Prevalence, Patterns, and Clinical Relevance of Hypoxic-Ischemic Injuries in Children Exposed to Abusive Head Trauma

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ABSTRACT

BACKGROUND AND PURPOSE: **Hypoxic-ischemic injuries (HIIs) are a scarcely investigated but important cause of morbidity and mortality in children who suffered abusive head trauma (AHT). The purpose of this study is to determine: (a) prevalence, types, and clinical relevance of cytotoxic edema compatible with HII in nonpenetrating AHT, (b) their relationship to other classic neuroimaging findings of AHT, and (c) their correlation with clinical outcomes.**

METHODS: **Diffusion-weighted imaging sequences of magnetic resonance imagings performed on children under 5 years diagnosed with AHT were reviewed to detect the most common patterns of acute parenchymal damage. Patterns of cytotoxic edema were described, and HII-compatible ones divided in subtypes. Correlation between HII, fractures, and subdural hemorrhages (SDHs) and with clinical outcomes was determined using imaging and available follow-up data.**

RESULTS: **Out of 57 patients, 36.8% showed lesions compatible with HII. A predominantly asymmetric cortical distribution was observed in 66.7% of cases, while 33.3% had diffused both cortical and deep gray/white matter distribution injury. Traumatic axonal injuries and focal contusions were less common. There was no significant correlation between the presence of SDH ($P = .6$) or skull fractures ($P = .53$) and HII. HII was the most severe form of parenchymal damage in terms of in-hospital mortality and morbidity at follow-up.**

CONCLUSIONS: **HII is the most common type of parenchymal damage in children victim of AHT, being present in 1/3 of patients with this condition, and correlates with more severe outcomes. Its presence is independent from other classic traumatic findings such as SDH and fractures.**

Keywords: Hypoxia-ischemia, hypoxic-ischemic, abusive, trauma, pediatric.

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Introduction

Abusive head trauma (AHT) is the most common cause of death in children suffering from inflicted or nonaccidental trauma in the United States.[1–4] Children who survive the initial traumatic event often develop severely impairing sequelae including developmental delays, seizures, para- or tetraplegia, ventilation dependence, deafness, blindness, or behavioral abnormalities.[5,6] Outcomes are shown to be worse for children who are victims of AHT than for those sustaining accidental injuries.[7] Clinical presentation of AHT is often nonspecific, and the history provided at admission usually is not reliable. Imaging is hence of paramount importance to confirm or raise the suspicion of child abuse. Computed Tomography (CT) has long been used as a primary imaging modality in patients with suspicion of AHT, with well-known findings such as subdural hemorrhages (SDHs), skull fractures, contusions, and retinal hemorrhages.[8–11] More recently, magnetic resonance imaging (MRI) has been employed for a more accurate assessment of the degree and quality of injury, especially in the acute setting. Diffusion-weighted imaging (DWI) sequences can detect cytotoxic edema within 20–30 minutes of injury with excellent anatomic definition, and T2 and fluid attenuation inversion recovery (FLAIR) sequences are positive within 4 hours from the injury. These MRI sequences, with the addition of susceptibility-weighted imaging (SWI), allow the visualization of ischemic foci and small hemorrhagic lesions that could be potentially missed by CT.[12,13] This improved sensitivity, as well as contrast resolution, have showed that parenchymal cytotoxic edema, likely conducible to hypoxic-ischemic injury (HII) mechanisms, can be a significant cocontributor to severe neurological damage in terms of both mortality and morbidity in AHT. The pathomechanism of this kind of damage has not yet been clarified.[2,14–18] Thus far, only a few studies have specifically investigated DWI lesional patterns in AHT patients. These articles have typically observed a partition between focal lesions interpretable as direct consequence of a blunt or penetrating trauma, and more diffuse/global injury/lesions likely secondary to hypoxic-anoxic or shear stress mechanisms.[19–22]

The aim of this study is to retrospectively analyze MRIs in all patients treated at a single Institution for nonpenetrating AHT, in order to (a) determine the prevalence and patterns of DWI abnormalities compatible with HII (b) to correlate them with the presence of SDH and skull fractures, ie, the findings that are most likely to be evident on a noncontrast CT of the head, and

(c) to correlate them with other types of parenchymal damage in terms of clinical outcomes.

Methods

Patient Selection and Data Analysis

This retrospective study was approved by the hospital IRB and is HIPAA compliant. We included all patients aged less than 5 years who had been diagnosed with nonpenetrating AHT in an 8-year-long period between January 2009 and December 2017. Patient selection was conducted through a search performed on the institutional radiology report database. First, we identified all children aged less than 5 years with at least one MRI that included DWI sequences. Second, one of the authors (EO) proceeded to analyze clinical notes of these patients to identify those in which an AHT diagnosis had been established beyond any reasonable doubt by the primary team of physicians and social workers. Patients in which the diagnosis of AHT was considered uncertain or unlikely by the primary care team were excluded. Children with prior history of congenital or neurological diseases at the time of admission were also excluded.

Image review was performed in consensus by two subspecialty-trained neuroradiologists with experience in pediatric neuroradiology (EO, II). CTs and MRIs obtained at admission were evaluated in order to determine the presence of intra- or extra-axial hemorrhages, focal or diffuse areas of cytotoxic edema characterized by DWI hyperintensity and matching low apparent diffusion coefficient (ADC) values, and skull fractures. Location, distribution, and laterality of DWI lesions compatible with cytotoxic edema were described. In agreement with what was described by Zimmerman et al,[20] we considered large supratentorial areas of parenchymal cytotoxic edema suggestive of infarction and not consistent with a contusion or with a single-vessel territorial infarction as lesions /injuries compatible with HII. Unless otherwise specified, these lesions will be referred to as "HII" in the remainder of the paper. Patients with cervical or intracranial vascular injuries were excluded.

Follow-up data were also extracted from the patients' electronic charts, when available. The last pertinent office visit was considered as the most recent follow-up available. Clinical status of the patients and residual or secondary morphologic abnormalities were recorded.

Statistical analysis with Fisher's or χ^2 test, depending on the number of subjects involved, was performed in order to determine correlation between the presence of SDH and skull fractures and the presence of HII. P values $<.05$ were considered to be statistically significant. Analyses were performed using STATA 13 (STATA Corp, College Station, TX, USA).

Clinical and Imaging Protocol

At our Institution, children who are suspected victims of AHT are evaluated by a multispecialty team that comprises pediatricians, neurologists, ophthalmologists, pediatric neuroradiologists as well as social workers. These children routinely receive a head CT (120 KeV, 120 mAs, 5 and .75 mm images) and skeletal survey at admission, followed by an ophthalmologic exam. The diagnostic work-up is completed by an MRI performed on the same day or within 3 days from admission. All included patients were scanned on either a 3T or 1.5T scanner (Siemens, Erlangen, Germany). Our standard protocol includes 3D T1-weighted images (time of repetition/time of echo [TR/TE]: 1,900/2.53 milliseconds, time of inversion [TI]: 900 milliseconds, flip angle [FA] 180 degrees), axial T2-weighted images (TR/TE: 3,460/101 milliseconds, slice thickness: 4 mm), FLAIR (TR/TE: 9,000/112 milliseconds; IT: 2,500 milliseconds, slice thickness: 4 mm) images, diffusion tensor images with diffusion gradients applied along 21 directions (TR/TE: 7,500/82 milliseconds, slice thickness: 2.5 mm), and SWI (TR/TE: 28/20 milliseconds, MIP slice thickness: 1.2 mm). In noncooperative children, the examination was carried out with an adapted protocol that includes triplanar ultrafast T2-weighted images (HASTE, TR/TE: 3,000/79 milliseconds, slice thickness: 4 mm), DWI (TR/TE: 9,800/87 milliseconds, slice thickness: 4 mm), and SWI (TR/TE: 28/20 milliseconds, slice thickness: 1.2 mm) sequences. Unless otherwise specified, the term "DWI" in this article includes positive findings observed on the reconstructed trace of diffusion images from the diffusion tensor imaging sequence.

Results

The study population included 57 children: 37 males (65%) and 20 females (35%) with a mean age at diagnosis of 5.8 months (range: 1–36 months). Thirty subjects (52.6%) had hyperintense lesions on DWI sequences. Demographics of all patients with positive DWI imaging, including injury patterns and clinical outcomes, are summarized in Table 1.

In 21 patients (36.8% of the total cohort and 70% of the DWI-positive patients), DWI sequences showed areas of diffuse parenchymal cytotoxic edema affecting various extents of the cortex, subcortical white matter, and, to a lesser extent, the deep gray nuclei. These lesions were not morphologically consistent with a contusion and were not limited to a single vessel territory, and thus classified as HII. These 21 patients showed 2 distinct lesional patterns. The first was bilateral cytotoxic edema involving both the cortex and the subcortical white matter and was present in 14/21 patients (66.7%) (Fig 1). Ten of these 14 cortico-subcortical lesions were asymmetric (71.4%), involving one hemisphere more than the other (Fig 2), while the remaining four had a symmetric distribution. The second pattern of injury showed cytotoxic edema in an extensive bilateral cortical, subcortical, and deep gray matter distribution, and was seen in 7/21 patients (33.3%) (Fig 3). The basal ganglia were involved in all seven cases, while the thalamus showed acute ischemia in only one case. The cerebellum was involved in 2/30 cases (6.7%). There were no lesions compatible with watershed or single-vessel territorial infarctions.

In 5 patients (8.8% of the total cohort and 16.7% of the DWI-positive patients), the main finding was the presence of punctate or linear areas of restricted diffusion either at the gray-white junction or in the corpus callosum, compatible with traumatic axonal injury (TAI) (Figs 4A-B).

In 4 patients (7% of the total cohort and 13.3% of the DWI-positive patients), the main finding was a focal area of restricted diffusion associated with an adjacent fracture compatible with a parenchymal contusion (Figs 4C-D).

A total of 43/57 patients (75.4%) had SDH. Of these, 15 had HII lesions (34.9%). SDHs in all these patients were less severe than the coexistent HII lesion. χ^2-test showed no significant correlation between the presence of SDH and that of HII ($P = .6$).

Table 1. Demographics, Abnormality Pattern and Follow-Up on Patients with Positive Diffusion Weighted Imaging (DWI) Findings

Patient	Demographics	DWI pattern	Follow-Up
1	M, 4 months	HII–CSC	Lost
2	M, 1 months	HII–Diffuse	Severe DD, tetraplegia, pan-hypopituitarism
3	M, 6 months	HII–CSC	Lost
4	F, 3 months	HII–CSC	DD, brain atrophy, shunted hydrocephalus
5	M, 1 month	HII–CSC	Severe DD, seizures, feeding tube dependent
6	F, 2 months	HII–CSC	DD with cortical blindness and spasms
7	F, 6 months	Contusion	Lost
8	M, 2 months	TAI	Seizures
9	M, 7 months	HII–CSC	Seizures
10	F, 1 month	HII–Diffuse	Dead
11	M, 3 months	Contusion	DD with language impairment, seizures, cephalocele
12	M, 1 month	HII–CSC	DD, seizures
13	M, 8 months	HII–Diffuse	Dead
14	F, 3 months	TAI	Mild seizures
15	F, 7 months	HII–Diffuse	DD with language impairment and brain atrophy
16	M, 6 months	HII–CSC	Severe DD with diffuse spasms, non-verbal
17	M, 10 months	HII–CSC	Behavioral problems with ADHD
18	F, 1 month	TAI	Normal development
19	M, 24 months	HII–CSC	Lost
20	F, 2 months	HII–Diffuse	Severe DD tracheostomy and feeding tube dependent
21	M, 1 month	TAI	Normal development
22	F, 2 months	HII–Diffuse	Dead
23	F, 2 months	TAI	Ventriculomegaly with shunt placement
24	M, 5 months	HII–CSC	Severe DD with blindness, microcephaly, seizures
25	M, 10 months	HII–CSC	Dead
26	M, 36 months	HII–Diffuse	Dead
27	M, 16 months	HII–CSC	Dead
28	M, 3 months	HII–CSC	Severe DD with spastic quadriplegia and cerebral palsy
29	M, 2 months	Contusion	Normal development
30	F, 3 months	Contusion	Skull defect requiring cranioplasty

M = male; F = female; HII = hypoxic-ischemic injury; CSC = cortico-subcortical; TAI = traumatic axonal injury; DD = developmental delay; ADHD = Attention Deficit Hyperactivity Disorder.

A total of 15/57 patients (26.3%) showed one or more skull fractures. Of these, 4 (26.6%) had DWI findings compatible with HII. Fisher's exact test did not show a statistically significant correlation between the presence of a skull fracture and HII lesions ($P = .53$). Three of the patients showing skull fractures had epidural hematomas rather than SDH, while one showed no evidence of intra- or extra-axial hemorrhages.

An intraparenchymal hematoma was present in 5/57 (8.7%) patients, 1 of which showed intraventricular hemorrhage. Three of 5 children with intraparenchymal or intraventricular hemorrhage showed evidence of HII, while 2 had contusions.

Six out of 30 children with DWI abnormalities (20%) died during the admission, and all showed cytotoxic edema patterns compatible with HII on MRI. Two of these 6 children had extensive, asymmetric cortical injury and the remaining 4 had diffuse cortical and deep gray matter lesions. Four of these 6 children had concomitant SDH and HII, but their association was not significant in terms of mortality ($P = .9$). There were no in-hospital deaths in children without parenchymal damage or in those with DWI findings other than HII.

Mean follow-up time was 21 months (range: 0–101 months) for 20 out of 24 children with DWI-positive scans who survived. Four children were lost to follow-up. Eleven (55%) children showed various degrees of developmental delay. Ten out of 11 children with developmental delay (90.9%) showed findings consistent with HII, while 1 had TAI as the main DWI finding. The presence of HII correlated strongly with postinjury developmental delay using Fisher's exact test ($P = .007$) in the subgroup of patients with parenchymal damage. Eight of these 11 children (72.7%) showed severe posttraumatic morbidities in addition to developmental delay including tetraplegia, blindness, ventilation dependence, need for enteral nutrition, and hypopituitarism. Seizures were present in the posttraumatic period in 9/20 children (45%) and 2 (10%) children required neurosurgical shunting. Three children (15%) did not have any delayed sequela from their parenchymal damage. Two of these children had lesions that were classified as TAI and 1 had a contusion. None of the children with HII were free from sequelae.

Discussion

Our study showed that diffuse parenchymal cytotoxic edema compatible with HII had an overall prevalence of 36.8% in 57 patients diagnosed with nonpenetrating AHT and was the most common type of parenchymal damage. HII lesions could be subdivided in two main patterns: a mostly asymmetric cortico-subcortical distribution and an extensive both superficial and deep gray/white matter distribution. These prevalence rates for HII-compatible lesions are in accordance with two prior studies on similar patient cohorts. Ichord and colleagues found an HII prevalence of 31% in a cohort of 21 children with AHT and Zimmerman et al found that it was 39% in 31 children with DWI abnormalities.[20,21] These findings corroborate the assumption, also validated by neuropathological studies, that hypoxia-ischemia, perhaps secondary to a combination of central apnea, vascular compromise or strangulation is likely the

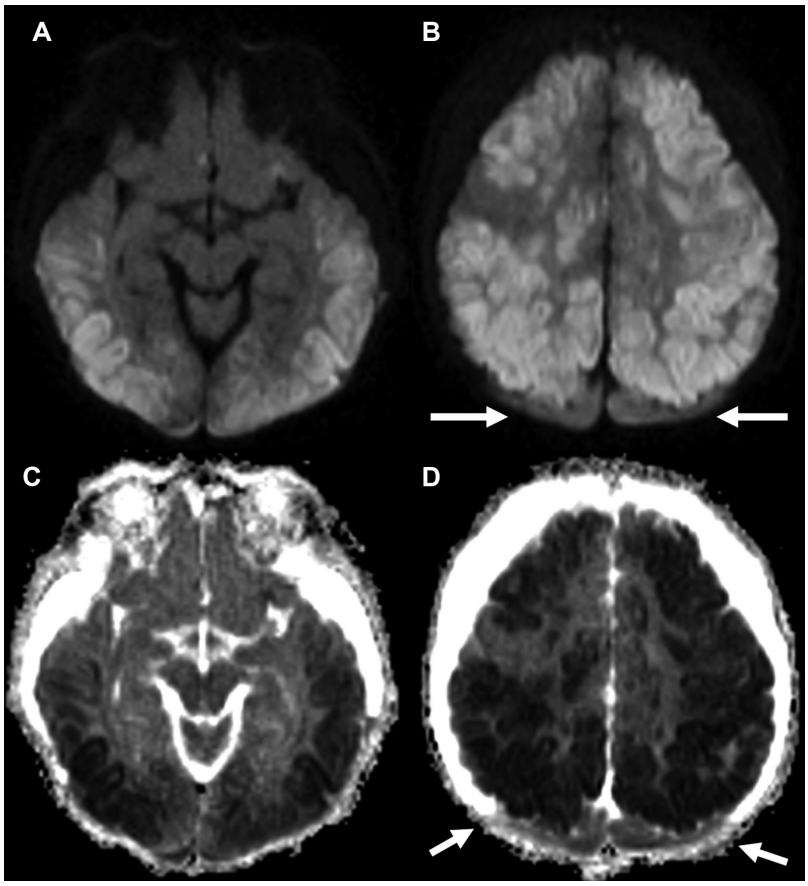

Fig 1. Three-month-old boy with diffuse, mostly symmetric cortico-subcortical diffusion restriction in a nonvascular distribution compatible with hypoxic ischemic injury. Diffusion tensor trace images (A, B) and apparent diffusion coefficient maps (C, D) obtained on the day after admission show extensive cytotoxic edema in the bilateral cortical-subcortical areas of the supratentorial brain. There was no fracture. Images B and D show the presence of bilateral posterior parietal subdural hematomas (white arrows), which showed mixed intensity in other sequences. The patient developed severe developmental delay with spastic quadriplegia on follow-up.

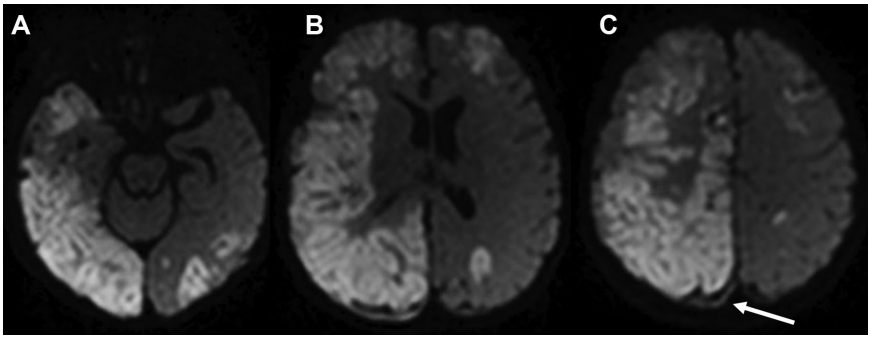

Fig 2. Four-month-old boy with diffuse, asymmetric cortico-subcortical diffusion restriction in a nonvascular distribution. Diffusion-weighted imaging trace images obtained on the day of admission show cytotoxic edema diffuse to the majority of the right hemispheric cortex gray and white matter and to parts of the left frontal and posterior temporal lobes without involvement of the deep gray matter. The cerebellum was also involved (not shown). There is a thin posterior right subdural hematoma (white arrow). There was no fracture. The patient was lost to follow-up.

most prominent contributing factor to parenchymal damage in children with AHT. On the other hand, TAI, once believed to be the most common injury pattern, was noted in only 8.8% of patients in our cohort, similar to other relatively recent studies.[23–26]

HII patterns and, more broadly, DWI patterns have been heterogeneously described in only a few articles in the pertinent literature. Zimmerman et al found five different DWI patterns of injury in children with AHT: (1) diffuse, bilateral supratentorial cortico-subcortical parenchymal infarction; (2) watershed infarctions, mostly between the middle and anterior cerebral arteries; (3) venous infarctions; (4) TAI; and (5) contusions. The authors associated types 1 and 2 with HII, supposing two different degrees of damage severity, type 1 being the most severe.[20] Ichord and colleagues described four patterns of DWI hyperintense lesions: (1) predominantly HII consistent with global hypoperfusion not colocalizing with concomitant traumatic lesions; (2) mixed, anatomically contiguous traumatic

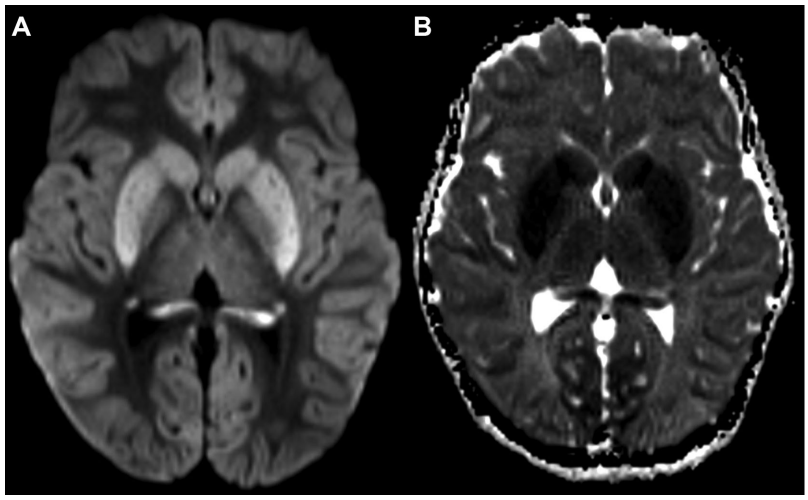

Fig 3. A 36-month-old boy presenting with head trauma and Glasgow coma scale 3 with diffuse, symmetric cortical and deep gray matter diffusion restriction. Diffusion tensor trace image (A) and apparent diffusion coefficient map (B) obtained on the day after admission show more profound diffusion restriction in the basal ganglia. This might be secondary to different timing of injury in different structures. There was no fracture or hematoma. The patient died shortly after admission.

and ischemic lesions; (3) traumatic lesions without associated HII, and (4) indeterminate.[21] Kadom et al reported three main patterns of DWI abnormalities: (1) bilateral ischemia, (2) unilateral ischemia, and (3) contusion.[19] In our series, we did not observe lesions clearly attributable to venous infarctions or in a watershed distribution or an overlap between HII and TAI or contusions, with a clear distinction between the different DWI patterns, likely reflecting different and not coexisting pathomechanisms. Interestingly, the reports by Zimmerman and Ichord do not mention an asymmetric distribution of the lesions, which we found to be a prominent feature in the subgroup of HII patients with cortico-subcortical cytotoxic edema. Asymmetry in HII distribution has been observed in a few cases by Kadom and in some smaller case reports/series addressing the distribution of HII in children diagnosed with the so-called shaken baby syndrome.[22,27] The mechanism behind prominently asymmetric HII has not yet been clarified, and might be different from that of global cytotoxic edema, with or without involvement of the deep gray nuclei. A possible explanation could be that these children have suffered a temporary compromise or occlusion of neck vessels more severe on one particular side during the traumatic event leading to a regional and side-specific occurrence of cytotoxic edema.[28] A similar mechanism has been demonstrated to be true in animal studies on rats undergoing induction of selective periods of hypoxia-ischemia.[29] Symmetric brain lesions that can also involve the deep gray nuclei, on the other hand, could be the result of a combination of cardiac arrest, central apnea, or stretching of the cervical cord at the craniocervical junction.[30] It has also been demonstrated that traumatic brain injury per se can induce central respiratory insufficiency, which might cause hypoxic injuries without cervical cord trauma.[31]

Our results do not show a correlation between HII and the presence of SDH and/or skull fractures, which are findings relatively easily evaluated by CT.[32–36] Considering HII is more often seen in patients with AHT than in patients with accidental head trauma, when clinical suspicion for AHT is high, it could be beneficial to obtain an early MRI with DWI sequences regardless of a "benign-appearing" CT scan.[21,26] While obtaining an MRI might not be feasible in all institutions, especially for very young and possibly noncooperative children, the use of screening/ultrafast MRI protocols that include DWI can obviate the need anesthesia assistance.[19,37] A recent study by Kralik et al with a protocol that included DWI and T2* sequences failed to demonstrate superiority of screening/ultrafast MRI over CT for detection of subarachnoid blood or cytotoxic edema. Given the known higher specificity of DWI sequences in detection of cytotoxic edema, it is likely that the latter finding is secondary to an incidentally lower prevalence of these lesions in the population studied in that paper, as is recognized by the authors.[38,39] Interestingly, 3 of 5 children with intraparenchymal or intraventricular hemorrhage showed evidence of HII suggesting a correlation between these two entities.

Finally, we showed that children with HII tend to have worse clinical outcomes than those with direct force-related posttraumatic parenchymal lesions both in terms of mortality and of morbidity, including various degrees of developmental delay and seizures. In particular, all in-hospital deaths were in patients with HII. The presence or absence of SDH in addition to HII was not significantly related to mortality, further corroborating the concept that HII is the most important outcome determinant in this particular patient population. These findings are in line with other clinical and pathological studies, the analysis of which is beyond the scope of this article.[2,18,21,40–42]

This study has some limitations: (1) by virtue of its retrospective nature, follow-up information is available only for a limited number of patients. A prospective database with a protocoled imaging flowchart would be most useful to obtain more homogeneous data, albeit difficult to put in practice due to the nature of AHT. (2) Due to the intrinsic difficulty in the diagnosis AHT, we had to rely on clinical notes by the treating team to include patients in the study cohort, possibly incurring a selection bias. (3) Due to nature of trauma and difficulty in assessment of these patients, images have most likely been acquired at different time points with regard to the exact time of trauma. (4) Due to the absence of dedicated cervicomedullary imaging in our acute

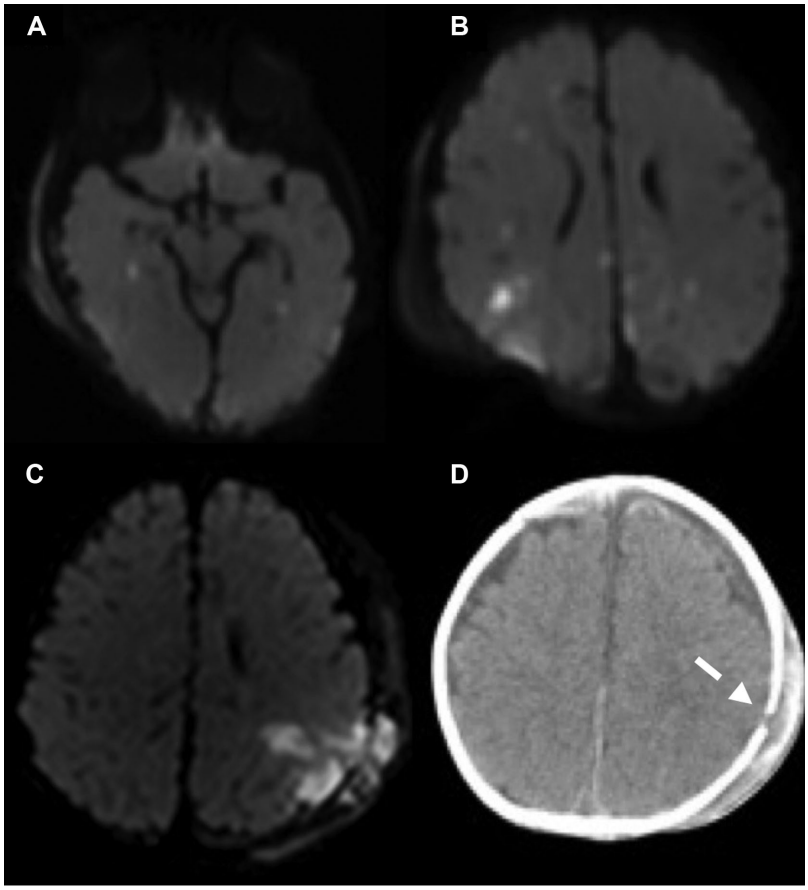

Fig 4. Images A and B show diffusion tensor images obtained on the day of admission in a 2-month-old boy with punctate areas of restricted diffusion at the cortico-subcortical junction compatible with diffuse axonal injury. The patient also had a left parietal comminuted fracture and bilateral, right greater than left subdural hematomas. The child developed long-term seizures in the follow-up. Images C and D show the case of a 3-month-old boy with a left parietal skull fracture (dotted arrow) with associated bilateral subdural hematomas, better seen in the CT axial image (D). There is an associated parenchymal ischemic contusion with cytotoxic edema (C). The child developed severe language delay, seizures, and a cephalocele at the level of the fracture.

phase brain MRI protocols, it is not possible to determine the extent of possible cervicomedullary lesions in these patients.

This study is focused on radiological findings and their association with HII. Future studies could assess correlation between HII and blood oxygenation clinical findings such as respiratory rates, saturation, and hemoglobin amounts. This could be studied by analyzing the hemispheric oxygen extraction fraction by quantifying the SWI signal at 3T in cortical veins. It would also be interesting to study the correlation between intraparenchymal or intraventricular hemorrhage and HII, given the suggestion that these two entities might be related.

In conclusion, we found that diffuse cytotoxic edema compatible with HII was present in 36.8% of patients admitted at our institution with a diagnosis of AHT. We observed two definite distribution patterns: a mostly asymmetric, bilateral cortico-subcortical infarction and a diffuse cortical and deep gray matter injury. TAI and parenchymal contusions were less commonly observed. HII lesions were associated with significantly worse outcomes both in terms of morbidity and mortality compared to other patterns of parenchymal damage. It is important that radiologists and clinicians alike maintain a high level of suspicion for HII in AHT, even in the absence of classic findings of AHT such as SDH and skull fractures. Performing MRI imaging with DWI sequences might help to diagnose and better define the extent of these ischemic lesions, especially in the hyperacute period, thus helping to establish a timely treatment for these children.

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