

# Maturation-Dependent Response of the Immature Brain to Experimental Subdural Hematoma

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## ABSTRACT

In children less than 2 years of age, the radiographic finding of a subdural hematoma (SDH) in the absence of trauma is highly suggestive of inflicted head injury. Little is understood about the unique pathophysiologic response of the immature brain to a SDH. The goal of the current study was to develop an experimental SDH model to determine whether there is a maturation-dependent response of the immature brain to SDH. Fifteen domestic Yorkshire piglets of three different age groups (five each of 5-days, 1-month, and 4-months old) were selected for study. A volume of blood equal to 10% of the intracranial volume (4.5 cc in the 5-day old, 5.4 cc in the 1-month old, and 9.4 cc in the 4-month old) was injected through a right frontal burr hole. Histologic analysis, including hematoxylin and eosin staining and TUNEL staining, was performed at 7 days survival. A significant difference in percentage of injured hemisphere was noted between the 5-day old group and the 1- and 4-month old animals ( $p = 0.0382$ ). The number of TUNEL-positive cells/HPF increased significantly with increasing animal age ( $p = 0.0450$ ). The current study demonstrates a significant maturation-dependent response of the immature brain to SDH, with the youngest animals being quite resistant to a SDH alone. This model will allow further study of additional cerebral insults, such as the addition of apnea or seizures, which may act synergistically along with a SDH to overwhelm the innate neuroprotective capacity of the immature brain to traumatic injury.

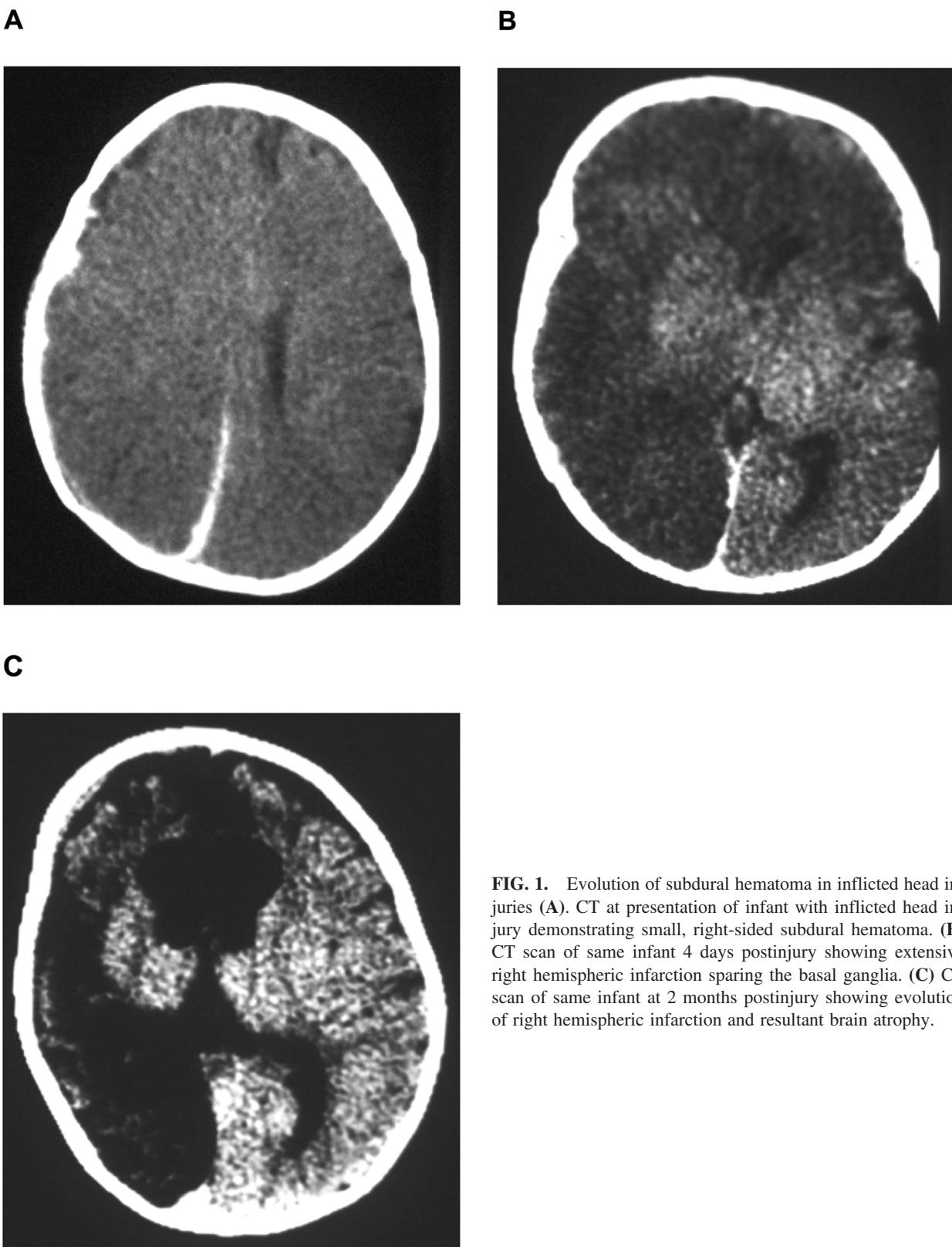
**Key words:** age; animal studies; models of injury; pediatric brain injury; traumatic brain injury

## INTRODUCTION

### *Subdural Hematoma in the Immature Brain*

THE RADIOGRAPHIC FINDING OF A SUBDURAL HEMATOMA in children less than 2 years of age in the absence of a history of trauma is highly suggestive of inflicted head injury (Barlow et al., 1999; Dias et al., 1990; Parizel et al., 2003). Although much attention, both medically and legally, has been focused on what biomechanical forces cause the subdural hematoma, little is understood about the unique pathophysiologic response of the immature

brain to a subdural hematoma. What is peculiar about the subdural hematoma in children with inflicted injury is the striking amount of underlying cerebral injury associated with the subdural hematoma in a large subset of patients (Biousse et al., 2002; Duhaime et al., 1996a; Giles and Nelson, 1998; Lo et al., 2003; Ransom et al., 2003; Suh et al., 2001). These children often present with marked cerebral edema and swelling of the involved hemisphere that progresses to what radiographically appears to be a hemispheric infarction (Fig. 1). This infarction pattern encompasses both the anterior and posterior cerebral cir-



**FIG. 1.** Evolution of subdural hematoma in inflicted head injuries (A). CT at presentation of infant with inflicted head injury demonstrating small, right-sided subdural hematoma. (B) CT scan of same infant 4 days postinjury showing extensive right hemispheric infarction sparing the basal ganglia. (C) CT scan of same infant at 2 months postinjury showing evolution of right hemispheric infarction and resultant brain atrophy.

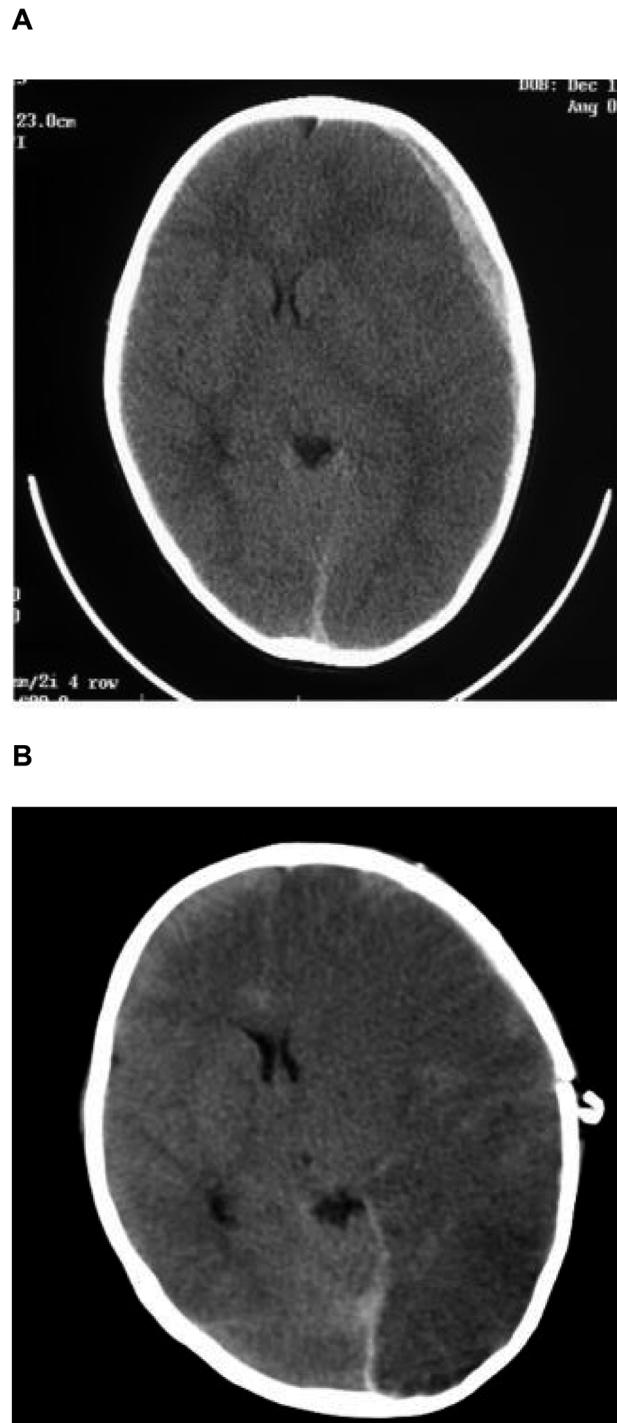
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culations but spares the basal ganglia, cerebellum, and brainstem, making large vessel occlusion, such as from strangulation or thromboembolic events, unlikely (Bioussse et al., 2002; Giles and Nelson, 1998; Ransom et al., 2003; Suh et al., 2001). This pattern of apparent cerebral infarction, which is almost never seen in older children or adults, has been described as “big black brain” because of the appearance of this injury on computed tomography scans in which the entire hemisphere appears hypodense (Duhaime et al., 1993) (Fig. 1C). This pattern is common in nonaccidental trauma and is occasionally seen in association with accidental subdural hematoma in infants as well, suggesting that age is a critical factor (Fig. 2). To date, there are no published reports of animal models comparing the response of the immature brain to subdural hematoma at different ages.

### *Animal Models of Subdural Hematoma*

Although the appearance of apparent cerebral infarction and resultant cerebral atrophy following subdural hematoma in infants and toddlers is well described in the literature (Bioussse et al., 2002; Duhaime et al., 1993, 1996a; Ewing-Cobbs et al., 2000; Giles and Nelson, 1998; Lo et al., 2003; Parizel et al., 2003; Ransom et al., 2003; Suh et al., 2001), little is understood about the underlying pathophysiologic cause of this devastating cerebral injury. While animal models of subdural hematoma in adult animals have been widely used over the past two decades (Duhaime et al., 1994, 1996b; Miller et al., 1990; Sasaki and Dunn, 2002; Sawauchi et al., 2002, 2003; Tomita et al., 2000), there are few published reports of subdural hematoma models used in the immature brain (Shaver et al., 1996). Most modern investigators use the experimental subdural model of brain injury initially described by Miller and colleagues (1990) in which a known volume of blood is injected into the subdural space. This model has been extensively used for the study of traumatic brain injury in rodents. The inherent difficulty with this model is that blood is injected into the subdural space of a normal animal rather than created by some traumatic event. The advantage of this model is that it allows us to study the brain’s response to subdural hematoma alone and in combination with other cerebral insults, thereby limiting other unknown confounding variables.

We have previously described a maturation-dependent response of the immature porcine brain to focal mechanical trauma in which the youngest animals appeared to be quite resistant to a contusional injury compared to older animals (Duhaime et al., 2000, 2003; Durham et al., 2000). We wished to expand upon this finding and



**FIG. 2.** (A) CT scan at presentation in 2-year old after witnessed accidental trauma demonstrating small, left-sided subdural hematoma. (B) CT scan of same toddler 4 days postinjury showing extensive left hemispheric infarction.

determine whether the response of the immature brain to subdural hematoma was maturation-dependent as well. We chose to study subdural hematoma because of the clinical observations of a significant age-dependent response in the immature brain. The goal of the current study was to develop a subdural hematoma model, which has been primarily used in rodents, for use in piglets, which are routinely used for developmental brain research, to determine whether there is a maturation-dependent response of the immature brain to an experimental subdural hematoma (Dickerson and Dobbing, 1967; Duhaime et al., 2000, 2003; Durham et al., 2000; Shaver et al., 1996).

## METHODS

### *Injury Model and Surgical Procedure*

The study protocol was approved by the Institutional Animal Care and Use Committee. A total of 15 domestic Yorkshire piglets of three different age groups were selected for study. Age groups were selected to correspond with human developmental stages, including infants (5-day old piglets), toddlers (1-month old piglets), and adolescents (4-month old piglets) (Duhaime et al., 2000; Durham et al., 2000). Each age group contained five piglets of the same age of mixed gender. The animals were housed for 48 h preoperatively to acclimate to the environment. Prior to the procedure, the animals were premedicated with ketamine (25 mg/kg) and xylazine (2.5 mg/kg). All animals were endotracheally intubated and anesthetized with 2% isoflurane. Oxygen saturation were measured continuously with pulse oximetry and kept above 95% by adjusting inspired oxygen levels. End-tidal partial pressure of carbon dioxide ( $pCO_2$ ) was kept at 35–40 mm Hg by adjusting minute ventilation. Core body temperature was maintained at 37–39°C using heating blankets and warming lights.

To create the experimental subdural hematoma, under sterile conditions a right parasagittal skin incision was made 2 cm off midline, centered over the coronal suture. A burr hole was then placed 2 cm to the right of the sagittal suture just anterior to the coronal suture to expose the dura. The location used for creation of the subdural hematoma is standardized by anatomic landmarks on the calvarium in an attempt to reduce variability of the lesion between subjects and to create a subdural hematoma that will cover the convexity of the cerebral hemisphere. After the dura was exposed, a 24-gauge angiocatheter was placed into the subdural space and advanced 1 cm in a posterior direction and secured into place with cyanoacrylate glue. A predetermined volume of autologous blood equal to 10% of the animal's intracranial volume,

based on age norms measured in prior experiments with this species, was then obtained via a subclavian vein puncture (Duhaime et al., 2000). Injection volumes were 4.5 cc in the 5-day old group, 5.4 cc in the 1-month old group, and 9.4 cc in the 4-month old group. The blood was then injected through the angiocatheter into the subdural space at a rate of 2 cc/min. Pilot studies determined that this rate was sufficient to prevent the coagulation of the unheparinized autologous blood in the catheter without causing mortality from a sudden increase in intracranial pressure as a result of a rapidly expanding mass lesion. This also reflects the clinical setting where the source of bleeding is likely venous and would be expected to accumulate at a relatively slow rate.

After injection, the catheter was removed and the dura sealed with cyanoacrylate glue. The scalp was then sutured over the site and the animal was allowed to recover and return to regular housing. No apparent neurologic deficits were noted in any of the animals. At 7 days postinjury, the animals were euthanized, formalin-perfused, and the brain was harvested for histologic analysis. Seven-day survival was chosen in order to compare histologic results of this injury model with our previously published studies using different methods of traumatic injuries, such as cortical impact, in similarly aged animals (Duhaime et al., 2000). This time period also allows histologic demarcation of the injured tissue for quantitative analysis.

### *Lesion Analysis*

A 1.5 cm thick coronal block centered under the injection site was processed and embedded in paraffin for histologic analysis. Serial 10  $\mu$ m thick sections were taken every 0.25 mm and mounted onto poly-L-lysine coated slides and stained with hematoxylin and eosin. For each animal, a corresponding coronal slice directly under the injection site was then selected for analysis. These brain slices were then reviewed by a single neuropathologist without knowledge of the age of the animal or the experimental conditions. Areas of brain injury, defined by the presence of necrosis with or without hemorrhage, neuronal dropout or injury, and/or reactive gliosis, were then identified by light microscopy and outlined on the slides to delineate normal from injured tissue. This histopathologically defined outline was used to determine lesion area. In order to compare relative lesion dimensions among ages, on each slice the area of the lesion and the corresponding contralateral hemisphere was then computed using an image analysis system (MCID, Imaging Research, Ontario, Canada).

The following data were obtained for each animal: (1) lesion area (in  $mm^2$ ) to allow for comparison of lesion size between subjects of the same age; (2) the ratio of le-

sion area to the area of the corresponding contralateral hemisphere to allow for comparison of lesion sizes between ages by providing an estimate of the percentage of hemisphere injured in the sampled region.

#### TUNEL Staining

In addition to hematoxylin and eosin staining, 10 animals (three from the 5-day old group, five from the 1-month old group, and two from the 4-month old group) were randomly chosen to undergo TUNEL staining as a quantitative measure of cell death. For each animal, a single 10  $\mu\text{m}$  thick paraffin-embedded section from a comparable anatomic region underlying the subdural injection was mounted onto a poly-L-lysine coated slide and processed using a commercially available TUNEL staining kit (ApopTag Peroxidase *In Situ* Apoptosis Detection Kit, Chemicon International, Temecula, CA). TUNEL-positive cells were then identified and quantified by number of TUNEL-positive cells per high-power field (cells/HPF at 40  $\times$  magnification) using light microscopy.

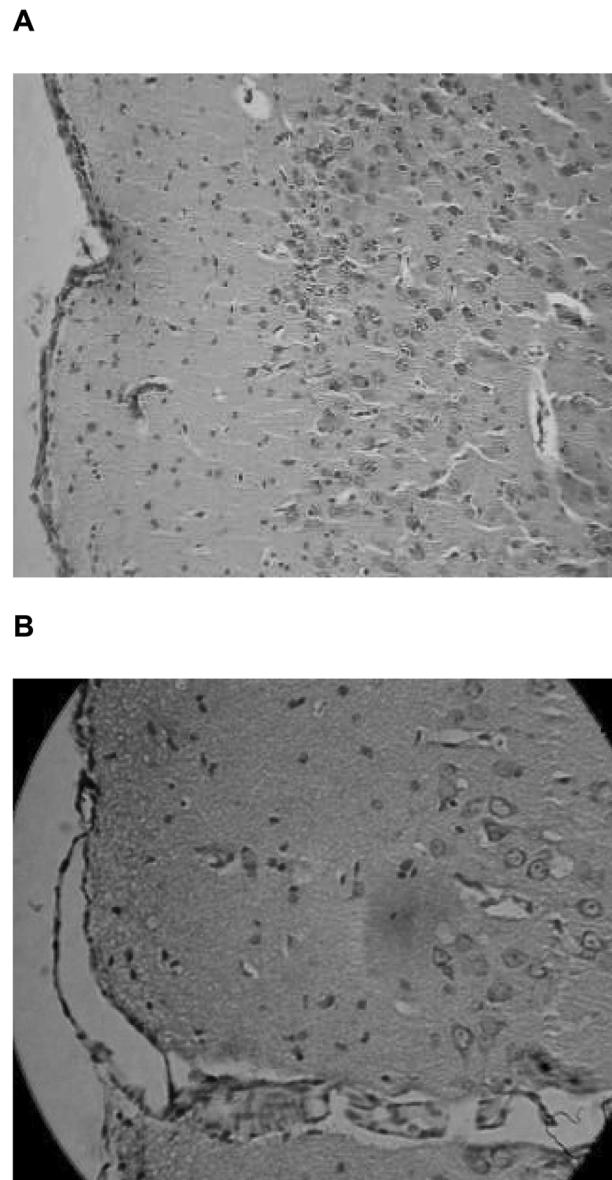
#### Statistical Analysis

Differences between the three groups in lesion area, percentage of hemisphere injured, and the number of TUNEL-positive cells per high-power field were determined using the Kruskall-Wallis test for nonparametric data. When groups were combined for post-hoc analysis into two groups (5 day vs. combined 1 and 4 month), the Mann-Whitney test was used. Results were considered significant for  $p < 0.05$ . Results are presented as mean  $\pm$  standard deviation of the mean.

## RESULTS

There were three males and two females in the 5-day old group. Mean weight was  $3.0 \pm 0.9$  kg. Hematoxylin and eosin staining revealed evidence of hypercellularity and meningeal thickness underlying the region of the subdural hematoma in three of the five animals (60%). In two animals, no histologic abnormality was noted. No quantifiable lesion area suggestive of cerebral ischemia or infarction could be demonstrated in any animal. No animal exhibited TUNEL-positive staining (Table 1) (Fig. 3).

In the 1-month old group, there were three males and two females. Mean weight was  $8.6 \pm 2.1$  kg. Hematoxylin and eosin staining revealed evidence of meningeal thickening and hypercellular aggregates consisting of well-demarcated regions of increased cell density in the subcortical region underlying the subdural hematoma in three animals (60%) without any areas suggestive of cerebral ischemia or infarction that could be quantified. Two animals (40%) had large areas of in-



**FIG. 3.** Five-day old piglet 7 days after experimental subdural hematoma. (A) There was thickening of the meningeal layer and increased cellularity throughout (H&E staining, 10  $\times$  magnification). No evidence of underlying infarction was noted. (B) Low-power TUNEL staining demonstrating absence of TUNEL-positive cells (20  $\times$  magnification).

farction and macrophage infiltration. The mean lesion size for this age group was  $19.9 \pm 30.5$  mm $^2$ . The mean ratio of lesion/contralateral hemisphere was  $0.05 \pm 0.07$ . Five animals underwent TUNEL staining with a mean of  $14.4 \pm 19.7$  cells/HPF (Table 1) (Fig. 4).

In the 4-month old group, there were three males and two females. Mean weight was  $38.1 \pm 6.1$  kg. Hematoxylin and eosin staining revealed evidence of

TABLE 1. FINDINGS FOR EACH ANIMAL IN STUDY

Group	No.	Gender	Wt (kg)	Histologic findings	Lesion area (mm <sup>2</sup> )	Ratio lesion/CL hemisphere	Tunel+ cells/HPF
5 day	1	M	2.0	Hypercellularity Meningeal thickening	0.0	0.0	0
5 day	2	M	4.3	Hypercellularity Meningeal thickening	0.0	0.0	0
5 day	3	M	3.0	Hypercellularity Subarachnoid blood	0.0	0.0	0
5 day	4	F	3.3	No abnormality	0.0	0.0	N/A
5 day	4	F	2.4	No abnormality	0.0	0.0	N/A
Mean			3.0		0.0*	0.0**	0***
	SD		0.9		0.0	0.0	0
1 month	1	F	8.2	Meningeal thickening Hypercellular aggregate	0.0	0.0	0
1 month	2	F	10.0	Meningeal thickening Hypercellular aggregate	0.0	0.0	0
1 month	3	M	6.0	Meningeal thickening	0.0	0.0	0
1 month	4	M	11.4	Infarction	69.07	0.16	35
1 month	5	M	7.5	Infarction	30.37	0.07	37
Mean			8.6		19.89*	0.05**	14.40***
	SD		2.1		30.48	0.07	19.73
4 month	1	F	46.4	Subpial gliosis	2.84	0.01	N/A
4 month	2	F	41.8	Meningeal thickening	0	0	N/A
4 month	3	M	36.9	Infarction	57.91	0.13	77
4 month	4	M	34.0	Infarction	55.93	0.13	102
4 month	5	M	31.3	Infarction	79.94	0.20	N/A
Mean			38.1		39.32*	0.09**	89.5***
	SD		6.1		35.88	0.09	17.7

\**p* < 0.0571.

\*\**p* < 0.0567.

\*\*\**p* < 0.0450 (Kruskall-Wallis).

N/A, not analyzed.

meningeal thickening and subpial gliosis in one animal (20%), no evidence of any apparent injury in one animal (20%), and large areas of infarction and hemorrhage in three animals (60%). The mean lesion size for this age group was  $39.3 \pm 35.9$  mm<sup>2</sup>. The mean ratio of lesion/contralateral hemisphere was  $0.09 \pm 0.09$ . Two animals underwent TUNEL staining with a mean of  $89.5 \pm 17.7$  cells/HPF (Table 1) (Fig. 5).

#### Differences in Lesion Size Between Groups

There was no significant difference between groups in either the lesion area or percentage of injured hemisphere (*p* = 0.0571 and *p* = 0.0567, respectively), although there was a strong trend for increased percentage of injured hemisphere as the age of the animal increased. If the two older age groups were combined into a single

“older” group, a significant difference in percentage of injured hemisphere was noted between the 5-day old group and the combined group of 1- and 4-month old animals (*p* = 0.0382).

#### Differences in TUNEL Staining

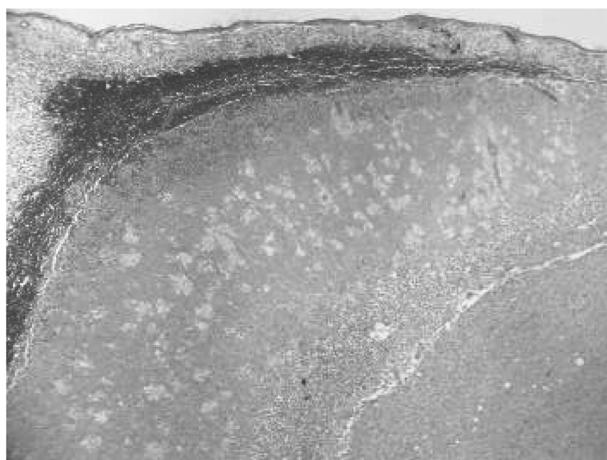
A significant difference in the number of TUNEL-positive cells/HPF was noted between the three age groups (*p* = 0.0450), with the number of TUNEL-positive cells increasing with increasing animal age.

## DISCUSSION

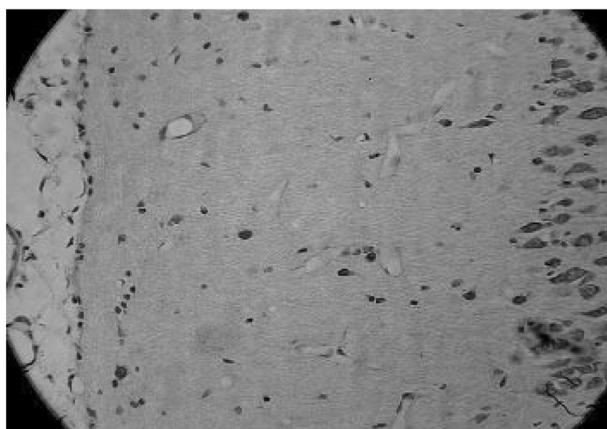
We have previously described a maturation-dependent response of the immature porcine brain to focal me-

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A



B



**FIG. 4.** One-month old piglet 7 days after experimental subdural hematoma. (A) H&E staining demonstrating underlying meningeal thickening, subarachnoid blood, and underlying tissue necrosis (10 × magnification). (B) Low-power TUNEL staining demonstrating scattered TUNEL-positive cells through the cortical and subcortical layers (20 × magnification).

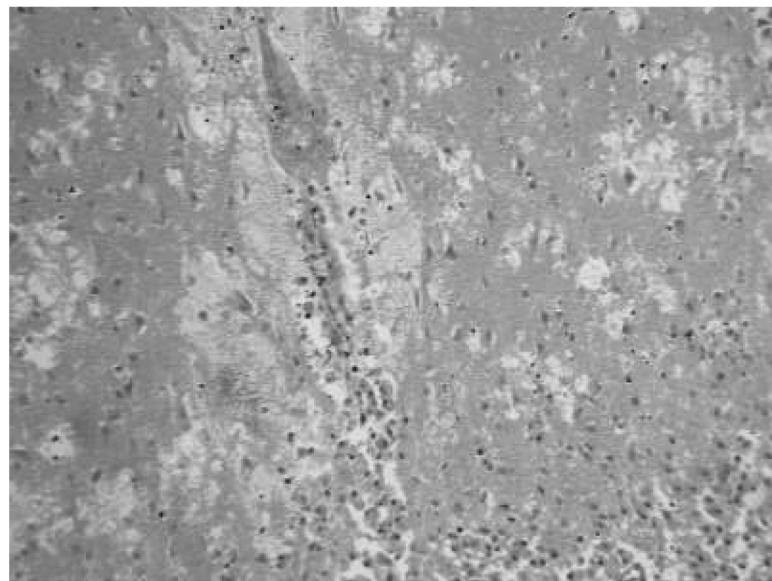
chanical trauma in which the youngest animals appeared to be quite resistant to a focal-type injury compared to older animals (Duhaime et al., 2000, 2003; Durham et al., 2000). We wished to expand upon this finding and determine whether this relative “neuroprotection” in the very immature animals could be applied to other forms of traumatic injury such as a subdural hematoma, especially since this is the injury in which infants appear uniquely vulnerable in the clinical setting. We selected subdural hematoma because it is a very common injury in infants and young children, and based upon clinical observations, it is likely to show a significant age-de-

pendent response. In addition, an age-dependent response to subdural hematoma in an animal model has not been previously reported.

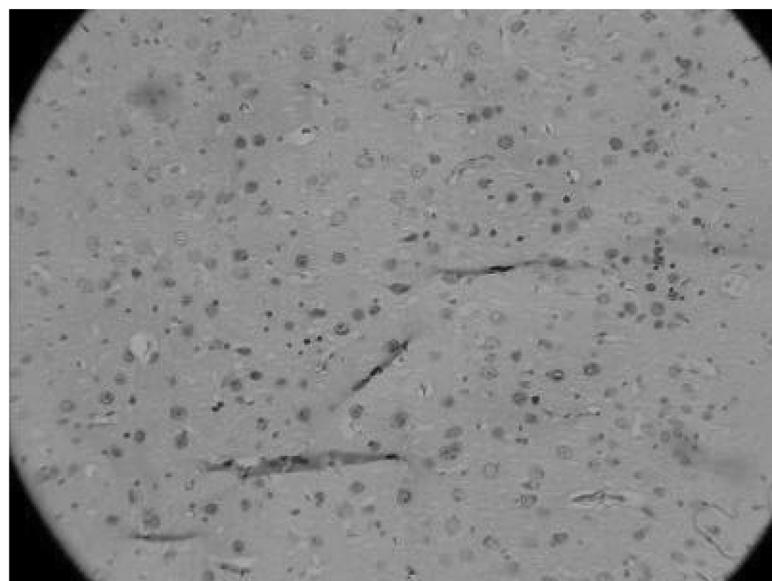
The subdural hematoma in very young children is most often suspected to be a result of inflicted head injury (Barlow et al., 1999; Dias et al., 1990; Parizel et al., 2003). It was originally postulated that the violent shaking of an infant, in addition to causing the subdural hematoma, would cause diffuse axonal injury by shearing of the axons, resulting in profound neurologic injury (Calder et al., 1984; Gleckman et al., 1999; Lindenbergh and Freytag, 1969; Shannon et al., 1998). Recent neuropathologic studies of inflicted head injury have challenged this widely held theory and demonstrated that the primary neuropathologic injury in these children is relative ischemia, not diffuse axonal injury (Geddes et al., 2001a, 2001b). Neuroradiologic studies utilizing diffusion-weighted magnetic resonance imaging and magnetic resonance spectroscopy have also supported a hypoxic/ischemic mechanism of injury rather than a diffuse axonal injury (Bioussse et al., 2002; Haseler et al., 1997; Parizel et al., 2003; Suh et al., 2001). These findings have led some investigators to conclude that an additional cerebral insult occurs at the time of injury that results in cerebral ischemia, and the subdural hematoma may just be a “marker” of some part of the mechanism involved in this type of injury, without necessarily being a sufficient causative component of the associated brain damage (Geddes et al., 2001a; Kemp et al., 2003).

Animal models of subdural hematoma in adult animals have been widely used over the past two decades (Duhaime et al., 1994, 1996b; Miller et al., 1990; Sasaki and Dunn, 2002; Sawauchi et al., 2002, 2003; Tomita et al., 2000). The inherent difficulty with this model is that blood is injected into the subdural space of a normal animal rather than created by some traumatic event. A traumatic subdural hematoma is thought to be created from tearing of bridging cortical veins or other venous structures as a result of rotational and/or impact forces; the exact mechanism likely varies among individual patients. There is no animal model currently in use for creating subdural hematoma by mechanical forces alone. The injected subdural hematoma model is a well-established model in lower mammals and has been used on a limited basis in higher mammals to study the response of the brain to subdural hematoma (Duhaime et al., 1994, 1996b; Miller et al., 1990; Sasaki and Dunn, 2002; Sawauchi et al., 2002, 2003; Tomita et al., 2000; Shaver et al., 1996). The advantage of this model is that it allows the study of the brain’s response to subdural hematoma alone and in combination with other cerebral insults, thereby potentially limiting other confounding variables.

**A**



**B**



**FIG. 5.** Four-month old piglet 7 days following experimental subdural hematoma. (A) H&E staining demonstrates large areas of liquifactive necrosis and macrophage infiltration (10  $\times$  magnification). (B) Low-power TUNEL staining shows a large number of TUNEL-positive cells (20  $\times$  magnification).

We wanted to adapt this model, which has been primarily used in rodents, for use in higher mammals such as piglets, which are routinely used for developmental brain research (Dickerson and Dobbing, 1967; Duhaime et al., 2000, 2003; Durham et al., 2000; Shaver et al., 1996). The piglet is considered to be the most ideal nonprimate model

of the immature brain because of its developmental and morphologic similarities to humans (Dickerson and Dobbing, 1967; Flynn, 1984; Pampiglione, 1971; Thomas and Beamer, 1971). We chose to study piglets of three different age groups to approximate human infants (5-day old piglets), toddlers (1-month old piglets), and adolescents

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(4-month old piglets). Because of the differences in the size of the animal's brain at the three age groups, we chose to standardize the volume of injection based on a fixed percent of estimated brain volume for each of the three age groups. For our preliminary studies, we chose to inject a volume of subdural hematoma equal to 10% of the estimated brain volume. This amount was based on rodent studies that showed significant cerebral infarction and mortality for injection volumes over 20% and a single piglet study using a 15% injection volume that demonstrated infarction (Miller et al., 1990; Shaver et al., 1996). Studies of subdural hematoma volume thresholds in rodents have reported that there appears to be a critical volume of subdural hematoma that can be tolerated without leading to cerebral infarction; however, volumes in excess of this critical volume were shown to lead to significant morbidity and mortality (Miller et al., 1990; Sasaki et al., 2002).

While we did not find a statistically significant difference in the percentage of injured hemisphere among the three age groups studied, we did note a significant difference between the very immature (5-day old) and the combined older (1- and 4-month old) groups. Because of the small number of animals in each group, the current study is not sufficiently powered to detect differences between each of the age groups; therefore we combined the older groups in order to determine statistical significance. We also felt that the 5-day old group best represented the cerebral maturation of infants who are most likely to suffer inflicted head injury and suffer subsequent cerebral infarction rather than the toddler or adolescent-equivalent ages in the older animals.

While the small number of animals included in this study precluded meaningful statistical analysis of gender effects, there was a clear trend among male animals of the older age groups to demonstrate a severer injury compared to that of the females. It is beyond the scope of this report to address possible neuroprotective mechanisms related to the female gender. We do hope to further address this compelling finding in the future.

We also noted significant variability in lesion size in the 1- and 4-month old groups that was not apparent in the 5-day old animals. We have noted similar variability in older animals in previous studies of the response of the immature brain to traumatic injury using different mechanisms of injury (Duhaime et al., 2000). While every effort was made to insure a uniform injury in each of the animals, it is possible that not all animals received an identical injury due to the nature of the injection model. We are currently investigating additional variables, such as intracranial pressure and other physiologic parameters (e.g., injection rates and animal positioning) to further insure a uniform injury among subjects. While all noninvasive measurements of variables, such as tem-

perature, oxygen saturation, end-tidal carbon dioxide, and anesthetic doses, were kept constant during the surgical procedure, it was not possible to perform invasive cerebral and systemic physiologic monitoring of the animals as the protocol called for a 7-day survival period. We have since begun to investigate the acute systemic and cerebral physiologic response of the immature brain to subdural hematomas in nonsurvival studies so that invasive measurements of cerebral blood flow, intracranial pressure, brain tissue oxygenation, mean arterial pressure, and other parameters can be performed. Our preliminary data demonstrates remarkably similar physiologic responses to the injection of the subdural hematoma between subjects of similar ages.

Despite the shortcomings of the current study, what was most striking from this pilot data was the complete absence of *any* quantifiable evidence of injury, notably the lack of ischemic damage and evidence of cellular death as determined by TUNEL staining, in any of the 5-day old animals. It appears that the presence of blood in the subdural space alone, even of a considerable volume, is not sufficient for the development of an extensive cerebral infarction in immature animals. Although it is doubtful the extensive cerebral injury seen in children who suffer inflicted head injuries can be replicated simply by the creation of an injected subdural hematoma, the current study is useful because it demonstrates that the presence of blood alone in the subdural space does not appear to be sufficient to cause severe cerebral injury in the immature brain. It is possible that the immature brain, while relatively resistant to a single cerebral insult such as a subdural hematoma, may lose its inherent neuroprotective capacity when simultaneous stressors are given.

This model will allow further study of additional cerebral insults, such as the addition of apnea or seizures, which may act synergistically along with a subdural hematoma to overwhelm the innate neuroprotective capacity of the immature brain to traumatic injury. Understanding the pathophysiology of this particular unique pattern of brain injury, a subdural hemorrhage with an underlying hemispheric infarction, is the key to understanding the range of devastating injuries seen most often in the setting of child abuse.

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