MR and CT evaluation of profound neonatal and infantile asphyxia.

A J Barkovich

AJNR Am J Neuroradiol 1992, 13 (3) 959-972
http://www.ajnr.org/content/13/3/959

MR and CT Evaluation of Profound Neonatal and Infantile Asphyxia

A. James Barkovich[1]

Purpose: To determine the CT and MR characteristics of the brains of infants who have suffered profound asphyxia and correlate those characteristics with pathophysiologic processes. **Methods:** MR and CT scans of 16 patients who suffered profound hypoxic-ischemic injury in the perinatal (12 patients) and postnatal (4 patients) periods were retrospectively reviewed in a search for characteristic imaging features. **Results:** Injury in the perinatal period: subacute MR showed short T1 and T2 in the ventral lateral thalami, posterolateral lentiform nuclei, posterior mesencephali, and hippocampi; MR 1 to 16 years after injury showed atrophy or T2 prolongation in the aforementioned regions, the lateral geniculate nuclei and perirolandic cerebral cortex. Asphyxia later in infancy: subacute MR showed T2 prolongation in the corpus striatum and most of the cerebral cortex (perirolandic sparing); MR weeks to months later showed atrophy of the aforementioned areas, the lateral geniculate nuclei and hippocampi. Acute CT in both groups showed basal ganglia hypodensity. **Conclusions:** The injury patterns observed in neonates and infants with profound hypoxic-ischemic injury vary with the age of the patient at the time of the injury. The change in pattern of damage is suggested to be the result of structural and physiologic changes in the maturing brain. The patterns appear to be consistent and are well demonstrated by MR.

Index terms: Asphyxia, in infants and children; Brain, computed tomography; Brain, magnetic resonance; Pediatric neuroradiology

AJNR 13:959–972, May/June 1992

Several recent articles have addressed the brain MR appearance of neonates and infants who have suffered hypoxic-ischemic brain injury (1–4). The predominance of deep gray matter injury was noted in a few neonates with profound hypoxic-ischemic injury (1, 4), a different pattern from that observed in less severely injured infants (1). However, the precise pattern of gray matter injury was never established, nor was a determination made concerning the frequency of predominant deep gray matter injury in profound asphyxia. The purpose of this study was to examine the imaging (computed tomography (CT) and magnetic resonance (MR)) studies of a larger number of patients with profound hypoxic-ischemic injury in order to determine whether the previously reported pattern of deep gray matter injury with relative cortical sparing is, indeed, the predominant pattern of injury in this subset of patients. Furthermore, this report hopes to further elucidate the patterns of injury in the profoundly asphyxiated newborn and infant brain, as assessed by modern imaging techniques.

Patients and Methods

The imaging studies of 16 full-term infants with profound hypoxic-ischemic episodes were retrospectively reviewed by the author. All scans were assessed for morphology and signal abnormalities of the structures in the brain. In particular, the deep gray matter nuclei of the cerebrum, the midbrain, the lateral geniculate nuclei, the hippocampal formation, the cerebral cortex, the superficial and deep white matter, and the cerebellum were scrutinized. The hippocampus was difficult to assess on axial images, particularly long TR images without flow compensation techniques. Therefore, coronal images were used in the assessment of the hippocampus whenever possible. In every case where the hippocampus was considered atrophic on axial images and coronal images were available, the coronal images confirmed hippocampal atrophy. The state of myelination was assessed as normal or delayed. The size of structures (normal vs small) was assessed subjectively by the author, based on clinical experience. As the posterior globus pallidus was difficult to differentiate

Received June 21, 1991; accepted and revisions requested September 9; revisions received October 19.

[1] Neuroradiology Section, L371, Department of Radiology, University of California, San Francisco, San Francisco, CA 94143-0625.

AJNR 13:959–972, May/June 1992 0195-6108/92/1303-0959

from the posterior putamen on most images, the lentiform nuclei were assessed with regard to the medial lentiform nucleus versus the lateral portion of the lentiform nucleus. The globus pallidus and putamen were not considered separately. The term basal ganglia refers to all of the deep gray matter nuclei, the caudate nuclei, putamina, globi palladi, and thalami. The term lentiform nuclei refers to the combination of the globi palladi and putamina. The term corpus striatum refers to the combination of the caudates, globi palladi, and putamina.

All MR scans were performed at 1.5 T. Sagittal, 3- to 5-mm (1 mm "gap") SE 450-600/11-25/1-2 (TR/TE/exc, msec) and axial 5-mm (2.5-mm "gap") SE 2500-3000/25-60, 70-150 images were obtained in all patients save one. Coronal 5-mm (2.5-mm "gap") SE 2500-2800/30-40, 70-80 images were available in five patients and coronal 5-mm (1-mm "gap") SE 600-800/20 images were available in three patients. Axial 5-mm (1-mm "gap") SE 600/20 images were available in five patients.

Noncontrast CT scans were obtained in six patients. They consisted of standard, contiguous axial 10-mm images in three patients, 8-mm images in one, and 5-mm images in the remaining two patients.

Perinatal Injuries

Twelve infants were injured in the perinatal period (within 48 hours of birth), including eight who had cardiocirculatory arrest lasting from 10 minutes to 30 minutes, and four who were delivered between 15 and 25 minutes after large maternal placental abruptions.

MR scans were available on all patients. Of those patients injured in the perinatal period, one was scanned at age 2 weeks (with a follow-up scan at age 3 years), two at age 3 weeks (one had a follow-up MR at age 15 months), one at age 1 month (follow-up MR was performed at age 12 months), one at age 2 months, one at age 3 months, two at age 12 months, one at age 3 years, one at age 8 years, one at age 10 years, and one at age 16 years (Table 1). Only two patients in this group had CT scans: patient 2 at ages 4 days and 22 days, and patient 6 at age 2 days.

Postnatal Injuries

Postnatal injuries occurred in four patients. One patient suffered a cardiocirculatory arrest of 20 minutes duration at age 7 weeks. Two patients were injured at age 12 months, one as a result of a cardiocirculatory arrest of unknown duration, followed by 40 minutes of CPR, and the other a result of 30 minutes of profound bradycardia and hypotension. The final patient suffered a cardiocirculatory arrest of unknown duration at age 23 months (Table 1).

CT and MR scans were available on all four patients. The patient injured at age 7 weeks was scanned by CT at 1 week and by MR at 2 weeks after injury. Of the infants injured at age 12 months, one was scanned by CT and MR within the first 24 hours after injury and then by MR 1 week later, while the other was scanned by CT at 48 hours and by MR 11 days after injury. The child injured at age 23 months was scanned by MR at 1 week, 2 weeks, and 6 months after injury and by CT at 3 weeks after injury.

Results (see Table 1)

Perinatal Injuries (12 Patients)

Of the 12 patients with injuries in the perinatal period, only two were imaged by CT, one at ages 4 and 22 days and the other at age 2 days. Those obtained at ages 4 and 2 days, in patients 2 and 6, respectively, showed hypointensity of the basal ganglia without cortical abnormality (Fig. 1A). The lateral ventricles were small, implying cerebral edema. A follow-up CT at 22 days in patient 2 showed high density of the lentiform nuclei (Fig. 1B), suggestive of hemorrhage or calcification.

MR was performed at ages of 2 weeks (one patient), 3 weeks (two patients), 4 weeks (one patient), 8 weeks (one patient), 12 weeks (one patient), 1 year (two patients), 3 years (one patient), 8 years (one patient), 10 years (one patient), and 16 years (one patient). Follow-up MR scans were obtained on three patients who were initially imaged during the first month of life, at age 12 months, at age 15 months, and at age 3 years.

Patients imaged by MR 1 to 4 weeks after perinatal injury showed a consistent pattern of injury. All had globular areas of shortened T1 relaxation, which were located primarily in the posterior lateral lentiform nuclei and ventral lateral thalami (Fig. 2). The medial lentiform nuclei also showed shortened T1 relaxation in two patients (Fig. 1) and the entire basal ganglia in one. Shortened T2 relaxation time was also present in the deep gray matter, although it was less extensive than the T1 shortening and primarily involved the posterior lentiform nuclei and ventral lateral thalami (Fig. 1); the remainder of the basal ganglia showed either normal or high signal intensity on long TR images. The tegmenta of the midbrains had abnormal signal intensity in three of the four patients, two exhibiting shortened T1 and the third exhibiting prolonged T1 relaxation. The lateral geniculate nuclei showed subtle T1 shortening in all four patients, with atrophy already present in the 4-week-old infant. Subtle T1 shortening was also present in the hippocampus in three of the four patients (Figs. 1 and 2). Myelination was delayed in all four. The centra ovale and cerebral cortices were normal in all.

TABLE 1: MR data

Patient	Age at Scan	Duration of Asphyxia	Caudates	Lateral LN	Medial LN	Thalami	Mid-brain	Cortex	WM-Deep	WM-Peripheral	Myelination	Cerebellum	LGN/SI	Hippocampus
Perinatal injury														
1 MR	3 wk	30 min arrest injured at birth	nl	post mixed T2 post short T1	long T1, T2	short T1 mixed T2	sl small post short 1	nl	nl	nl	sl delay	(dilantin) prom fissures	short T1, T2	short T1
2 CT, MR	3 wk	Arrest × 20–25 min injured at birth	long T2	short T1, T2 post	short T1 medially	short T1, T2 ventrolateral	short T1, T2 post	nl	nl	nl	delayed	subdural	short T1	short T1
	f/u 15 mo		small	small, long T2 post	small	small, long T2 ventrolateral	small	nl	thin, long T2	nl	delayed	nl	atrophy	atrophy
3 MR	14 days	10 min arrest injured at birth	nl	short T1, T2 post	nl	short T1, T2 ventrolateral	nl	nl	nl	nl	delayed	small SDH	short T1	short T1
	f/u 3 yr		nl	small, long T2 post	nl	long T2 laterally	? small	nl	sl diminished ? long T2	nl	nl	nl	long T2	nl
4 MR	1 mo	Large abruption 20 min prior to birth	nl	globular short T1 post	globular short T1	globular short T1	small long T2	nl	nl	nl	delayed	nl	atrophy short T1	atrophy
	f/u 1 yr		nl	small, long T2 post	small	small, long T2 lateral	small post	nl	diminished long T2	nl			atrophy	atrophy
5 MR	2 mo	20 min arrest injured at birth	small	small short T1, T2 post	small	small short T1, T2 lateral	small short T2 post	thin short T1, T2 perirolandic	diminished long T2 mottled	diminished perirolandic	delayed	prom fissures post	atrophy	atrophy
6 CT, MR	3 mo	>60% abruption 25 min prior to delivery	small	small, long T2	small long T2	small long T2 ventral/lateral	small	sl thin perirolandic	diminished long T2 post > ant	long T2 in fr-parietal	nl	prom-fissures	atrophy	atrophy
7 MR	12 mo	30 min bradycardia heart rate 40–60 bpm BP unknown	nl	long T2 post/inf small bilateral, symm	nl	long T2 ventral/lateral bilateral symmetrical	nl	long T2 atrophy perirolandic	long T2 post periventricular	long T2 perirolandic	sl delayed	nl	atrophy long T2	atrophy long T2
8 MR	12 mo	>60% abruption 20 min prior to birth	long T2 right	long T2 post/inf bilateral symmetrical	small	long T2 lateral bilateral symmetrical	small	long T2 atrophy perirolandic	diminished long T2	nl	nl	nl	atrophy long T2	atrophy long T2
9 MR	3 yr	Large abruption 15 min prior to delivery	small	small, long T2 post	small	small long T2 lateral	small	nl	diminished long T2	nl	nl	prom fissures	nl	atrophy
10 MR	8 yr	Apgars of 0 arrest at birth	nl	small long T1, T2	sl small ? short T1	small long T2	sl small	atrophy long T2	long T2 peritrigonal	long T2 perirolandic	nl	atrophy sup vermis	atrophy	atrophy
11 MR	10 yr	Cardiorespiratory arrest × 30+ min at age 2 days	v small	v small long T1, T2	v small	v small long T1, T2	v small	sl thin everywhere	diminished, long T2	small	nl	small post/inf CSF collection	atrophy	atrophy
12 MR	16 yr	Cardiocirculatory arrest × 30 min at birth	small	small inc T2 post	small	small long T2 lateral	nl	long T2, atrophy perirolandic	diminished post	nl	nl	sl prom fissures	nl	atrophy
Postnatal injury														
13 MR	2 mo	Cardiocirculatory arrest × 20 min at age 7 wk	nl	short T1, T2 post	nl	short T1, T2 lateral	short T1, T2 post	patchy short T1, T2	heterogeneous	nl	delayed	prom fissures post/inf	atrophy short T1, T2	atrophy short T1,T2

TABLE 1: *Continued*

Patient	Age at Scan	Duration of Asphyxia	Caudates	Lateral LN	Medial LN	Thalami	Mid-brain	Cortex	WM-Deep	WM-Peripheral	Myelination	Cerebellum	LGN/SI	Hippocampus
14 CT, MR	13 mo	1 hr arrest (BP = 0) at age 12 mo	long T2	long T2 post > ant	long T2	nl	nl	thin, long T2 occ + fr	long T2 peritrigonal	short T2 + enhancement right parietal	can't tell	nl	atrophy long T2	atrophy long T2
15 CT, MR	12 mo	Cardiocirculatory arrest × 35 min at age 12 mo	nl	nl	nl	nl	nl	long T2 insula	nl	nl	nl	nl	nl	nl
	f/u 1 wk		long T1, T2	long T1, T2	long T1, T2	nl	nl	long T2 fr occ (syl spare)	nl	nl	nl	nl	nl	long T2
16 MR, CT	23 mo	Cardiocirculatory arrest × 30 min at age 23 mo	long T2	long T2	? long T2	nl	nl	thick long T2 frontal occ (syl spare)	nl	nl	nl	nl	nl	nl
	f/u 1 wk		long T1, T2	long T1, T2	nl	nl	nl	thick, long T1, T2 (syl spare)	nl	long T2 (syl spare)	nl	nl	long T2	nl
	f/u 6 mo		small long T1, T2	small long T1, T2	small	nl	sl small	thin, long T2 (syl spare)	diminished, long T2 fr occ	diminished, long T2 (syl spare)	delayed	nl	atrophy long T2	atrophy long T2

Note.—Abbreviations: sl = slightly; post = posterior; ant = anterior; inf = inferior; fr = frontal; occ = occipital; SDH = subdural hematoma; v = very; prom = prominent; nl = normal; syl spare = sparing of sylvian and supralylvian regions; CSF = cerebrospinal fluid; inc = increased; f/u = follow-up; LN = lentiform nuclei; WM = white matter; LGN/SI = lateral geniculate nucleus/substantia innominata; BPM = beats per minute; BP = blood pressure; sup = superior.

The two patients imaged by MR 8 and 12 weeks after perinatal injury both had abnormal signal in small basal ganglia and mesencephali. The patient imaged 8 weeks after injury had shortened T1 and T2 relaxation times in small posterior lentiform nuclei, ventral lateral thalami, and the tegmentum mesencephali with normal signal in small caudates and medial lentiform nuclei (Fig. 3). The patient imaged at 12 weeks post injury had long T1 and T2 relaxation times in small lateral lentiform nuclei, medial lentiform nuclei, and thalami, with normal signal in the small caudates and the tegmentum mesencephali. Both had small hippocampi and lateral geniculate nuclei and cortical thinning in the perirolandic cerebral cortices bilaterally (Fig. 3). Both had delayed myelination and diminished white matter with mottled T2 prolongation in the periventricular white matter extending into the subcortical white matter in the region of the cortical thinning.

The nine scans of patients injured at birth and scanned more than 1 year later (six initial scans and three follow-up scans) all had similar findings on their MRs. All had prolonged T2 relaxation in the posterior lentiform nuclei and ventral lateral thalami (Fig. 4). In six of the nine, all of the deep gray matter nuclei were small. The seventh showed sparing of only the caudates, and, in the final two, the medial and lateral posterior lentiform nuclei were small. The tegmentum mesencephali was small in four patients, all having normal signal intensity. The lateral geniculate nuclei were variable in appearance, showing no abnormality in two patients, atrophy in four, atrophy and prolonged T2 relaxation in two, and prolonged T2 relaxation without atrophy in one. The hippocampus was normal in appearance in one patient, showed atrophy in six patients, and atrophy and prolonged T2 relaxation time in one (Fig. 4). The cerebral cortex was normal on three scans, showed thinning in the perirolandic gyri in five patients, and was diffusely thinned in one. The deep white matter was diminished, with prolonged T2 relaxation, in all eight patients. The peripheral white matter was diminished only subjacent to the aforementioned areas of perirolandic cortical thinning (Fig. 4). Myelination was delayed in three patients, age 12 months (two patients) and 15 months at the time of their scans.

Postnatal Injuries (Four Patients)

Of the four patients with postnatal injuries, the three injured at ages 12 months (two patients) and 23 months had very similar patterns, different from the patterns seen in the group injured peri-

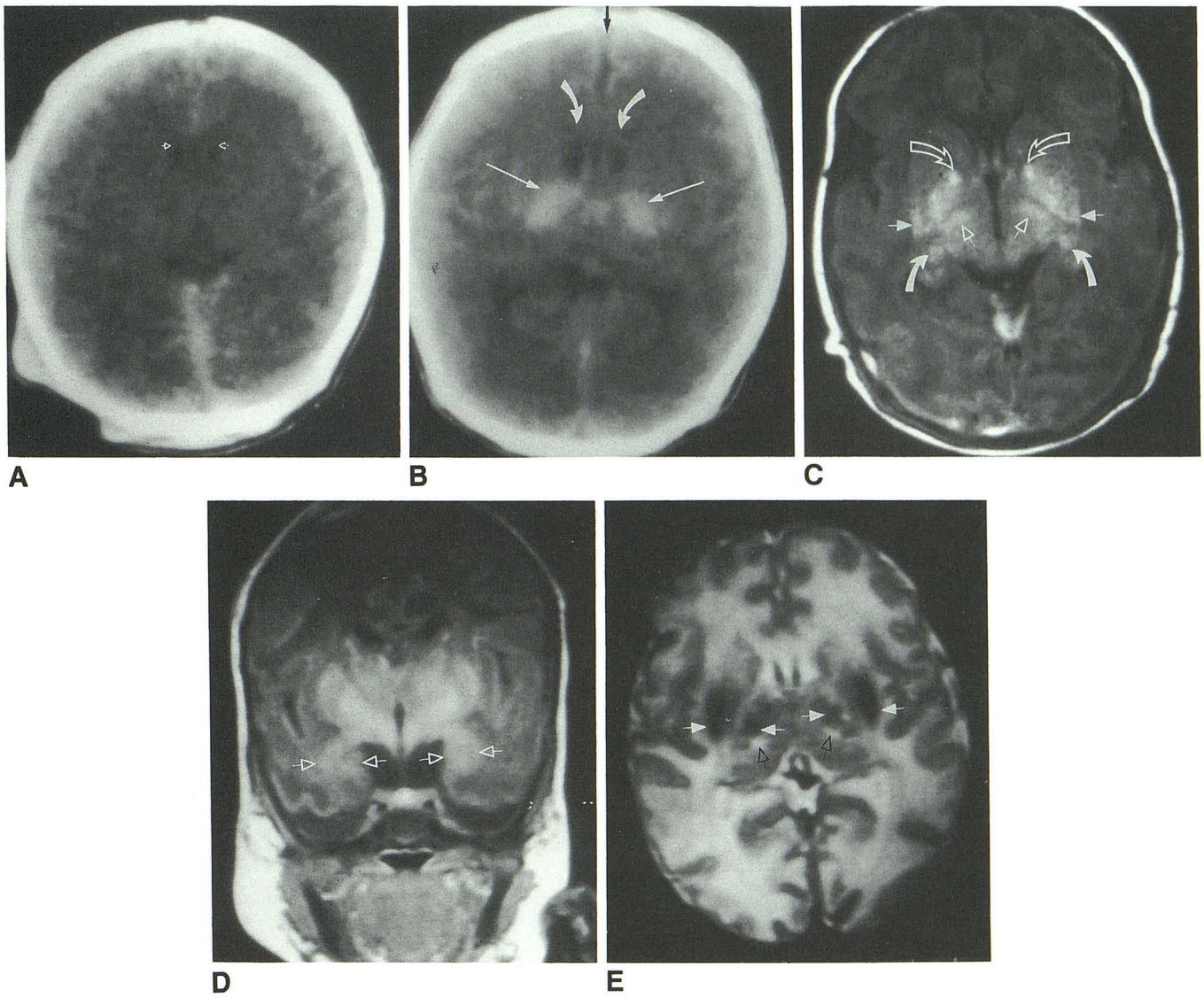


Fig. 1. Patient 2; cardiocirculatory arrest at birth.

A, Noncontrast CT scan obtained at age 4 days shows hypodensity of the deep gray matter nuclei, which are isodense with the surrounding white matter. The frontal horns of the lateral ventricles (*arrows*) are small, implying cerebral edema.

B, Noncontrast CT scan obtained at age 22 days. The frontal horns (*curved white arrows*) and anterior interhemispheric fissure (*black arrow*) are enlarged compared with *A*, implying resolution of edema and probable atrophy. The lentiform nuclei (*straight white arrows*) are now hyperdense, suggesting the presence of hemorrhage or, perhaps, calcification.

C, Axial SE 600/20 image obtained at age 21 days. Globular areas of T1 shortening are present in the lateral geniculate nuclei (*closed curved arrows*), lateral thalami (*open straight arrows*), posterolateral lentiform nuclei (*closed straight arrows*), and medial lentiform nuclei (*open curved arrows*). Note that the relative hyperintensity normally seen in the posterior limb of the internal capsule at this age, secondary to myelination, is absent, indicating delayed myelination. The posterior half of the right hemisphere appears bright in this figure and in Figure 1E as a result of "shading" artifact, secondary to lack of static field homogeneity.

D, Coronal SE 700/20 image obtained at age 21 days shows hyperintensity in the hippocampi (*arrows*), left side more prominently than the right, in addition to the hyperintensity in the lentiform nuclei.

E, Axial SE 300/120 image obtained at age 21 days shows globular T2 shortening (*white arrows*) and punctate T2 prolongation (*black arrows*) in the lateral lentiform nuclei and thalami.

natally. All had T1 and T2 prolongation involving the corpus striatum and majority of the cerebral cortex with sparing of the thalami and suprasylvian/perirolandic cortex on subacute scans (1 to 2 weeks post injury) (Fig. 5). Interestingly, the one patient imaged by MR in the acute phase (less than 24 hours post injury) had a nearly normal study, with minimal T2 prolongation in the insular cortices (Fig. 6A). A CT scan obtained 3 hours later showed profound hypodensity of the deep gray matter structures (Fig. 6B). Follow-up MR 1 week later revealed characteristic pro-

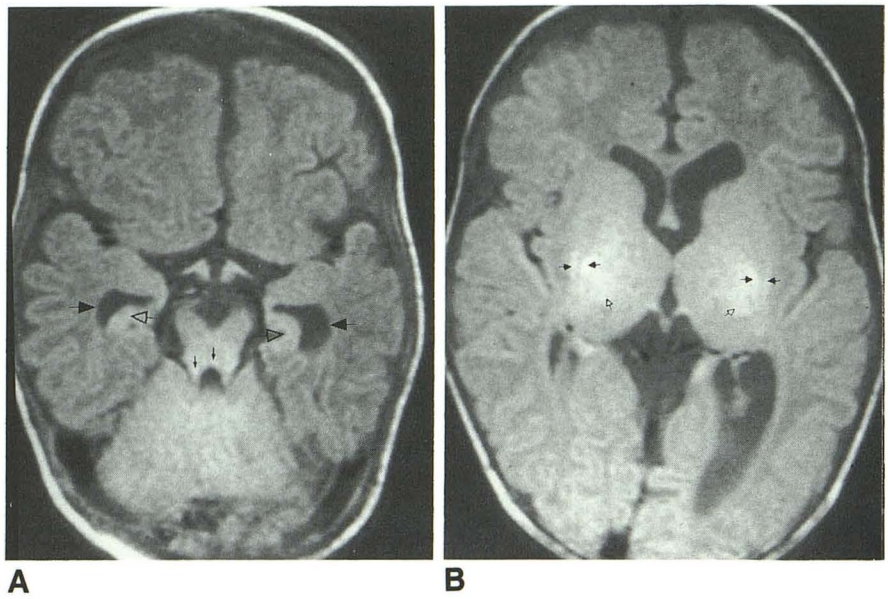
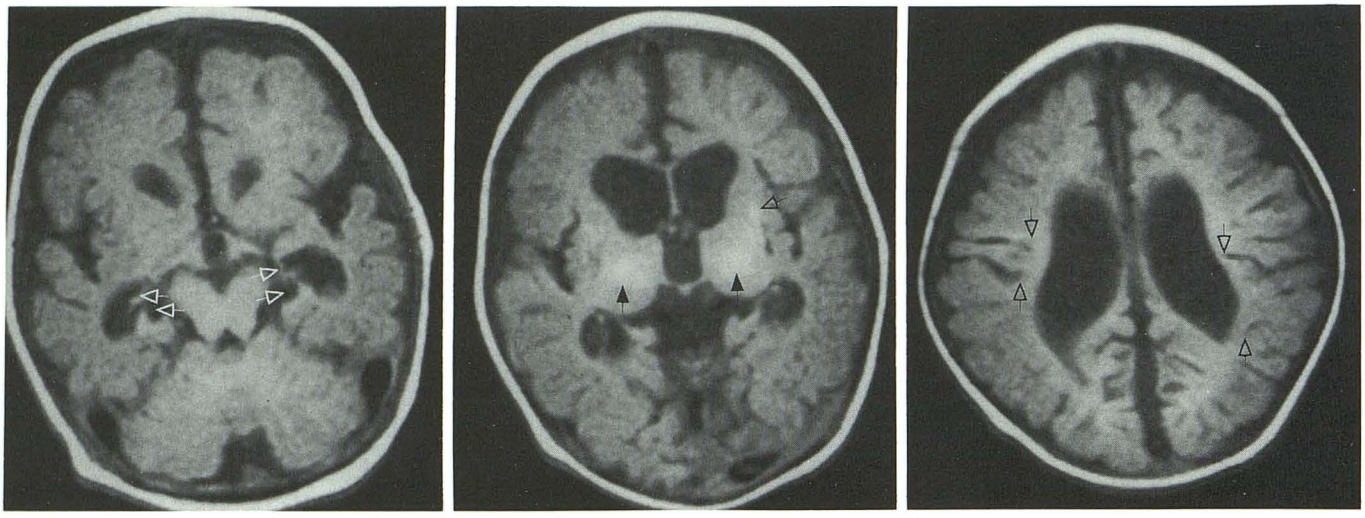


Fig. 2. Patient 4; greater than 60% abruption 20 minutes prior to birth. MR scan obtained at age 27 days.

A, Axial SE 600/20 image shows that the temporal horns (*closed black arrows*) are enlarged and the hippocampal formations (*open black arrows*) show mild T1 shortening. Speckled hyperintensity (*small black arrows*) is present in the shrunken dorsal midbrain.

B, Axial SE 600/20 image shows globular T1 shortening in the posterolateral lentiform nuclei (*closed black arrows*) and ventrolateral thalami (*open black arrows*), left greater than right. Notice the absence of the normal hyperintensity of the posterior limb of the internal capsule.



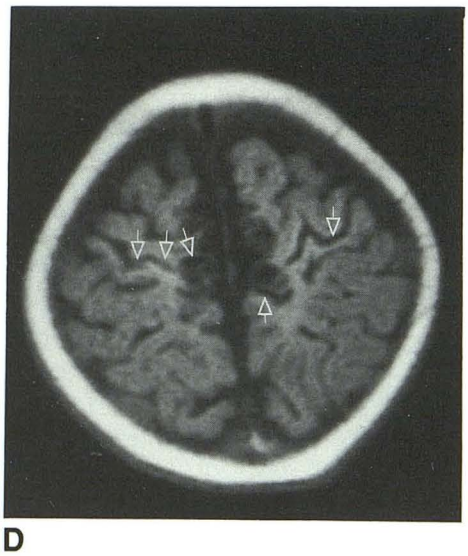


Fig. 3. Patient 5; cardiocirculatory arrest at birth. This scan was obtained at age 2 months.

A, Axial SE 700/20 image shows enlarged temporal horns with significant tissue loss in the hippocampi and lateral geniculate nuclei (*arrows*).

B, Axial SE 700/20 image shows small basal ganglia with T1 shortening in the ventrolateral thalami (*closed arrows*) and in the region of the posterolateral lentiform nucleus on the left (*open arrow*).

C, Axial SE 700/20 image shows enlarged bodies of lateral ventricles and diminished periventricular white matter, resulting in proximity of the depths of the cortical sulci (*arrows*) to the lateral ventricular walls.

D, Axial SE 700/20 shows shrunken perirolandic cortex (*arrows*) over the cerebral convexities.

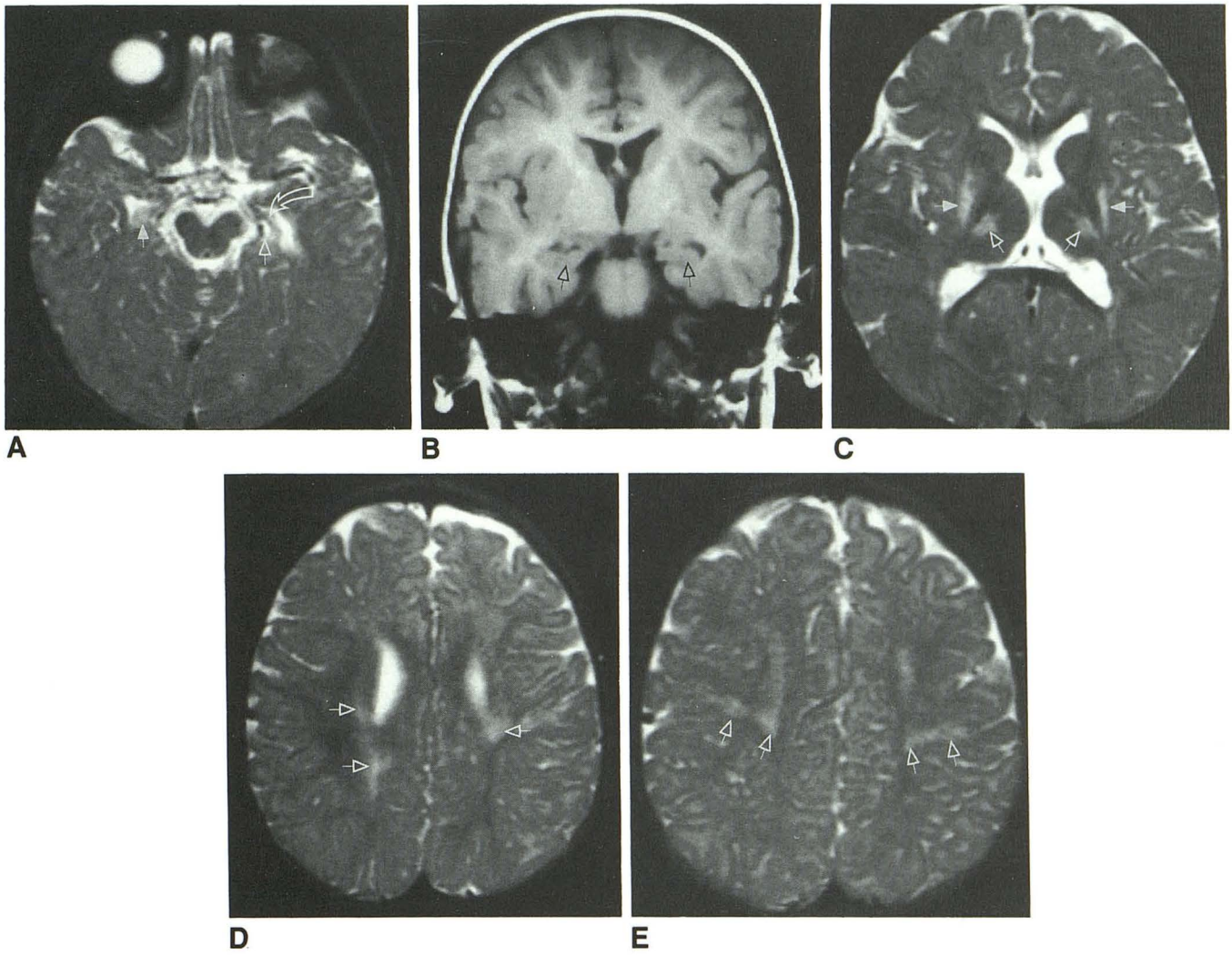


Fig. 4. Patient 8; large abruption 20 minutes prior to delivery. MR scan was obtained at age 12 months.

A, Axial SE 3000/120 image shows T2 prolongation and mild loss of brain substance in the left hippocampus (*curved open arrow*), left lateral geniculate body (*straight open arrow*), and, to a lesser extent on this image, the right hippocampus (*closed arrow*). The region of the right lateral geniculate nucleus was seen on the next higher image and showed atrophy, as well. The midbrain is small.

B, Coronal SE 600/20 image confirms bilateral hippocampal atrophy (*arrows*).

C, Axial SE 3000/120 image shows T2 prolongation in the ventrolateral thalami (*open arrows*) and posterolateral lentiform nuclei (*closed arrows*).

D, Axial SE 3000/20 image shows diminished periventricular white matter with some periventricular T2 prolongation (*arrows*). This image resembles the pattern of periventricular leukomalacia seen in premature infants and infants injured prenatally.

E, Axial SE 3000/120 shows prolonged T2 relaxation time of the subcortical white matter in the perirolandic regions bilaterally (*arrows*).

longed T1 and T2 relaxation times of the corpus striatum and of the cerebral cortex and subcortical white matter in all areas but the suprasylvian/perirolandic regions (Fig. 6C). A similar pattern of cortical injury was seen in the other two patients. CTs in all three patients showed the same pattern: cortical and basal ganglia hypodensity with sparing of the suprasylvian/perirolandic region.

The patient injured at 7 weeks and scanned subacutely (2 weeks later) had features reminiscent of both those injured at birth and those injured at ages 1 to 2 years. Globular areas of T1 and T2 shortening were present in the posterior lentiform nuclei, lateral thalami, and tegmentum of the midbrain, as in the perinatal injuries, but cortical damage, manifest as patchy areas of short T1 and T2 relaxation, was present as well. A CT scan, performed 6 days prior to the MR, showed patchy cortical hypo- and hyperdensity, hypodensity in the caudates, and high density in the lentiform nuclei, suggestive of hemorrhage.

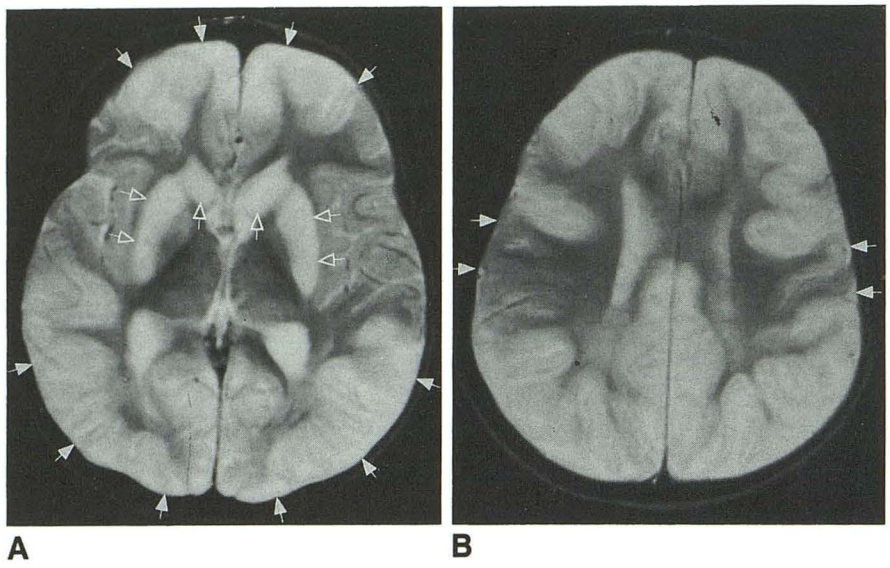


Fig. 5. Patient 16; patient injured at age 23 months by a cardiocirculatory arrest of at least 30 minutes. This MR scan was performed 2 weeks after the injury.

A, Axial SE 2500/90 image shows prolonged T2 relaxation time, primarily in the caudates and putamina (*open arrows*) and the frontal and posterior temporal-occipital cortex (*closed arrows*). Note that the globi palladi, thalami, and opercular cortex are relatively spared.

B, Axial SE 2500/90 image at the level of the bodies of the lateral ventricles shows thickening and T2 prolongation of most of the cerebral cortex with relative sparing of the perirolandic region (*arrows*).

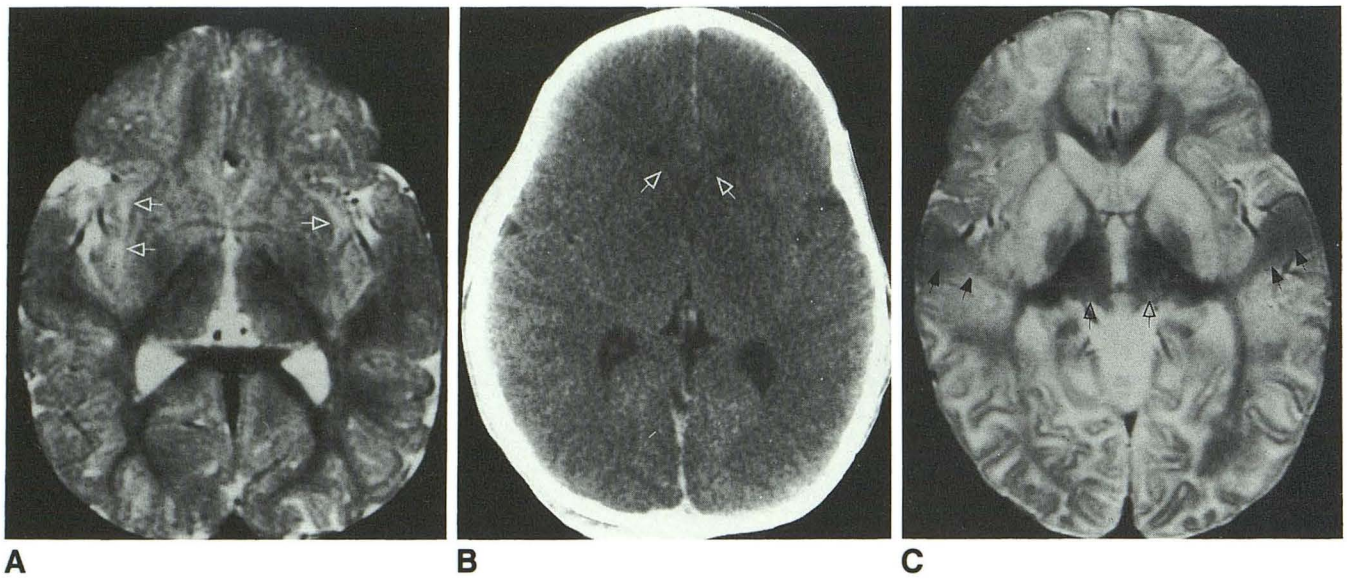


Fig. 6. Patient 15; cardiocirculatory arrest for 35 minutes at age 12 months.

A, Axial SE 2500/90 image obtained less than 24 hours after the injury. Mild T2 prolongation (*arrows*) is present within the region of the extreme capsule. No other significant abnormalities were appreciated on this scan.

B, Noncontrast CT scan obtained 3 hours after *A*. Marked hypodensity is present in the basal ganglia, particularly the corpus striatum. The frontal horns of the lateral ventricles (*arrows*) are mildly compressed, presumably by cerebral edema.

C, Axial SE 2500/90 image obtained 1 week after injury. Profound T2 prolongation is present in the caudate nuclei, putamina, medial globus pallidus, and most of the cerebral cortex and subcortical white matter. Note the relative sparing of the sylvian/perirolandic region (*closed black arrows*) and the thalami (*open black arrows*).

Discussion

A recent paper concerning MR findings in perinatal asphyxia (1) reported two patients with abnormalities limited primarily to the deep gray matter structures and postulated that the pattern of injury resulted from a profound asphyxic event. Three other reports have appeared in the literature reporting similar injury patterns on MR studies of asphyxiated neonates (2–4); one (4) noted the similarity of the injury pattern to that found in experimental acute total asphyxia (5) and in previous pathologic studies of infants with "cardiac arrest encephalopathy" (6–9).

The present study adds further evidence that the pattern of deep gray matter injury with relative cortical sparing is a manifestation of profound asphyxia in the perinatal period. The predominant involvement of the hippocampi, lateral geniculate

nuclei, posterolateral aspects of the lentiform nuclei, ventral lateral thalami, and dorsal mesencephali correlates well with the locations of injury described in pathologic studies of profound asphyxia (5–7, 9); the major difference was that the present study detected considerably less brain stem injury. Although it is possible that fewer brain stem injuries were detected in the present study because pathologic techniques are more sensitive to injury in that location, a more likely reason is that patients with severe brain stem injury succumb to their injuries rapidly and, therefore, never undergo MR. As a consequence, our series may be biased toward patients with less severe brain stem injuries and the pathologic studies biased toward patients with more severe brain stem injuries.

The results of this study also seem to indicate a different pattern of injury in neonates than in older infants, an observation that has not been reported previously. All infants injured in the neonatal period in this study had damage in the posterior lentiform nuclei and ventral lateral thalami, with occasional involvement of the medial lentiform nuclei and the perirolandic cortex (Figs. 1–4 and 7, and Table 2). Those infants injured at the ages of 1 to 2 years showed injury to the corpus striatum, anterior frontal cortex, and parietal-occipital cortex with relative sparing of the thalami and the perirolandic cortex (Figs. 5–7 and Table 2). Both groups showed a high incidence of injury to the lateral geniculate nuclei and hippocampus. The change in the injury pattern and its potential causes is deserving of some discussion.

Excitatory Amino Acids

In the past few years, the neuroscience literature has been filled with articles concerning the role of excitatory amino acids (ie, glutamate, aspartate, and structurally related compounds) in brain development and brain injury (10–13). Excitatory amino acids help to promote neuronal survival, growth, and differentiation, and aid in the development and regulation of neuronal circuitry and cytoarchitecture (12). They function at special receptor sites, the most common being the *N*-methyl-D-aspartate (NMDA) receptor (12). The locations within the brain in which the excitatory amino acids and their receptors are expressed vary with the stage of brain development, possibly in relation to their functions in the process of normal brain development (11, 12, 14, 15). A number of papers have presented evidence implicating excitatory amino acids in brain injury secondary to hypoxia-ischemia (16, 17), hypoglycemia (18), status epilepticus (19), and physical trauma (20). The proposed mechanism of injury is that of either excessive release of excitatory amino acids into, or impaired uptake of excitatory amino acids from, the intersynaptic cleft. Both excessive release and impaired uptake of these substances result in an overabundance of excitatory amino acids at NMDA receptors. This overabundance results in depolarization of neuronal membranes, followed by excessive calcium influx via NMDA receptor-induced calcium channel activation, activation of second messenger systems, mobilization of internal calcium stores, activation of lipases and proteases, generation of free fatty acids and free radicals, mitochondrial dysfunction, and depletion of energy stores (12, 21). These derangements lead to ultimate cell death.

In view of the changing location of the excitatory amino acid expression and its established relationship to hypoxic-ischemic injury, the excitatory amino acid theory seems a plausible hypothesis for the changing pattern of brain injury in neonates and infants. In fact, Ikonomidou et al (22) have demonstrated that changes in the sensitivity to and location of hypoxic-ischemic brain damage in rats parallels the changes in the sensitivity to and location of brain damage secondary to excitatory amino acid toxicity at NMDA receptors. Furthermore, the histologic appearance of acute brain degeneration following hypoxic-ischemic injury is identical to that following glutamate-induced damage at NMDA binding sites (22, 23), and both hypoxic-ischemic damage and excitotoxic damage can be blocked by the administration of NMDA antagonists (24, 25). Although the precise topology of the excitatory amino acid binding sites in the developing human brain does not precisely correlate with the locations of neonatal brain damage observed in this and other studies (6, 9), considerable overlap is observed. Excitatory amino acid binding sites are believed to be most numerous in the globi pallidi, subthalamic nuclei, hippocampi, lateral geniculate nuclei, and substantia innominata in newborn brains (11, 12, 15, 22), whereas the primary damage observed in newborns involves the ventral lateral thalami, posterior lentiform nuclei, posterior periventricular white matter, lateral geniculate nuclei, hippocampi, and perirolandic cortex. Despite these similarities in location, even

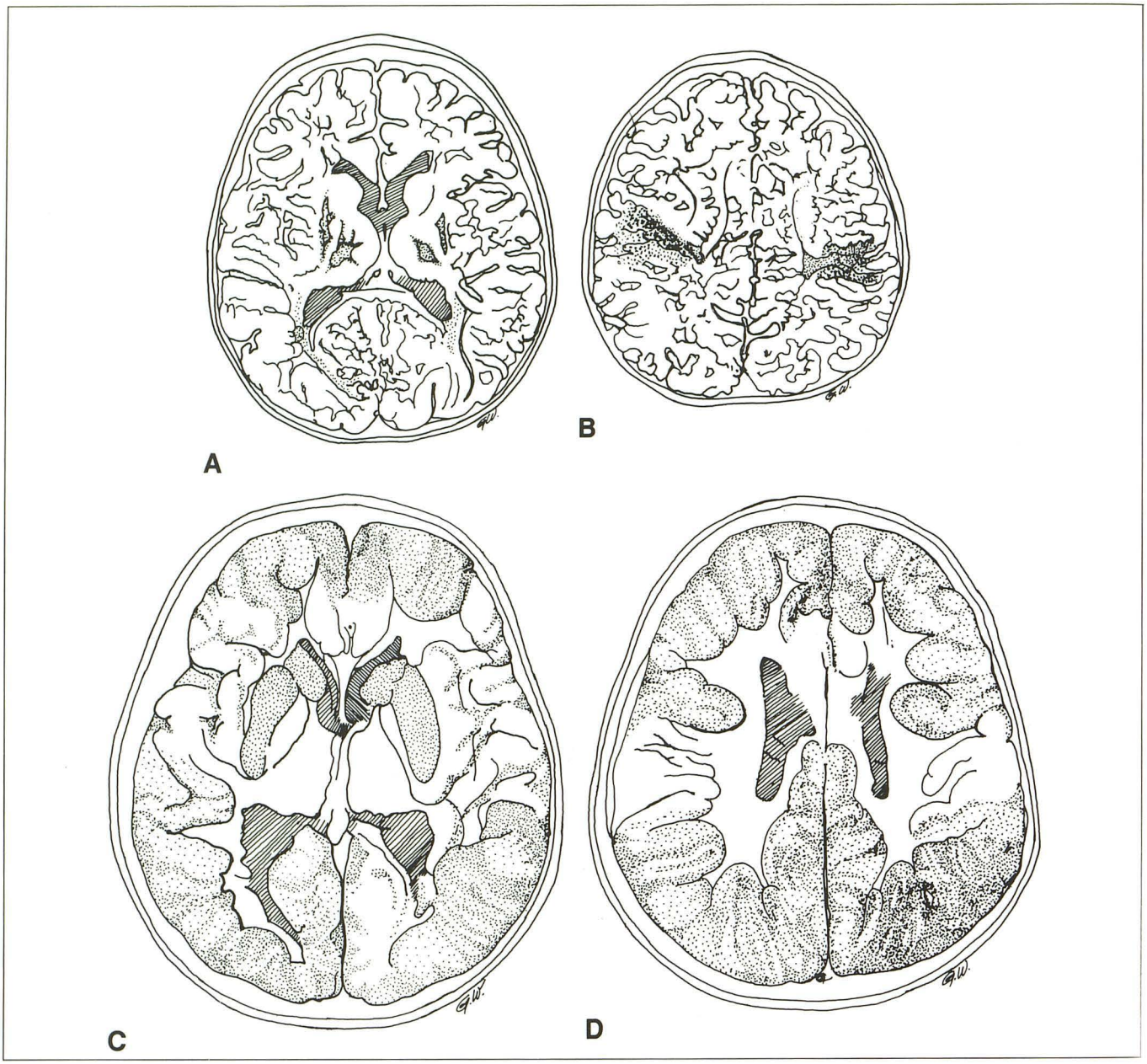


Fig. 7. Schematics illustrating location of brain damage in profoundly asphyxiated newborns and infants.
A and *B*, In newborns, the lateral thalami, posterior lentiform nuclei, and perirolandic cortex are primarily involved (*stippled areas*).
C and *D*, In older infants, the caudate nuclei, lentiform nuclei, and cortex other than the perirolandic regions are affected most (*stippled areas*), with conspicuous sparing of the thalami and perirolandic cortex.

those authors championing excitatory amino acid toxicity as being a major factor in hypoxic-ischemic injury note some inconsistencies between the location of excitatory amino acid binding sites and that of hypoxic-ischemic injury (12, 22). As a result, some have proposed that other factors, such as high local energy requirements, are superimposed upon excitatory amino acid receptor concentration (12, 22). A review of the locations of injury in this study seem to indicate that, with the exception of the hippocampus, the areas of damage in newborns with profound hypoxic-ischemic injury seem to correlate quite closely with areas that are in the process of myelinating. This observation suggests that areas undergoing active myelination are highly susceptible to injury in profound hypoxic-ischemic injury in newborns. The hippocampus, which appears to be affected consistently and early in all age groups studied, is known to have a high level of NMDA receptors

TABLE 2: Summary

Location	Signal-Acute (3 patients)	Signal-Subacute (3 patients)	Signal-Chronic (9 patients)
Perinatal injuries (12 patients, 15 scans)			
Caudates	nl or long T2	nl or small	small (long T2)
Thalami	short T1, T2 laterally	short T1, T2 laterally	small, long T2 laterally
Lateral lentiform	short T1, T2 posteriorly	small, variable signal	small, long T2 posteriorly
Medial lentiform	nl or variable	small, variable signal	small
Hippocampi	short T1	small	small
Lateral geniculate nuclei	short T1 (+T2)	small	small
Perirolandic cortex	nl	nl or thin (short T1, T2)	nl or thin (long T2)
Peritrigonal white matter	nl	diminished (long T2)	diminished, long T2
Perirolandic subcortical white matter	nl	diminished or long T2	nl or long T2
	Signal-Acute (5 patients)	**Signal-Subacute (1 patient)**	**Signal-Chronic (1 patient)**
Postnatal injuries (4 patients, 7 scans)			
Caudates	nl or long T2	long T2	small, long T1, T2
Thalami	nl	nl	nl
Lateral lentiform	nl or long T2	long T2	long T1, T2, small
Medial lentiform	nl or long T2	long T2	small
Caudates	nl or long T2	long T2	small, long T2
Hippocampi	nl or long T2	small, long T2	small, long T2
Lateral geniculate nuclei	nl or long T2	small, long T2	small, long T2
Cerebral cortex (non-rolandic)	thick, long T2	thin, long T2	thin, long T2

Note.—Acute = up to 3 weeks; subacute = 3 weeks to 3 months; chronic = >3 months; data in parentheses was uncommon; nl = normal.

at all ages (11, 12, 22, 23). Excitatory amino acid toxicity, therefore, may be the predominant or only mechanism active in the hippocampus, which does not myelinate early.

Myelination

A number of studies, both histochemical (26, 27) and by imaging methods (28) have shown that myelination in the newborn is present in the dorsal brain stem, ventral lateral thalami, dorsal lentiform nuclei, lateral geniculate nuclei, and corticospinal tracts extending up to the perirolandic cortex, which is partially myelinated at birth. It is known that the process of myelination is energy intensive, requiring a considerable expenditure of energy on the part of both the oligodendrocytes and the participating neurons and axons (29, 30). Therefore, it seems reasonable to propose that the process of active myelination, perhaps superimposed upon transiently high local concentrations of excitatory amino acids and NMDA receptors in certain areas of the newborn brain (and possibly other, as yet unknown, mechanisms) make the aforementioned regions especially susceptible to damage in the case of profound asphyxia. The sparing of the majority of the cerebral cortex is consistent with the known high degree of resistance of the newborn cortex, which appears to have relatively little function in the newborn brain (31, 32), to anoxic brain damage (33, 34). The observations that the infant injured at age 7 weeks had substantial cortical involvement suggests that the susceptibility of various brain regions changes rather rapidly with brain maturation, as has been shown in rats (22, 23).

Changes in Cerebral Blood Flow

The cause for the different pattern seen in older infants, with more cortical involvement, injury to the entire corpus striatum, and relative thalamic sparing, does not appear to correlate with active myelination, since similar patterns are observed at ages 12 months and 23 months, ages at which the states of myelination are considerably different (27, 28). A possible explanation for the relative sparing of the thalami is the known redistribution of cerebral blood flow from the anterior to the posterior circulation following severe asphyxia in laboratory animals (35, 36). The sparing of the perirolandic cortex is much more difficult to explain, as no obvious collateral pathways from the posterior circulation to the suprasylvian region exists. It must be presumed, therefore, that some sort of physiologic difference exists between the perirolandic cortex and the

remainder of the cortex in older infants that renders the perirolandic region more resistant to anoxic brain damage. Whether the mechanism involves excitatory amino acids or some other, as yet unknown, process remains to be determined.

CT Scanning

Another interesting result in this study is the appearance of the CT scans in the acutely injured patients. A pattern of hypodensity in the deep gray matter structures with relative cortical sparing was present on the CT scans of both asphyxiated newborns in which they were obtained (Fig. 1) and in all four of the acute CTs obtained in older patients. The pattern of deep gray matter hypodensity has been reported previously in asphyxiated children (37) and adults (38), but has never been emphasized in newborns. As newborns have a higher brain water content and, therefore, lower CT density of the white matter than adults (39, 40), the hypodense deep gray matter structures are subtly abnormal, appearing isodense to the surrounding white matter. Appreciating abnormalities caused by symmetrical "absence" of normal structures seems more difficult than seeing abnormalities of different signal that stand out from surrounding tissues; the initial CTs in both of the newborns were thus originally misinterpreted as normal. Compounding the problem of low conspicuity is the fact that the basal ganglia of newborns can hemorrhage after anoxic injury (22). If petechial in nature, such hemorrhage can conceivably mimic the intensity of normal gray matter, further masking the abnormality of the deep gray matter structures. It is the author's belief that the two cases purportedly showing normal CTs in the setting of severe abnormalities on MR studies (4) actually show the heterogeneous high signal of hemorrhage (or possibly calcium) in the lentiform nuclei. This observation puts in question a statement that MR imaging is more sensitive than CT in hypoxic-ischemic injury of newborns and infants (4). In fact, in the single case in the present study in which both MR and CT studies were obtained in the first 24 hours after injury, the MR showed only very subtle changes in the region of the insular cortex, whereas the CT (done 3 hours later) was obviously abnormal, showing hypodensity of the basal ganglia (Fig. 6). Unfortunately, the number of patients with both early CTs and early MRs in this study is insufficient to draw firm conclusions concerning which study is more sensitive in the early detection of hypoxic-ischemic injury in newborns and infants. Our cases do, however, establish the pattern of injury seen on CT in profoundly asphyxiated newborns and infants and demonstrate that, at least in some cases, CT is more sensitive in the acute phase of injury.

Nature of T1 and T2 Shortening

The nature of the tissue causing the T1 and T2 shortening, particularly in the lentiform nuclei and thalami, on the MR studies of asphyxiated newborns studied subacutely is worthy of some discussion. Hemorrhage is not reported, and calcification is only occasionally seen, in pathologic studies of cardiac arrest encephalopathy (6–9); however, basal ganglia hemorrhage was commonly seen in newborn rats subjected to anoxic brain injury and to excitatory amino acid toxicity (22). A third possibility is the release of lipids secondary to a breakdown of the myelin sheath, as has been proposed to explain T2 shortening in subacute adult infarcts (41, 42). The T2 shortening associated with myelin breakdown reportedly develops 4 weeks after injury and persists for 10–14 weeks (42). As T1 and T2 shortening was seen frequently on subacute (less than 4 weeks) scans, disappeared from all follow-up studies, and was not seen in any patients imaged more than 2 months after injury, blood seems the most likely cause of the signal abnormalities. Although calcification can not be entirely ruled out as the cause of the signal abnormality (43), the rapid resolution of the signal abnormality makes calcium a less likely cause. One CT scan, performed 3 weeks after injury and 1 day prior to an MR that showed T1 and T2 shortening in the basal ganglia, demonstrated high density in the basal ganglia (Fig. 1), compatible with either blood or calcium, and making myelin degradation very unlikely.

A final point that should be made in this study concerns the damage to the white matter. All patients examined in the chronic phase in this study showed marked reduction of white matter with variable T2 prolongation that was most pronounced in the periventricular region. The white matter injury may be secondary to degeneration of corticopetal fibers from the deep gray matter nuclei (especially likely in older infants in whom the white matter damage was diffuse) or a result of hypoxic-ischemic damage to oligodendro-

cytes, with subsequent lack of myelination and axonal degeneration. However, the predominantly posterior, peritrigonal location of the white matter damage in those infants asphyxiated perinatally seems to correlate very closely with those systems actively myelinating at birth, the cortical spinal tracts and visual pathways (26, 28). In several cases, in fact, white matter hyperintensity could be seen extending along the corticospinal tracts, from the internal capsule through the corona radiata to the perirolandic gyri. This distribution suggests, once again, the increased vulnerability of regions with the increased metabolic demands of myelination. The white matter loss and periventricular white matter T2 prolongation seen in the chronic phase of our patients bears a strong resemblance on MR studies to endstage periventricular leukomalacia, as seen in asphyxiated premature infants (1). Careful scrutiny of the images to find the atrophy and prolonged T2 relaxation in the basal ganglia and hippocampus, along with the extension of the damage along the corticospinal tracts to the perirolandic region, should allow differentiation of these two patterns of injury.

To summarize, the imaging studies of 16 children who suffered profound hypoxic-ischemic injury as neonates or infants have been analyzed. Infants suffering an injury in the perinatal period showed a characteristic pattern of injury, with involvement of the ventral lateral thalami, posterolateral lentiform nuclei, lateral geniculate nuclei, hippocampi, and perirolandic cerebral cortices (Table 2, Figs. 7A and 7B). Those with injury at ages 1 to 2 years suffered injury to the corpora striata, lateral geniculate nuclei, hippocampi, and the majority of the cerebral cortex (with sparing of the anterior aspect of the suprasylvian cortex (Table 2, Figs. 7C and 7D)). A single patient injured in the early infantile/late neonatal period showed an intermediate pattern. An attempt has been made to explain the changing patterns of damage based on metabolic and structural changes in the developing brain. Furthermore, we have noted a characteristic CT appearance in the acute and subacute post injury. This appearance of symmetrical basal ganglia isodensity with adjacent white matter in the acute phase with occasional symmetric iso- to hyperdensity in the subacute phase is subtle and may be overlooked if not specifically sought.

References

1. Barkovich AJ, Truwit CL. MR of perinatal asphyxia: correlation of gestational age with pattern of damage. *AJNR* 1990;11:1087–1096
2. Keeney S, Adcock E, McArdle C. Prospective observations of 100 high-risk neonates by high field (1.5 Tesla) magnetic resonance imaging of the central nervous system. I. Intraventricular and extracerebral lesions. *Pediatrics* 1991;87:421–430
3. Keeney S, Adcock E, McArdle C. Prospective observations of 100 high-risk neonates by high field (1.5 Tesla) magnetic resonance imaging of the central nervous system. II. Lesions associated with hypoxic-ischemic encephalopathy. *Pediatrics* 1991;87:431–438
4. Pasternak J, Predley T, Mikhael M. Neonatal asphyxia: vulnerability of basal ganglia, thalamus, and brainstem. *Pediatr Neurol* 1991;7: 147–9
5. Myers R. Two patterns of perinatal brain damage and the conditions of occurrence. *Am J Obstet Gynecol* 1977;112:246–276
6. Leech R, Alvord Jr E. Anoxic-ischemic encephalopathy in the human neonatal period: the significance of brain stem involvement. *Arch Neurol* 1977;34:109–113
7. Dambska M, Dydyk L, Szretter T, Wozniewicz J, Myers R. Topography of lesions in newborns and infant brains following cardiac arrest and resuscitation: damage to brain stem and hemispheres. *Biol Neonate* 1976;29:194–206
8. Friede RL. *Developmental neuropathology*. 2nd ed. Berlin: Springer-Verlag, 1989
9. Schneider H, Ballowitz L, Schachinger H, Hanefeld F, Droszus J-U. Anoxic encephalopathy with predominant involvement of basal ganglia, brain stem, and spinal cord in the perinatal period: report on seven newborns. *Acta Neuropathol* 1975;32:287–298
10. Cambray-Deakin M, Foster A, Burgoyne R. The expression of excitatory amino acid binding sites during neuritogenesis in the developing rat cerebellum. *Dev Brain Res* 1990;54:265–271
11. Greenamyre T, Penney J, Young A, Hudson C, Silverstein F, Johnston M. Evidence for transient perinatal glutamatergic innervation of globus pallidus. *J Neurosci* 1987;7:1022–1030
12. McDonald J, Johnston M. Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. *Brain Res Rev* 1990;15:41–70
13. Young R, Petroff O, Novotny EJ, Wong M. Neonatal excitotoxic brain injury: physiologic, metabolic, and pathologic findings. *Dev Neurosci* 1990;12:210–220
14. Baudry M, Arst D, Oliver M, Lyndh G. Development of glutamate binding sites and their regulation by calcium in rat hippocampus. *Dev Brain Res* 1981;1:37–48
15. Barks J, Silverstein F, Sims K, Greenamyre J, Johnston M. Glutamate recognition sites in human fetal brain. *Neurosci Lett* 1988;84: 131–136
16. Rothman S. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J Neurosci* 1984;4: 1884–1891
17. Silverstein F, Torke L, Barks J, Johnston M. Hypoxia-ischemia produces focal disruption of glutamate receptors in developing brain. *Dev Brain Res* 1987;34:33–39
18. Wieloch T, Lindval O, Blomqvist P, Gage F. Evidence for amelioration of ischemic neuronal damage in the hippocampal formation by lesion of the perforant path. *Neurol Res* 1985;7:24–26
19. Labuyere J, Fuller T, Olney J, Price M, Zorumski C, Clifford D. Phenylcyclidine and ketamine protect against kainic acid-induced seizure related damage. *Soc Neurosci Abstr* 1986;12:344
20. Faden A, Simon R. A potential role for excitotoxins in the pathophysiology of spinal cord injury. *Ann Neurol* 1988;23:623–626
21. Choi D. Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1988;1:623–634

22. Ikonomidou C, Mosinger J, Salles K, Labruyere J, Olney J. Sensitivity of the developing rat brain to hypobaric/ischemic damage parallels sensitivity to *N*-methylaspartate neurotoxicity. *J Neurosci* 1989;9: 2809–2818
23. Ikonomidou C, Price M, Mosinger J, et al. Hypobaric-ischemic conditions produce glutamate-like cytopathology in infant rat brain. *J Neurosci* 1989;9:1693–1700
24. McDonald J, Silverstein F, Johnston M. MK-801 protects the neonatal brain from hypoxyic/ischemic damage. *Eur J Pharmacol* 1987;140: 359–361
25. Olney J, Ikonomidou C, Mosinger J, Frierdrich G. MK-801 prevents hypobaric-ischemic neuronal degeneration in infant rat brain. *J Neurosci* 1989;9:1701–1704
26. Yakovlev P, Lecours A. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, ed. *Regional development of the brain in early life.* Oxford, England: Blackwell, 1967:3–70
27. Brody B, Kinney H, Kloman A, Gilles F. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J Neuropathol Exp Neurol* 1987;46:283–301
28. Barkovich AJ, Kjos BO, Jackson JD Jr, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology* 1988;166:173–180
29. Dobbing J. Vulnerable periods of brain development. In: Dobbing J, ed. *Lipids, malnutrition and the developing brain.* Amsterdam: Elsevier, 1972:9–23
30. Bourre J-M. Developmental synthesis of myelin lipids: origin of fatty acids—specific role of nutrition. In: Evrard P, Minkowski A, ed. *Developmental neurobiology.* New York: Raven, 1989:111–152
31. Marin-Padilla M. Structural organization of the human cerebral cortex prior to the appearance of the cortical plate. *Anat Embryol* 1983; 168:21–40
32. Marin-Padilla M. Early ontogenesis of the human cerebral cortex. In: Peter A, Jones E, eds. *Cerebral cortex, vol 7: development and maturation of the cerebral cortex.* New York; Plenum, 1988:1–34
33. Duffy T, Kohle S, Vanucci R. Carbohydrate and energy metabolism in the perinatal rat brain: relation to survival in anoxia. *J Neurochem* 1975;24:271–276
34. Volpe J. *Neurology of the newborn.* Philadelphia: Saunders, 1987
35. Ashwal S, Majcher J, Longo L. Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia: studies during the post-hypoxic recovery period. *Am J Obstet Gynecol* 1981;139: 365–372
36. Behrman R, Lees M, Peterson E, DeLannoy K, Seeds A. Distribution of the circulation in the normal and asphyxiated fetal primate. *Am J Obstet Gynecol* 1970;108:956–969
37. Taylor S, Quencer R, Holzman B, Naidich T. Central nervous system anoxic-ischemic insult in children due to near-drowning. *Radiology* 1985;156:641–646
38. Kjos B, Brant-Zawadzki M, Young R. Early CT findings of global central nervous system hypoperfusion. *AJR* 1983;141:1227–1232
39. Brant-Zawadzki M, Enzmann D. Using computed tomography of the brain to correlate low white matter attenuation with early gestational age in neonates. *Radiology* 1981;139:105–108
40. Barkovich AJ. *Pediatric neuroimaging.* New York: Raven, 1990
41. Uchino A, Imada H, Ohno M. MR imaging of wallerian degeneration in the human brain stem after ictus. *Neuroradiology* 1990;32: 191–195
42. Kuhn MJ, Mikulis DJ, Ayoub DM, Kosofsky BE, Davis KR, Taveras JM. Wallerian degeneration after cerebral infarction: evaluation with sequential MR imaging. *Radiology* 1989;172:179–182
43. Henkelman M, Watts J, Kucharczyk W. High signal intensity in MR images of calcified brain tissue. *Radiology* 1991;179:199–206

Please see the Commentary by Roland and Hill on page 973 in this issue.