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CHAPTER 20

Traumatic brain injury in infants: the phenomenon of subdural hemorrhage with hemispheric hypodensity (“Big Black Brain”)

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Abstract: Clinical and experimental studies of traumatic brain injury during immaturity have been far less numerous than those involving adults, and many questions remain about differences in injury responses among patients of different ages. This chapter reviews a distinctive injury pattern common in infants, the so-called “big black brain” response to acute subdural hematoma. The pathophysiology of this injury remains incompletely understood. Insights from both clinical observation and experimental studies have helped to clarify the probable causes of this injury pattern, which appears to require a combination of stressors during a particular period of maturation.

Keywords: subdural hematoma; infant; black brain; child abuse; pathophysiology

Introduction

There are a number of unique phenomena seen in clinical practice that distinguish infant traumatic brain injury from that occurring in older children or adults. One of the most dramatic of these is the so-called “big black brain,” a pattern of tissue loss affecting the entire supratentorial hemisphere in association with acute subdural hematoma. The circumstances required to cause this injury pattern and the pathophysiology of the extensive parenchymal destruction remain incompletely understood. This chapter will address insights gained into this injury by both clinical observations and experimental strategies. Both approaches have contributed to advancing understanding of the response of the infant to brain trauma, and illustrate how clinicians and scientists work synergistically in head injury research.

Early clinical observations

It has long been recognized that acute subdural hematoma in infancy could be associated with profound brain injury. The pioneering observations of Guthkelch (1971) and Caffey (1972, 1974) linked infantile subdural with a range of neurologic deficits including chronic disability, coma, and death. These injuries were hypothesized to occur most often from violent manual shaking. The hypothesis that shaking caused these injuries was based on statements from some perpetrators and witnesses who described shaking, the frequent paucity of visible external cranial injury in affected infants, an association with distal metaphyseal and rib fractures, and contemporaneous experimental findings on the role of rotational forces in subdural

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hematoma and diffuse brain injuries (Ommaya and Yarnell, 1962; Ommaya et al., 1968, 1973). The forces and mechanisms necessary to cause acute subdural hematoma in infancy remain uncertain, and many affected infants with accidental or inflicted events do, in fact, have evidence of head impact (Hahn et al., 1983; Duhaime et al., 1987, 1998; Alexander et al., 1990; Ghahreman et al., 2005). In this chapter we will focus on a specific pattern of immature brain response to acute subdural hematoma, regardless of mechanism of injury.

Not all infants with acute subdural hematoma develop severe brain injury. The spectrum of clinical outcomes ranges from no deficits to death (Ludwig and Warman, 1984; Duhaime et al., 1987, 1996; Gilles and Nelson, 1998; Ewing-Cobbs et al., 1999; Ghahreman et al., 2005). As CT scanning became widely available, patterns of brain damage emerged in the premorbid state and in survivors. Areas of hypodensity often were seen which might be patchy in distribution or could involve the entire supratentorial compartment unilaterally or bilaterally (Zimmerman et al., 1979; Cohen et al., 1986; Dias et al., 1998; Gilles and Nelson, 1998). Because of the typical dark-appearing, homogeneous, and extensively distributed low density seen on the CT scan of such infants, the term ''big black brain'' has been used to describe those with hypodensity involving the entirety of one or both hemispheres (Duhaime et al., 1993; Graupman and Winston, 2006). This nomenclature evolved from the use of the term ''black brain'' to describe the CT appearance of diffuse bilateral hypodensity and loss of gray-white differentiation, with or without relative sparing of the thalami (''reversal sign''), seen most often in cases of severe or fatal pediatric head injury (Cohen et al., 1986; Whyte and Pascoe, 1989). In a subset of infant subdurals, hypodensity is seen which extends from the frontal pole to the occipital pole, crosses multiple vascular territories, and stops abruptly at the tentorium. This pattern may be present at presentation to the hospital or evolve over several days (Dias et al., 1998). In unilateral cases, a contralateral frontal wedge-shaped region of low density also typically is seen, but the rest of the supratentorial compartment does not exhibit hypodensity or loss of gray-white differentiation (Fig. 1). The hypodense hemisphere(s) typically go on to sustain rapidly progressive atrophic changes indicative of severe, diffuse brain destruction

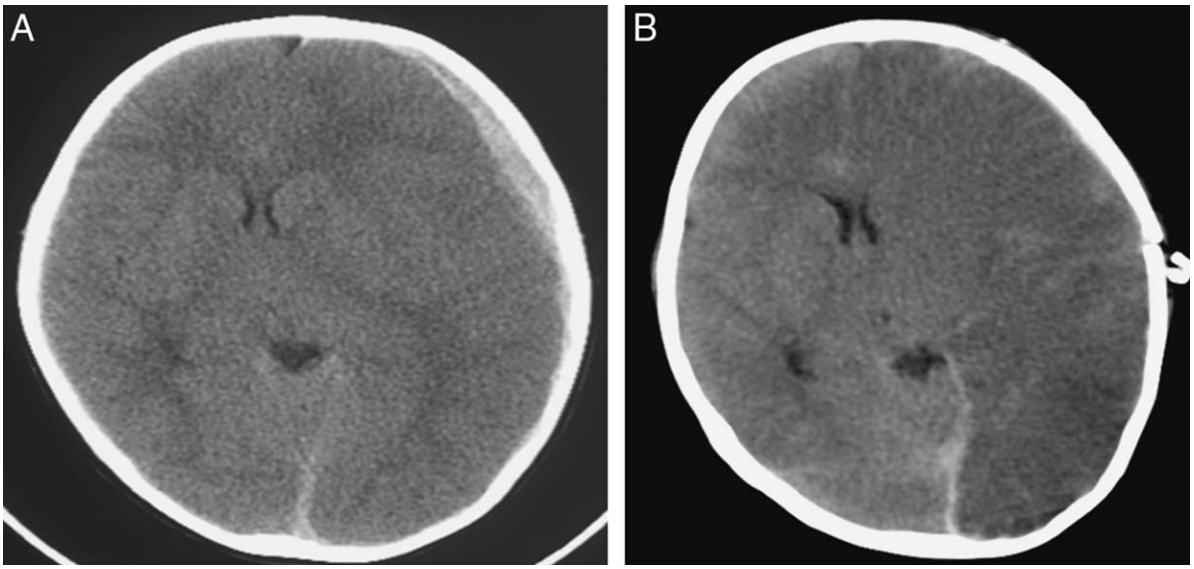

Fig. 1. Two-year-old boy with a fall from a bunk bed resulting in acute left subdural hematoma. (A) Acute CT scan, with midline shift. Hemispheres appear to have similar density at this time-point. The patient underwent emergency clot evacuation. (B) Four days post-injury. The child has developed hypodensity and swelling of the entire left hemisphere. He underwent aggressive management of intracranial pressure and survived with a right hemiparesis and hemianopsia.

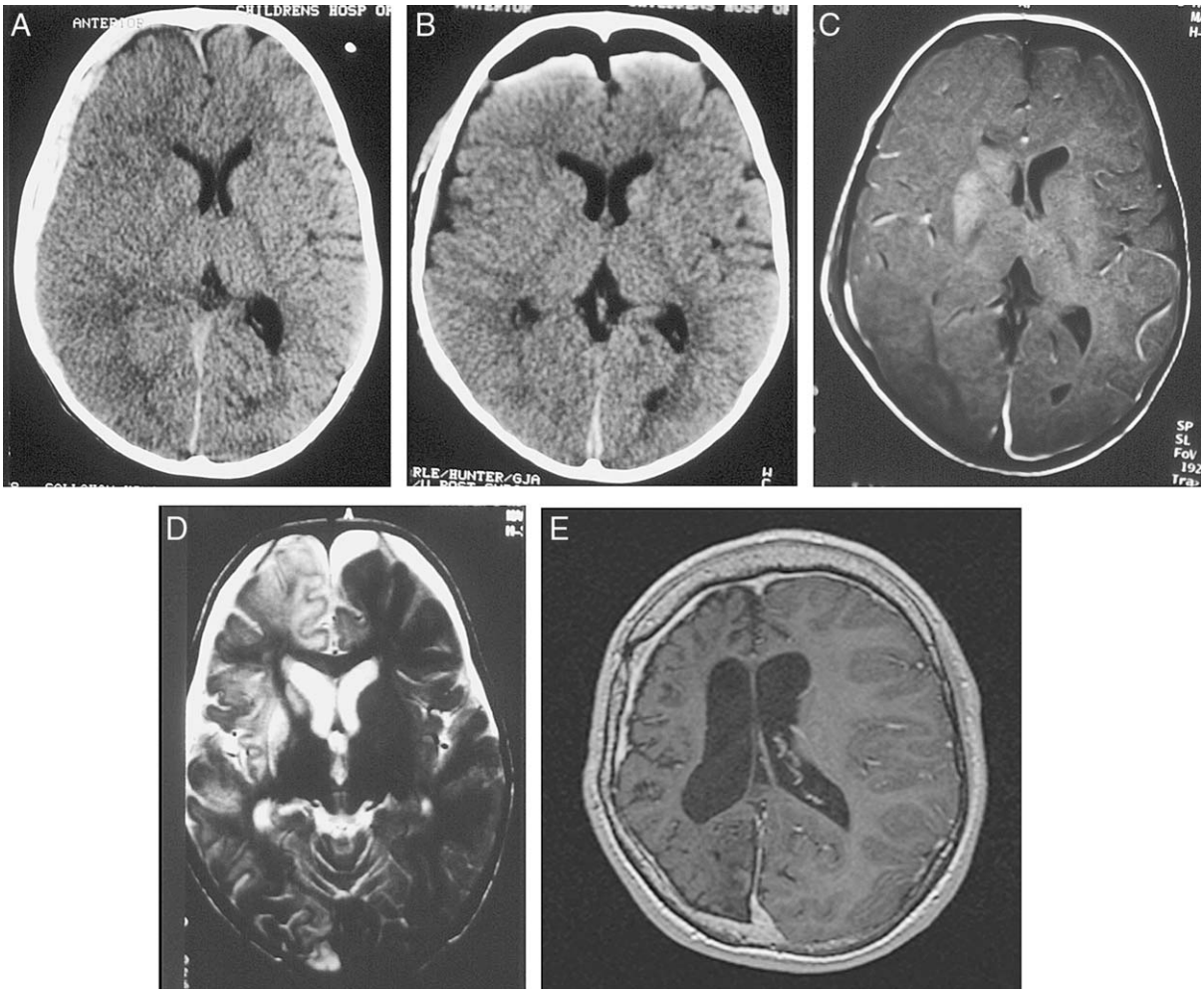

Fig. 2. Twenty-three month old boy who sustained a witnessed accidental injury with an acute right subdural hematoma. He stood up initially but then had a generalized seizure within seconds after impact. He received medical attention within minutes, and there was no apnea or hypoventilation noted. (A) Acute CT scan. (B) CT scan after clot evacuation. There was no brain swelling at surgery. Note lack of hypodensity, and bifrontal air. The patient regained consciousness promptly after surgery. Despite the symmetric radiologic appearance of the hemispheres, the child was noted to have a left hemiparesis postoperatively. (C) MRI scan done on postoperative day 2, FLAIR sequence. Note the high signal in the basal ganglia. (D) MRI, T2 weighted sequence, several months post-injury. Note the widespread signal change and atrophy in the right hemisphere. (E) MRI, T1 sequence with contrast, 10 years after injury. There is marked atrophy of the right hemisphere. The patient had a persistent hemiparesis and hemianopsia, developmental delays, and a seizure disorder. He became seizure-free with no new deficits after hemispherectomy.

(Fig. 2). In children with subdural hematomas, the bilateral pattern is seen about twice as commonly as the unilateral pattern, and occurs more commonly in very young infants, while older infants and toddlers more often develop the unilateral form of ''big black brain'' (Duhaime et al., 1993; Gilles and Nelson, 1998). The extent of the hypodensity correlates with worse acute clinical status and with worse prognosis (Duhaime et al., 1996; Ewing-Cobbs et al., 1998; Gilles and Nelson, 1998). Mortality in children with unilateral or bilateral hemispheric involvement is 67% (Duhaime et al., 1993). Even many years after injury, survivors of bilateral ''big black brain'' remain blind,

non-ambulatory, nonverbal, and profoundly developmentally delayed. Those with the predominantly unilateral form may make a better functional recovery but remain severely impaired (Duhaime et al., 1996).

While many workers have described the areas of hypodensity seen on CT as "edema" or "infarction," these terms should be used with caution. This is because the pathophysiologic processes these terms most often connote, in other ages and with adult disorders, may not apply in this context. For instance, excitotoxic lesions, to which the immature brain may be particularly vulnerable, can occur in the setting of normal vascular perfusion. The pathology and radiology of this type of process may look similar to that occurring from vascular occlusion, since both represent a mismatch between metabolic demand and substrate delivery. If such a pathophysiology were in play, it might not be necessary to postulate a mechanism requiring large vessel occlusion, such as strangulation, as some authors have done (Bird et al., 1987). Thus, care should be taken to describe findings rather than ascribing mechanisms that might be associated with these radiologic findings in other ages and clinical contexts (Gilles and Nelson, 1998).

Older children and adults with acute subdural hematoma may suffer extensive concomitant brain damage, presumably due to the effects of primary mechanical brain injury and/or to secondary insults including hypoxia, ischemia, or elevated intracranial pressure. However, the rapid appearance of extensive, diffuse supratentorial hypodensity with loss of gray-white differentiation in the unilateral or bilateral patterns described is seen routinely only in infants and toddler-aged children. The vast majority of children with the specific injury type reviewed in this paper are under 3 years of age. For the sake of brevity we most often use the term "infants" in this chapter, but it should be understood that this phenomenon occurs in toddlers as well.

More recent studies using magnetic resonance imaging (MRI) have shown changes on diffusion-weighted imaging which corroborate the idea that some form of hypoxic-ischemic injury or perfusion-demand mismatch is particularly common in inflicted injury (Ichord et al., 2007). Early involvement of the basal ganglia can also been seen on MRI (Figs. 2 and 3). Therefore, the question has arisen as to whether this striking injury pattern reflects a unique mechanism of injury, the presence of a particular type of secondary injury, or a unique response of the immature brain to trauma. Since bilateral "black brain" can occur from diffuse hypoxic-ischemic insults as well as in the setting of subdural hematomas, we will focus on the unilateral pattern as the traumatic entity requiring a unique pathophysiologic explanation. Both experimental and clinical investigations offer insights, as reviewed below.

Experimental models

The rodent subdural hematoma model most widely in use presently was first described by Miller et al. (1990). The model created a subdural hematoma by injecting autologous blood into the subdural space of the cerebral convexity through a small burr hole. Histopathology demonstrates a bowl-shaped volume of brain damage underlying the clot. By measuring brain metabolism and cerebral blood flow, investigators have demonstrated that perfusion in the area of the clot is decreased, while metabolism is increased, creating a relative mismatch between substrate delivery and demand. The perfusion abnormality appears to be mediated by microvessel vasospasm rather than by large vessel abnormalities (Inglis et al., 1990; Kuroda and Bullock, 1992). Microdialysis studies with the model have shown an increase in extracellular glutamate, and treatment with glutamate receptor blockers limits the volume of damage, suggesting that the increased metabolism seen under the hematoma is related to excitotoxic stress (Bullock et al., 1990, 1991; Inglis et al., 1992). Similar damage was not seen if a comparable volume of blood was simply layered over the exposed cortical surface in rodents and a clot left in place for several days (Duhaime et al., 1992). This demonstrates that the presence of blood alone is insufficient to cause damage, but that the blood must be injected into a closed space to cause injury.

While these studies are intriguing, the pathology using the rodent subdural hematoma model does

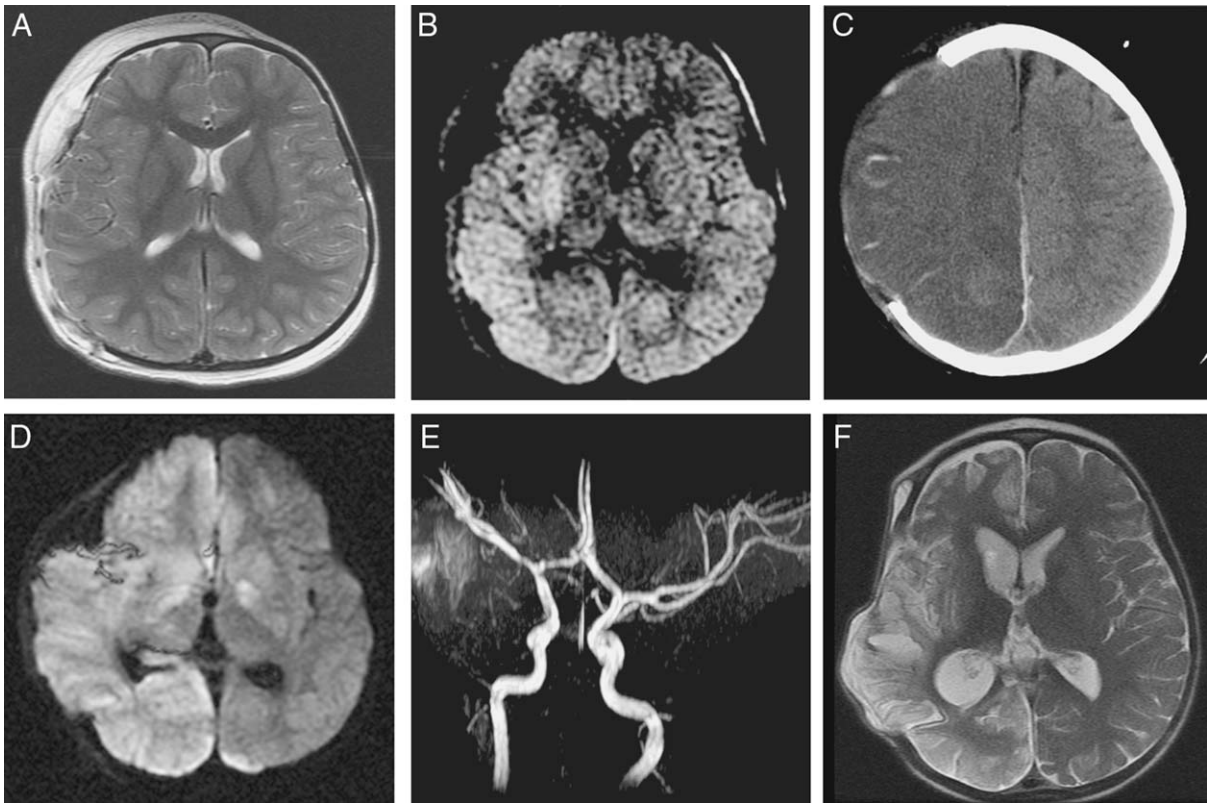

Fig. 3. Two-year-old girl with injury, suspicious for inflicted trauma with acute right subdural hematoma. She had a seizure witnessed in an outside emergency department, and was unresponsive with a dilated right pupil on presentation. The clot was evacuated and the brain was noted to be slightly full at surgery, so a hemicraniectomy was performed. Intracranial pressure was measured and easily controlled, and excellent brain perfusion was maintained. The patient was intubated but responsive and was able to follow commands. (A) MRI, T2 sequence, done 1 day after surgery. Note symmetric appearance of brain parenchyma. (B) Diffusion-weighted sequence. Note bright signal in basal ganglia and temporal and occipital cortex. (C) CT scan, postoperative day 3. Note development of hypodensity of entire right hemisphere, with increased swelling. (D) MRI, diffusion sequence, one week postoperatively. Note bright signal in entire hemisphere, as well as contralateral basal ganglia. (E) MR angiogram. All arteries appear patent. (F) MRI, fast spin-echo T2 weighted sequence, 2 months post-injury. Note widespread damage to right hemisphere. The patient has a hemiparesis and hemianopsia.

not reproduce the pathology of the ''big black brain.'' Injection of blood causes a localized lesion rather than one involving the entire hemisphere. To learn whether the infantile pattern could be reproduced by adapting the rodent model to an immature, gyrencephalic brain, Shaver et al. (1996) injected blood into the subdural space of three-week-old piglets. Their model was modified by use of a ''cranial window'' through the bone that allowed confirmation of a thin but extensive subdural clot overlying the hemisphere, comparable to that seen most often in human infants. This model also failed to reproduce the ''big black brain'' phenomenon, as it too created a localized injury. However, unlike the rodent lesion, which was largely cortical, the piglet lesion preferentially affected the underlying white matter. The authors hypothesized that the white matter was affected because of its increased vulnerability during early life, when the metabolic rate is relatively high in white matter but the vascular supply is immature and may respond inadequately to increased demand. It is for this reason that the white matter in infants is thought to be preferentially vulnerable to

damage from perinatal hypoxic-ischemic insults and prematurity (Rorke, 1992).

Both the rodent and the piglet subdural injection models fail to mimic the mechanical trauma that occurs during the injury event in patients. Since the presence of blood in the subdural space was insufficient to cause the hemispheric damage seen in infant subdural injuries, Duhaime et al. (2000) performed a series of studies using piglets to isolate the effect of mechanical trauma on the immature brain. This was done to test the hypothesis that the infant brain might be particularly vulnerable to damage from mechanical trauma relative to other ages, thus explaining the extensive hemispheric injuries seen with acute subdural hematoma. The group developed a model of scaled cortical impact that delivered a mechanically comparable strain load to the same brain structures at different ages. These studies showed that rather than being selectively vulnerable to mechanical trauma, the infant brain was relatively resistant to injury from mechanical deformation (Duhaime et al., 2003). Therefore, another explanation for the unique pattern of extensive brain damage seen with subdurals in infancy was needed.

Other workers have attempted to more closely reproduce the mechanical forces that might be responsible for infant subdural hemorrhage using animal models. Because of the long-held concept that the injury might be caused by manual shaking of an infant, Smith et al. (1998) subjected rats to prolonged mechanical shaking. While subarachnoid hemorrhage and surface contusions were found, hemispheric tissue loss was not produced in this model. Anesthetized, immature sheep subjected to 30 min of intermittent, violent manual shaking exhibited similar finding to the shaken rats, without hemispheric loss (Finnie et al., 2006). Piglets subjected to a single or double high-velocity head rotation showed diffuse axonal injury and focal frontal subdural hemorrhage, but have not to date demonstrated the ''big black brain'' phenomenon (Raghupathi and Margulies, 2002; Raghupathi et al., 2004).

It can be seen that in all these experimental models, elements of injury occur in isolation, whereas in the clinical setting, multiple pathophysiologic stressors may occur in combination. We will now return to the clinical arena, where additional observations relevant to this issue have been made.

The role of apnea

It has long been recognized that infants are susceptible to apnea from a variety of causes, including head injury. That children with subdurals often present with hypoventilation or frank apnea is well known (Johnson et al., 1995; Kemp et al., 2003; Ichord et al., 2007). Therefore, it has been hypothesized that hypoxia/ischemia, rather than trauma itself, is the cause of the diffuse hypodensity pattern seen in the most severe of these injuries. The fact that many of these infants have been the victims of inflicted trauma has been thought to contribute to this association. Specifically, it has been speculated that after the infant is injured, the perpetrator does not seek immediate medical attention, hoping the child will recover spontaneously. This leads to delay in care. If the child hypoventilates during this delay period, diffuse hypoxic brain damage may result.

This scenario matches the histories obtained in many cases, and likely contributes to the damage seen in many infants. However, it is not a sufficient explanation for all aspects of the ''black brain'' phenomenon. This is because there are well-documented accidental cases of subdural hematoma in infants and toddlers that were witnessed and in which children got immediate medical attention with no apparent apnea or hypoventilation, but in which the phenomenon of hemispheric hypodensity nonetheless appeared (Figs. 1 and 2). The other limitation of apnea as the sole explanation for the phenomenon is that it fails to account for the fact that in one-third of the cases, the hypodensity is unilateral. One would generally expect a diffuse insult like hypoxia to affect the brain symmetrically. The observation that one hemisphere can be totally destroyed while the other remains relatively preserved suggests that more than one factor is in play. Gilles and others have noted that in unilateral cases, the hypodensity occurs on the side of the subdural hematoma (Duhaime et al., 1998; Gilles and Nelson, 1998;

Gilles et al., 2003). Therefore, it appears that some synergistic effect of the hemorrhage (or the forces that caused it) and a second insult may be needed.

The role of seizures

Infants with head injury and other neurologic insults often present with seizures, which also may occur subclinically, especially in very young children. The incidence of clinical seizures in inflicted head injuries has been reported in 40–79% of patients (Ludwig and Warman, 1984; Johnson et al., 1995; Gilles and Nelson, 1998; Ghahreman et al., 2005; Bechtel et al., 2006). Clancy et al. (1988) have noted that up to 79% of seizures in neonates are subclinical, that is, are only detected on EEG recordings. This would suggest the possibility that even more seizure events may occur in infants with inflicted injury than are apparent clinically, especially in the youngest patients. Pharmacologic agents used for sedation and/or paralysis during head trauma management in the intensive care unit could influence clinical epileptic events, with some agents (such as midazolam) potentially protecting against seizures, and others (narcotics, paralytics) potentially obscuring their detection. Seizures are known to increase excitotoxic stress in animal models and to be associated with increased metabolic demand and worse outcome in human patients. Therefore, some workers have hypothesized that the frequent occurrence of seizures in infants with traumatic brain injury may contribute to the pathophysiology of an infarct-like picture, such as occurs in hemispheric hypodensity (Duhaime et al., 1998). However, the exact contribution of seizures, clinical or subclinical, to this phenomenon remains unknown.

Neuropathology and clinical neurophysiology

As immunohistochemical techniques have become available, additional detail about the neuropathology of fatal infant inflicted injuries has been determined. Geddes reported that contrary to older studies in which light microscopy was used to assess neuropathology, in her series most patients exhibited little in the way of diffuse axonal injury as determined by both immunohistochemistry and light microscopic findings. However, patients frequently did exhibit "ischemic" findings (Geddes et al., 2001a, b). Additionally, damage at the cervicomedullary junction was often encountered, also raising the question whether apnea due to damage in this location might contribute to the findings; this has been hypothesized by others as well (Hadley et al., 1989; Johnson et al., 1995). However, Geddes and colleagues did not address the specific phenomenon of unilateral "big black brain" in their series.

Kohanek and colleagues have measured a wide variety of cerebrospinal fluid markers from ventriculostomy samples from infants with traumatic brain injury compared to those found in lumbar puncture samples from uninjured infants. They have reported higher levels of excitatory amino acids and other markers of cellular damage in fluid from infants with inflicted injuries and in younger infants compared to older children and those with accidental mechanisms (Ruppell et al., 2001; Berger et al., 2006). Whether these differences reflect an age effect or more extensive damage in the inflicted injury patients (primary or secondary) remains unclear.

Brain swelling, variability, and decompressive craniectomy

Most babies with bilateral or unilateral hemispheric hypodensity develop brain swelling and increased intracranial pressure. Survival is better in the youngest infants, probably because of their ability to split the sutures to relieve some of the pressure. Interestingly, in some cases brain swelling is not problematic, and why some children do not develop significant swelling remains unknown (see Figs. 1–3). It may be that acute injury factors or genetic differences determine this variability.

In recent years, hemicraniectomy has gained increasing acceptance as a means to alleviate the brainstem compressive effects of brain swelling in infants and young children (Cho et al., 1995). It is not yet clear in which children and at what timepoint this should be undertaken, and the effect of this practice on outcome has been difficult to

assess, although it does appear to be effective in lowering intracranial pressure (Taylor et al., 2001). At present it appears that even in those cases in which the hypodensity appears over several days, the processes involved have already begun at presentation and do not appear reversible with current therapies (Duhaime et al., 1996; Dias et al., 1998; Graupman and Winston, 2006). Therefore, treatment strategies are aimed at protecting the undamaged hemisphere. It has been hypothesized that the nearly universal finding of a wedge of damage in the contralateral medial frontal lobe results from subfalcine herniation with trapping of the callosomarginal branch of the anterior cerebral artery against the falx, resulting in focal infarction (Gilles and Nelson, 1998). In the setting of hemicraniectomy, this internal herniation is ameliorated. However, the authors have observed that some contralateral progression can occur despite early relief of pressure, raising the possibility of a neurochemically-mediated process rather than a purely vascular occlusive one (Fig. 3).

Pathophysiology of the "Big Black Brain": a hypothesis

Both experimental and clinical evidences support the idea that no single insult is sufficient to explain all cases of unilateral hemispheric hypodensity in association with subdural hematoma in infants and toddlers. Not all children with subdural hemorrhage develop this finding; thus subdural blood itself appears to be an insufficient cause. Global physiologic insults cannot fully explain the distribution in unilateral cases. Hemispheric hypodensity can be seen in nonaccidental and accidental injuries, with apnea and with no apparent apnea, with clinical seizures and without. Brain swelling usually but not always occurs. Atrophy is rapid and profound. The phenomenon of subdural blood with unilateral hemispheric hypodensity has not yet been reproduced in an experimental model.

In many situations, infants and children demonstrate a remarkable ability to compensate for systemic physiologic stresses. A common example is the child's ability to maintain blood pressure in the face of hypovolemia. However, the immature organism has a limit to its ability to compensate, and when this limit is reached, the resulting decompensation is often precipitous.

It has been demonstrated in a number of contexts that the immature brain's response to insult varies from the adult response. Its response to global hypoxia-ischemia varies, with some ages and in some outcome measures having increased vulnerability to cell death and in others, increased resistance compared to the mature brain (Painter, 1995; Johnston et al., 2001; Vanucci and Hagberg, 2004). Resistance to other insults seen in the context of trauma has been demonstrated by a number of experimental models cited above, including isolated focal mechanical trauma and injected subdural hematoma with increased intracranial pressure; in these contexts, immaturity confers protection.

In cases of infantile subdural hematoma with hemispheric hypodensity, it appears likely that the brain is subjected to a combination of stresses that exceed its capacity to compensate. Most clinical scenarios would point to a combination of local perfusion decrement over the surface of the cerebral hemisphere related to the presence of subdural blood, in combination with a second, more global insult. This could include apnea/hypoxia, hypercarbia, hypotension, or increased metabolic demand from seizures. There may be additional insults that are at present difficult to discern or measure. Why the process involves the entire hemisphere, even beyond the extent of visible subdural blood, remains incompletely understood. It appears to represent a diffuse decompensation resulting in widespread parenchymal death that under certain circumstances may reach threshold only on the side of the larger hemorrhage. Individual differences with respect to cerebrovascular responses, acute injury cascades, inflammation, apoptotic pathways, or other neurochemical processes likely influence why some patients have profound swelling and others do not.

Conclusion

The unique infant pattern of unilateral hemispheric hypodensity associated with accidental or inflicted acute subdural hematoma provides

insight into age-related differences in brain injury response. This pattern of extensive and homogeneous tissue destruction appears to require a combination of insults that overwhelm the immature brain's ability to compensate and affects the entire hemisphere. Because the specific physiologic stresses vary from case to case, including hypoxia, hypotension, hypercarbia, and seizure activity, different factors that decrease substrate delivery or increase metabolic demand may be at play for different patients. The observation that this pattern occurs uniquely in infants and toddlers more likely reflects their age-dependent brain response to combined stresses rather than reflecting a single, specific mechanism or circumstance of injury.

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