8	<0.001
Skull fractures present	13	13	n.s.
ICP monitoring and treatment	3	2	n.s.
Neurosurgical intervention (evacuation of SDH, craniectomy)	3	13	0.03
Disposition at discharge			
Home or foster care	18	22	n.s.
In-patient rehabilitation	4	8	

AT, accidental trauma; IT, inflicted trauma; GCS, Glasgow Coma Scale; ICP, intracranial pressure; SDH, subdural hematoma.

TABLE 5. CLINICAL FACTORS ASSOCIATED WITH HYPOXIC-ISCHEMIC INJURY (HII)

	<i>HII present</i>	<i>HII absent</i>	<i>p value</i>
Injury type (no. of patients)			
Accidental trauma	2	20	0.03*
Inflicted trauma	11	19*	
GCS at presentation: mean \pm SD	8.5 \pm 4.6	13.4 \pm 3.2	0.002**
Intubation at presentation (no. of patients)			
Yes	10	9	<0.001*
No	3	30	
Seizures at presentation or within 24 h of admission (no. of patients)			
Yes	8	4	0.01*
No	5	35	
Neurosurgical intervention or treatment, monitoring for ICP (no. of patients)			
Yes	6	4	0.01*
No	7	35	
Discharge status (no. of patients)			
Home or foster care	4	34	
In-patient rehabilitation	10	4	<0.001*

Patients with HII differ from those without HII by: *Fisher exact test or **Mann-Whitney rank sums test.

GCS, Glasgow Coma Scale; ICP, intracranial pressure.

commonly focal, brief and recurring, beginning in some children with IT as much as several days prior to presentation. They were described as increasing in some children over hours or days, and evolved to status epilepticus in three patients (all in the IT group). Skull fractures were common in both groups, affecting 13 of 30 (43%) in IT, and 13 of 22 (59%) in AT. Neurosurgical intervention for evacuation of extra-axial hemorrhage or decompressive craniectomy was more common among children with IT than AT (13 of 30 in IT versus three of 22 in AT, $p = 0.03$). Hospitalization was generally brief, with LOS of <3 days in most children with AT and somewhat longer in those with IT. LOS was extended in many children with IT due to procedures to establish post-discharge social disposition and legal oversight. Discharge status was similar in AT and IT groups, with a majority going home or to foster care. Patients transferred to in-patient rehabilitation among the AT group were older (all near or older than 1 year of age) as compared to the IT group. Mean age of patients transferred to rehabilitation was 4.6 months in children with IT and 18 months in children with AT. A low GCS at admission (<10) did not predict discharge to rehabilitation. Discharge to in-patient rehabilitation was associated with greater injury severity. Children transferred to in-patient rehabilitation had a higher ISS (26 vs. 17, $p = 0.005$) and lower TS (median 11 vs. 15, $p = 0.004$), as compared to children discharged to home or foster care.

Imaging Characteristics

The time interval to MRI examination was similar in both groups, averaging 2.1 and 1.9 days after admission respectively for children with IT and AT. The relationship of imaging abnormalities to clinical features is illustrated in Table 5. Hypoxic-ischemic injury (HII) was more common among children with IT than AT, affecting 11 of 30 (37%) children with IT, and two of 22 (9%) children with AT, $p = 0.03$ (Table 5 and Fig. 1). HII was associated with lower GCS on admission, need for intu-

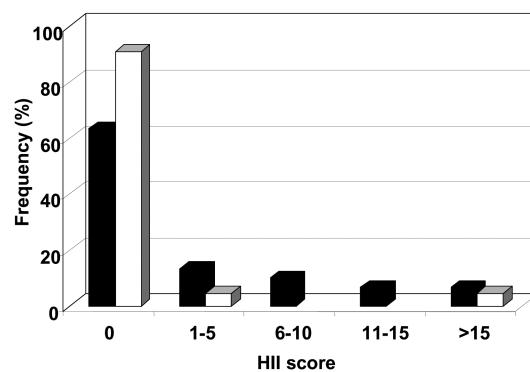


FIG. 1. Frequency of hypoxic-ischemic injury (HII) is higher in inflicted trauma (IT; ■) compared with accidental trauma (AT; □) patients.

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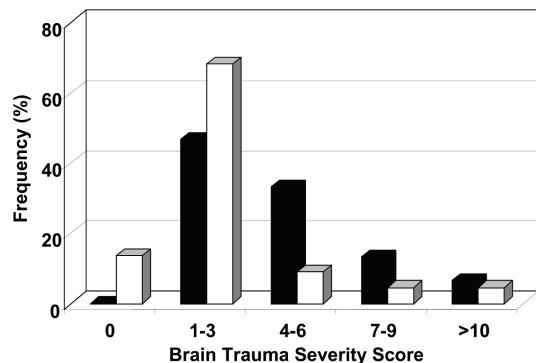


FIG. 2. Brain trauma severity scores are higher in inflicted trauma (IT; ■) compared with accidental trauma (AT; □) patients.

bation at the time of presentation, occurrence of seizures, and need for neurosurgical intervention. Patients with HII had a lower GCS on admission than patients without HII (mean 8.5 vs. 13.4, respectively, $p = 0.002$). However, among patients with HII, a higher HII score was not associated with lower GCS (Fig. 3). The occurrence of respiratory decompensation as shown by the need for intubation was greater in patients with HII than patients without HII. Among AT patients, two of five patients requiring intubation developed HII, compared with zero of 17 patients who did not require intubation. Among IT patients, eight of 14 patients requiring intubation developed HII, compared with three of 16 patients who did not require intubation ($p < 0.01$ for both groups combined). The majority of patients with HII were transferred to in-patient rehabilitation (10 of 14 cases), compared to a small minority of children without HII (four of 38, $p < 0.001$). An association between clinical features and bTS scores was less robust than with HII scores. Higher bTS scores were associated with lower GCS on admission among AT patients, but not among IT patients (Fig. 4). bTS scores of patients with seizures (4.1 ± 1.3) did not differ from bTS scores of patients without seizures (mean 3.9 ± 3.0). bTS scores in patients discharged to home were not different from bTS scores of patients discharged to in-patient rehabilitation.

Children with IT had slightly higher median bTS scores than those with AT (4.0 vs. 3.0, $p = 0.003$; Fig. 2). Frequency and type of traumatic lesions were similar in IT and AT groups (Table 6). The most common were extra-axial hemorrhages, which affected 26 of 30 (86%) children with IT and 18 of 22 (80%) children with AT. White matter shearing injury was judged to be present in only two cases: (1) one AT case on the basis of its location (splenium of corpus callosum) and (2) the other an IT case, in frontal lobe subcortical white matter on the

basis of location (frontal lobe subcortical white matter) along with presence of scant blood products on susceptibility-weighted imaging. There were no isolated, purely hemorrhagic lesions in white matter. All children with IT had some evidence of intracranial trauma by imaging, whereas 3 of 22 children with AT had brain trauma scores of 0. These 3 children had head trauma involving soft tissue or bone with no signs of intracranial injury.

The types and severity of imaging lesions in individual patients were grouped together into one of four patterns (Table 7). These four patterns were (1) predominantly bilateral HII in a distribution consistent with global hypoperfusion, and not colocalizing with specific traumatic lesions; (2) focal or multifocal lesions with mixed features of ischemic and traumatic lesions; (3) traumatic lesions without associated ischemic lesions; and (4) indeterminant—focal lesions not conforming to vascular patterns and lacking features suggestive of trauma such as hemorrhage or edema. As shown in Table 7, pattern 1 was more common in children with IT (nine of 30) than those with AT (one of 22). All children with pattern 1 abnormalities also had traumatic lesions which were of lesser morphologic extent when compared to the HII abnormalities, mostly extra-axial hemorrhages (not shown in the table). These cases were classified as pattern 1 because the predominant finding was hypoxic-ischemic in nature. Representative images of each pattern are shown in Figures 5–9.

DISCUSSION

This study characterizes the relationship between clinical features and findings on DWI of the brain in a prospective consecutive cohort study that includes and compares infants and young children hospitalized for IT

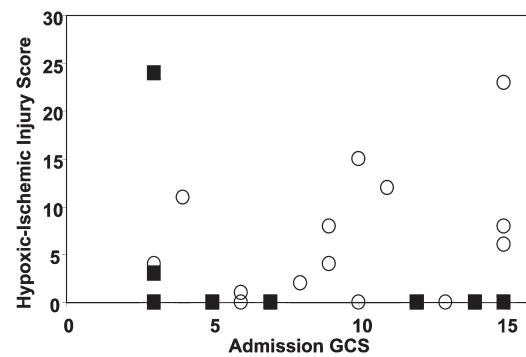


FIG. 3. Admission Glasgow Coma Scale (GCS) score versus hypoxic-ischemic injury (HII) score, shown for accidental trauma (AT; ■) and inflicted trauma (IT; ○) patients. $R^2 < 0.01$.

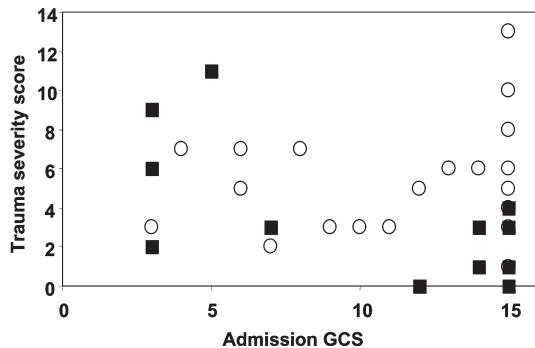


FIG. 4. Admission Glasgow Coma Scale (GCS) score versus trauma severity score, shown for accidental trauma (AT; ■) and inflicted trauma (IT; ○) patients. For AT patients, $R^2 = 0.91$, $p < 0.001$.

to those with AT. We found a higher rate of imaging abnormalities consistent with HII among young infants with IT (37%), as compared to a contemporary cohort of infants in the same age range with AT (9%). The clinical significance of this observation is shown by the need for in-patient rehabilitation for the majority of patients with imaging evidence of HII.

There are several possible explanations for the occurrence of brain lesions with restricted diffusion on MRI in this cohort of children. DWI demonstrates regions where water has shifted from the extracellular to the intracellular compartment, which reduces the diffusion of water molecules within that region of tissue compared to undamaged regions. Changes on DWI appear very early after acute cell injury, preceding the changes in appearance of tissue on T2-weighted sequences by hours to days, providing superior sensitivity for detection of acute cellular injury (Phillips and Zimmerman et al., 1999). Restricted diffusion on MRI indicates the presence of cytotoxic edema, and can be distinguished radiologically from the finding of increased diffusion seen with vasogenic edema on the basis of lower values for ADC. This modality is especially useful in the infant brain, in which acute abnormalities are more difficult to detect by T1- and T2-weighted sequences because of the normal high water content and immature myelination. In TBI, cytotoxic edema may occur as a result of direct traumatic injury, HII, or both (Alsop et al., 1996). The anatomic distribution of DWI abnormalities, and the type and localization of associated traumatic lesions were used in this study to infer whether the underlying mechanism was most consistent with HII or direct traumatic injury. For example, a pattern of bilateral symmetric restricted diffusion in the anterior cerebral artery–middle cerebral artery and middle cerebral artery–posterior cerebral artery watershed

zones is most consistent with global hypoperfusion (Fig. 5). The involvement of predominantly subcortical white matter bilaterally and symmetrically may also reflect hypoperfusion affecting the watershed zone between superficial penetrating and deep central branches of the cerebral circulation (Fig. 6C,D). In contrast to these diffuse bilateral patterns of presumed ischemic injury, some children developed patterns of restricted diffusion of a focal nature contiguous to or colocalizing with traumatic lesions, such as the focal contusion with hemorrhage shown in Figure 8.

Our study found a greater incidence of imaging abnormalities consistent with HII in children with IT than those with AT. There are several possible explanations related to the associated clinical features in these two groups. The high incidence of intubation for ventilatory insufficiency in children with IT strongly suggests they were exposed to periods of hypoxemia. When combined with the delays of hours and sometimes days between symptom onset and medical treatment reported in some cases of IT, the exposure to hypoxemia may have been repeated and prolonged in children with IT as compared to AT. Younger age among the children with IT may have compounded the risk of hypoxemia from respiratory insufficiency, as very young infants have less robust airway protective reflexes and in our experience develop airway occlusion more readily than older infants. In addition, TBI per se has been demonstrated to produce hyperacute (within minutes) central apnea and dysfunctional respiration due to damaged central respiratory control in animal models (Atkinson et al., 1998). Traumatic injury to the lower brainstem and cervical cord has been implicated as a cause of apnea and HII in children with IT based on autopsy studies (Geddes et al., 2001a). Although brainstem injury was demonstrated on MRI in only one case in our series, it is possible that brainstem or upper cervical cord injury occurred, but was beyond the resolution or sensitivity of MRI. Other studies have

TABLE 6. PATTERNS AND FREQUENCY OF TRAUMATIC LESIONS ON MAGNETIC RESONANCE IMAGING

Lesion type	No. of patients	
	AT	IT
1. Extra-axial hemorrhages, including subdural, epidural, subarachnoid, and intraventricular hemorrhages	18	26
2. Cortical contusion	5	14
3. White matter shear injury	2	5
4. Parenchymal hemorrhage	2	11

AT, accidental trauma; IT, inflicted trauma.

TABLE 7. PATTERNS AND FREQUENCY OF HYPOXIC-ISCHEMIC INJURY (HII) LESIONS ON MAGNETIC RESONANCE IMAGING

Lesion pattern	No. of patients	
	AT	IT
1. Predominantly HII: HII is the major finding, with associated traumatic lesions not anatomically contiguous or colocalizing	1	9
2. Mixed: Traumatic and ischemic lesions are anatomically contiguous or colocalizing	1	3
3. Predominantly traumatic: Traumatic lesions are the major finding without ischemic lesions		
Extra-axial hemorrhage only	14	7
Contusion only	1	2
Multiple traumatic lesions	2	9
4. Indeterminant focal lesion	—	1
5. No lesions	3	—

AT, accidental trauma; IT, inflicted trauma.

reported an association between apnea and suspected HII in children with IT (Kemp et al., 2003; Johnson et al., 1995). Our study is the first to demonstrate this association in a prospective cohort using the superior sensitivity and anatomic resolution of diffusion-weighted MRI.

The greater incidence of seizures in IT compared to AT may also be related to the frequency and the pattern of HII lesions. Seizures in acutely injured brain may exacerbate injury directly through excitotoxic mechanisms, or indirectly by exacerbating respiratory insufficiency (Kochanek et al., 2000, 2006). Seizures are a manifestation of acute injury from any mechanism, be it direct trauma, excitotoxic or metabolic, in an age-dependent manner, most commonly in the neonatal period and early infancy. The greater incidence of seizures in children with IT than those with AT may also be related to more severe direct traumatic injury to brain, as suggested by our finding of higher brain trauma severity scores defined by MRI in IT compared to AT. It is not possible to determine in this study whether seizures were a symptom of, or a cause of, HII in this cohort. Studies of seizures in neonatal HII suggest that acute symptomatic seizures exacerbate the primary injury (Miller et al., 2002). The same may be true in TBI, particularly in children with IT (Barlow et al., 2000).

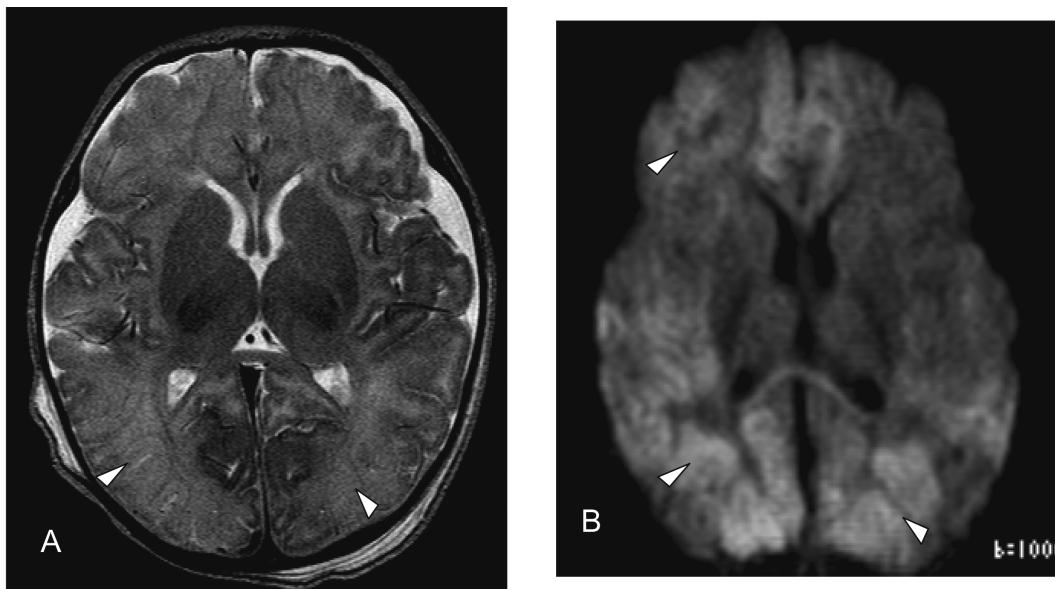


FIG. 5. Injury pattern 1, predominantly hypoxic-ischemic injury (HII) lesions. Magnetic resonance imaging (MRI) shows watershed ischemia involving cortical gray and subcortical white matter in a 2-month-old child with inflicted trauma. (A) T2-weighted sequence shows multiple foci in watershed zones of subtle hyperintensity and loss of gray-white differentiation (Δ). (B) Diffusion-weighted sequence shows multiple confluent areas of restricted diffusion (Δ) in watershed zones involving cortical gray and subcortical white matter.

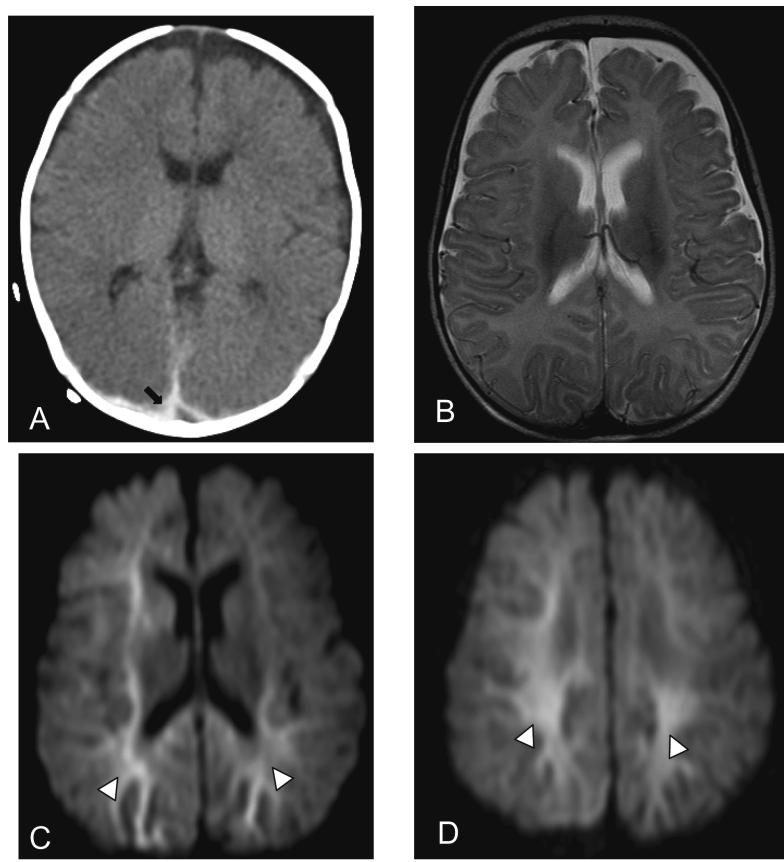


FIG. 6. Injury pattern 1, predominantly hypoxic-ischemic injury (HII) lesions. Magnetic resonance imaging (MRI) shows watershed ischemia predominantly involving subcortical white matter in a 3-month-old infant with inflicted trauma. (A) Head computed tomography (CT) shows only posterior and interhemispheric subdural hemorrhage (→). (B) T2-weighted sequence shows no convincing parenchymal abnormality. (C, D) Diffusion-weighted sequence shows multiple confluent areas of restricted diffusion in watershed zones involving subcortical white matter bilaterally (Δ).

Neurosurgical intervention for intracranial mass–occupying hemorrhage or life-threatening cerebral edema affected children with IT more commonly than those with AT, and was associated with a greater incidence of HII in our study. Cerebral ischemia may occur in any condition where elevated intracranial pressure (ICP) lowers the cerebral perfusion pressure (CPP) to ischemic thresholds. Although data on ICP and CPP values preceding surgery were not available in our study, it is likely that cerebral perfusion and/or oxygenation may have been compromised at some time during the pre-operative course. Moreover, animal studies have shown that trauma is associated with decreased cerebral blood flow and impairs cerebral circulatory autoregulation (Grundl et al., 1994). The mechanisms for impaired perfusion and oxygen utilization in traumatic brain injury are incompletely understood, and are likely multifactorial (Kochanek et al., 2000). Recent studies illustrate the complexity of trauma-induced injury mechanisms by showing that thrombosis

in the cerebral microcirculation occurs and may contribute directly to the evolution of secondary ischemic injury in TBI (Stein et al., 2004). Infants are more vulnerable to intravascular thrombosis compared to older children because of low-flow states, hemoconcentration, and immature native antithrombotic pathways. Clinical studies suggest that infants and very young children may be especially vulnerable to post-traumatic cerebral hypoperfusion (Adelson et al., 1997). If this is true, then the likelihood of secondary cerebral ischemic injury is enhanced in the youngest children following head trauma as a result of even minor perturbations in systemic perfusion, oxygenation, ICP, or coagulation status. Our data suggests that multiple injury mechanisms are contributing simultaneously to the evolution of cerebral injury in many children, and more so in those with IT than AT.

We observed a greater degree of clinical neurologic abnormalities among children with HII compared to those without HII, as shown by lower initial GCS scores and

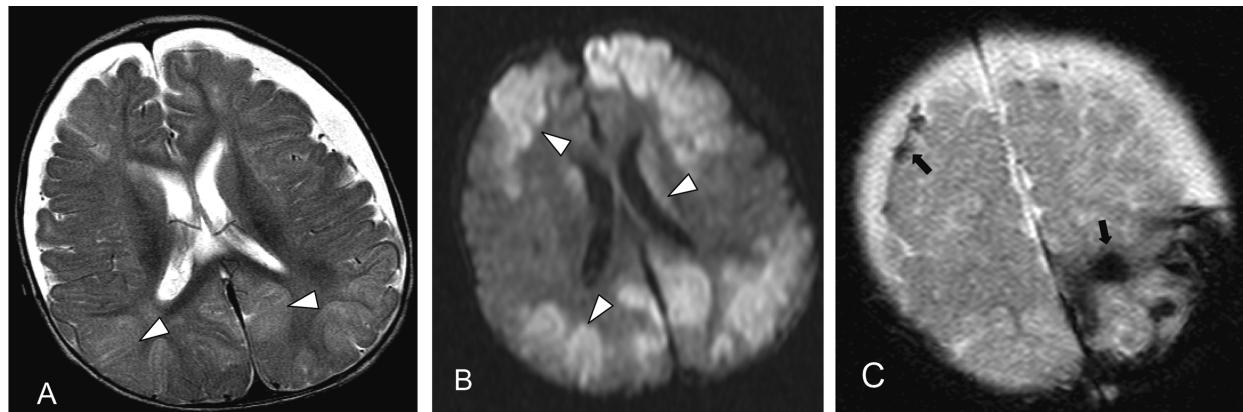


FIG. 7. Injury pattern 1, predominantly hypoxic-ischemic injury (HII) lesions. Magnetic resonance imaging (MRI) shows global ischemic injury involving supratentorial and infratentorial structures, gray and white matter regions bilaterally in a 4-month-old infant with inflicted trauma. (A) T2-weighted sequence shows multiple foci of subtle hyperintensity and loss of gray-white differentiation (\triangle) in watershed zones and putamen, as well as chronic subdural hygromas. (B) Diffusion-weighted image shows corresponding multiple confluent areas of restricted diffusion (\triangle). (C) Susceptibility-weighted sequence shows acute extra-axial hemorrhage over the convexity posteriorly and frontally (\rightarrow).

a higher probability of discharge to in-patient rehabilitation. The relationship between neuroimaging abnormalities and GCS scores in our study, however, is complex. The severity of traumatic lesions on imaging as measured by the neuroimaging-defined bTS score was correlated with the degree of depressed consciousness as measured by GCS only in the AT group, but not the IT group. This may reflect the greater degree of mixed HII and traumatic injury among the IT group. On the other hand, severity of HII as measured by the HII scores did not correlate

with initial GCS in the IT group. This dissociation between clinical and radiologic evidence of HII has several explanations. First, the GCS is difficult to score and less reliable in young infants, who were over-represented in the IT group compared to the AT group (Durham et al., 2000). Others have reported that the GCS may systematically underestimate the severity of acute TBI in children, and particularly among young infants with IT (Arbogast et al., 2005). Finally, the GCS score was taken from a single point in time, whereas the MRI reflected

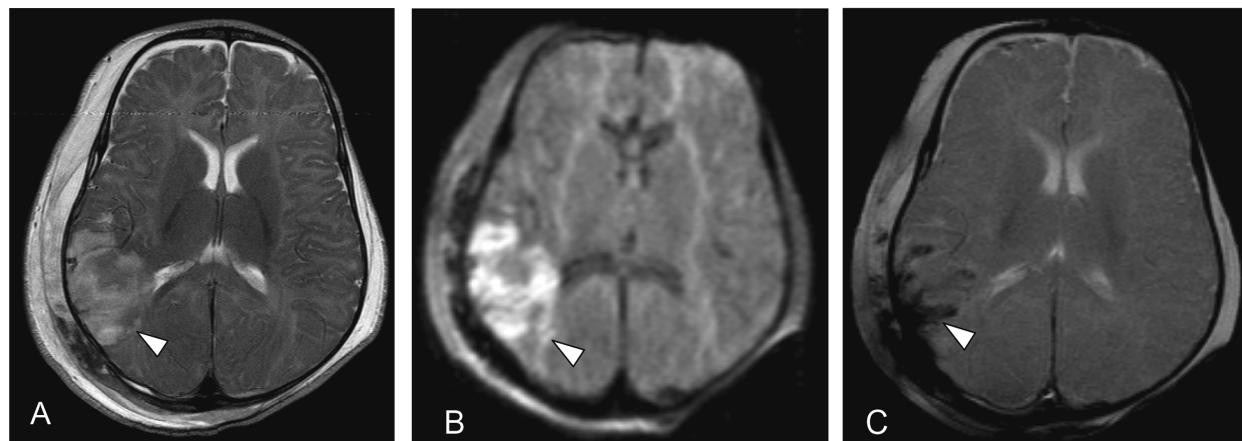


FIG. 8. Injury pattern 2, mixed traumatic and hypoxic-ischemic injury (HII) lesions. Magnetic resonance imaging (MRI) shows focal contusion with corresponding area of restricted diffusion in a 5-month-old infant with inflicted trauma. (A) T2-weighted sequence shows a focus of hyperintensity, swelling, and loss of gray-white differentiation in focal region contiguous to parietal skull fracture (B) Diffusion-weighted sequence shows corresponding areas of restricted diffusion. (C) Susceptibility-weighted sequence shows hemorrhagic contusion in a corresponding area associated with small subdural hemorrhage.

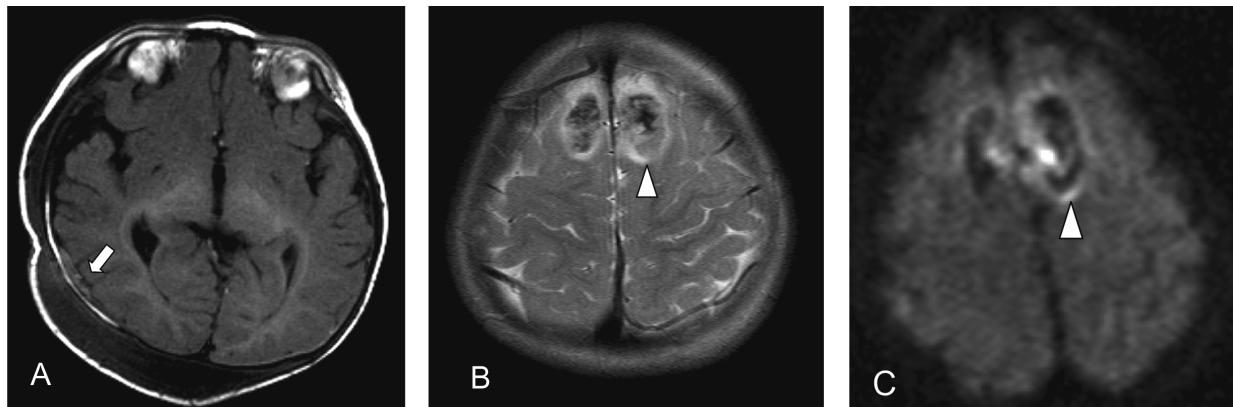


FIG. 9. Injury pattern 3, predominantly traumatic lesions. **(A)** Extra-axial hemorrhage only: T1-weighted sequence shows a small subdural hemorrhage over the right posterior temporal region (\rightarrow) in a 6-month-old infant with accidental trauma. **(B)** T2-weighted sequence in a 16-month-old child with inflicted trauma shows two frontal contusions (Δ) with intraparenchymal hemorrhage and contiguous region of restricted diffusion **(C)**.

the cumulative effects of multiple time-dependent processes that evolved over a period of several days. It bears emphasis here that clinical assessment of the severity of acute brain injury from any cause in young infants is notoriously unreliable, and that symptoms such as seizures and even minor alteration in consciousness should be taken as potential indicators of severe and acutely evolving brain injury.

Our study has several limitations. Patients were included in this study if they were admitted to hospital and underwent a brain MRI, which was obtained for clinical indications only. Our inclusion criteria differ from those used in many other studies of TBI based on severity as defined by admission GCS. While the basis for admission was neither controlled nor measured in our study, it provided a cohort more representative of the full spectrum of injury, hence more inclusive, than studies in which inclusion was based on GCS. This strategy of inclusion also circumvents the problems arising from the fact that GCS is not well validated in young infants. On the other hand, the strategy of including patients based on their having had a clinically indicated MRI likely introduced selection bias. The rationale for obtaining MRI varied among clinicians, was not determined prospectively by a study protocol and was not specifically evaluated in our analysis. Moreover, the full radiologic definition of traumatic or HII injury cannot be determined on the basis of a single examination. Acute brain injury evolves over days and weeks. An accurate and complete characterization of the incidence, type, severity, and topography of MRI abnormalities from head injury among infants and young children is unknown, and would

require a study with a prospectively defined population of children with head trauma who uniformly undergo repeated imaging at predetermined time intervals. The classification scheme we used assigned severity scores to different patterns of abnormalities based on assumptions derived from clinical experience whose validity is uncertain. For example, a pattern of small bilateral lesions received a higher severity score than a pattern with a large unilateral lesion. The validity of this assumption and others underlying the classification scheme awaits evaluation in a prospective study. We evaluated limited measures of the physiologic and clinical neurologic course of these children, including the presenting GCS, the presence or absence of seizures, and the status at discharge. It is well known that bedside assessment of encephalopathy in young infants is difficult to perform reliably, and that clinical diagnosis of seizures in very young infants is highly unreliable (Kellaway and Mizrahi et al., 1990). The accuracy and full extent of seizure detection in this study, and by inference the adequacy of their treatment, are likely under-represented by the data in our study. Our data show a significant relationship between need for intubation and occurrence of HII, supporting the possibility that the imaging findings might in fact reflect the consequences of deficits in oxygen delivery due to perturbed systemic physiology. However, the retrospective nature of the study precluded more systematic evaluation and analysis of systemic physiologic parameters in a uniform and rigorous manner. It is not possible in this study to attribute the imaging findings suggestive of HII definitively to identifiable and quantified deficits in cerebral oxygen delivery or perfusion.

The use of discharge status to home versus rehabilitation has not typically been reported in outcome studies for TBI. The basis for clinicians' decisions in individual cases was not evaluated, and the predictive significance of discharge status has not been validated in the current study. Nonetheless, discharge status likely represents a constellation of factors which taken together distinguish the two groups in important aspects clinical function. By comparison, it is worth noting that other standard outcome instruments such as GOS have not been well validated in young infants. A more complete and accurate characterization of the clinical manifestations of the imaging abnormalities we reported would require systematic serial neurologic examinations during hospitalization, systematic electroencephalographic (EEG) monitoring, and a functional profile at discharge using an age-appropriate standardized functional assessment instrument. The long-term outcome of the children in this cohort is unknown, and would be important to ascertain in order to fully understand the clinical significance of our observations.

In conclusion, we have observed in a consecutive cohort of infants and young children with inflicted and accidental head trauma that MRI-defined lesions with restricted diffusion are common, and more frequent in children hospitalized for IT as compared to AT. The pattern of MRI abnormalities suggests that hypoxia-ischemia is an important contributing factor. Associated clinical observations show that GCS underestimates the severity of injury, whereas the occurrence of respiratory insufficiency, seizures, and need for neurosurgical intervention are risk factors for more severe injury. Prospective studies that include more comprehensive and serial examinations of clinical status, accurate seizure detection, repeated and comprehensive MRI with DWI, and long-term outcome assessment are needed to clarify the possible causes and clinical implications of our findings. Our study does suggest that management of very young infants with head injury, and particularly from IT, should include meticulous attention to optimizing ventilation, oxygenation, perfusion and the diagnosis and treatment of seizures. New therapies directed at mitigating hypoxic-ischemic injury in infants and young children should be considered as part of the management approach to young infants with TBI, and in particular infants suffering IT.

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