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Patterns and Implications of MR Contrast Enhancement in Perinatal Asphyxia: A Preliminary Report

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PURPOSE: To determine the presence and location of MR contrast enhancement in infants with perinatal asphyxia and to evaluate the utility of enhancement in assessing extent of brain damage.

METHODS: Precontrast and postcontrast MR examinations within the first 10 days of life were evaluated in 10 infants with suspected hypoxic-ischemic birth injury. Findings were correlated with clinical birth history and short-term neurologic follow-up. **RESULTS:** All four infants with MR signal abnormalities and contrast enhancement in the basal ganglia and brain stem had early seizures and profound neurologic deficits at early follow-up. Two infants had abnormal scans but no contrast enhancement; one with MR signal abnormality within the basal ganglia is neurologically healthy at 10-month follow-up, whereas the other, in status epilepticus at the time of imaging at age 2 days, died. Two infants with minimal parasagittal subcortical white matter enhancement had no early seizure activity and only mild developmental delay at early follow-up. Two infants with normal precontrast and postcontrast MR had no early seizures and remain healthy at early follow-up, despite initial clinical parameters similar to more severely injured infants. **CONCLUSION:** Although the number of patients is small, our results indicate that the presence of contrast enhancement in asphyxiated neonates may indicate more severe brain damage and, hence, a poorer prognosis.

Index terms: Infants, newborn; Brain, magnetic resonance; Asphyxia

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Perinatal asphyxia is a leading cause of neurologic damage in the newborn. Of infants with hypoxic-ischemic injury, 64% will be healthy, 25% will have long-term neurologic deficits, and 11% will die (1). Thus, the prognosis for any given infant is uncertain. Multiple clinical parameters have been developed in an effort to predict outcome, but few have been successful, because they are all indirect measures of central nervous system injury (2). Studies of asphyxiated neonates by magnetic resonance (MR) imaging have proved it to be a powerful tool in the evaluation of perinatal hypoxic-

ischemic injury (3-6). Abnormalities demonstrated by brain MR as early as 4 days after injury have been correlated with severe future neurologic impairment (6). Recently, a study of blood-brain barrier permeability in normal and stressed infants showed that term infants that had suffered severe asphyxia had significantly higher blood-brain barrier permeability than healthy infants (7). Because blood-brain barrier permeability, as detected by contrast-enhanced MR imaging, has been shown to correlate with tissue necrosis in nonocclusive ischemia (8, 9), we reasoned that evaluation of blood-brain barrier injury may be of value in the assessment of the affected neonate. In this study, we describe and correlate presence and location of MR contrast enhancement with severity of the hypoxic-ischemic injury and short-term clinical outcome.

Methods

The MR and clinical history of 10 neonates were reviewed retrospectively. All patients met one or more of the following criteria that are being used as inclusion criteria in

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TABLE 1: Ten neonates with suspected hypoxic-ischemic birth injury

Patient	Gestational age at birth, wk	Interval between injury and MR, d	Enhancement	Outcome
1	40	5	Lateral putamen and perirolandic cortex	Severe neurologic deficits, seizures on day one
2	41	5 d	None	Neurologically healthy, no seizures
3	38	3	Dorsal midbrain, basal ganglia posterior lateral thalamus	Severe spastic quadriplegia at 2-3 mo, seizures on day 2
4	40	3	None	Neurologically healthy at 10 mo, no seizures
5	35	7	Peritrigonal white matter	No seizures, developmental delay, difficulty visual tracking
6	42	8	L frontal white matter (sagittal sinus thrombosis)	No seizures, developmental delay
7	41	10	Brain stem, basal ganglia, hypothalamus, perirolandic cortex	Severe hypoxic-ischemic encephalopathy, died
8	35	7	Periventricular white matter, perirolandic cortex, hypothalamus	Seizures on day 1, severe spastic quadriplegia
9	39	2	None	Severe hypoxic-ischemic encephalopathy, seizures on day 1, died
10	40	3	None	Neurologically healthy at 4 mo, no seizures

a larger prospective study currently underway at our institution: (a) Apgar score less than or equal to five at 5 minutes; (b) cord blood pH less than or equal to 7.2; and (c) base deficit greater than 10. Eight patients were born at term and two at 35 weeks of gestational age. All infants were imaged between 2 and 10 days after the hypoxic-ischemic injury. Standard spin-echo axial 4-mm 400-600/12-26/2 (repetition time/echo time/excitations) MR images were obtained before and immediately after intravenous administration of 0.3 mmol/kg gadoteridol in patients 4, 5, 6, 9, and 10. Patients 1, 2, 3, 7, and 8 received 0.1 mmol/kg gadoteridol intravenously. The dose of 0.3 mmol/kg was given to patients enrolled in a larger study that includes dynamic-perfusion imaging; results of the perfusion studies will be reported in a future communication. Spin-echo 3000/60, 120/1 images also were obtained in all patients. All scans were performed at 1.5 T. MR data of all patients were also initially reviewed independently by two of the authors, who were blinded to clinical outcome. Locations and degree of abnormal signal within the brain on the precontrast study and locations and degree of enhancement on the postcontrast study were recorded. Disagreements regarding findings on the scans were resolved by discussion and mutual agreement. The clinical course and results of follow-up examinations were reviewed, with attention to perinatal parameters such as Apgar score, umbilical artery pH, base deficit, and the presence of signs and symptoms of hypoxic-ischemic encephalopathy within the first few days of life. Follow-up neurologic examination was performed at ages ranging from 3 months to 2 years in nine infants. All neurologic examinations were performed by an experienced neonatal neurologist who was blinded to the findings of the MR studies.

The imaging protocol was evaluated and approved by the Committee on Human Research of our institution. Par-

ticipation was voluntary and consent was obtained after counseling the parents about the risks and benefits of the procedure.

Results

Imaging

The 10 patients were placed into 4 groups based on the patterns of signal abnormalities identified on their precontrast MR. These patterns of damage in the human neonate have been described previously in the literature (3, 10).

Group 1. Patients 1, 3, and 4 had areas of precontrast T1 shortening involving predominantly the basal ganglia, brain stem, and perirolandic cortex. All had abnormal hypointensity in the posterior limb of the internal capsule on T1-weighted images. No infant in this group had abnormality of the cortex on T2-weighted images, although in one patient the images were degraded partially by motion artifact.

Review of postcontrast T1-weighted images allowed further subdivision of these patients into enhancing and nonenhancing groups. Patients 1 and 3, scanned on days 5 and 3 of life, respectively, had unequivocal enhancement (Table). Patient 3 had enhancement not only within the areas of precontrast T1 shortening (globi pallidi and posterior lateral thalami), but also within the dorsal midbrain and posterior putamen. Patient 1 had such extensive and se-

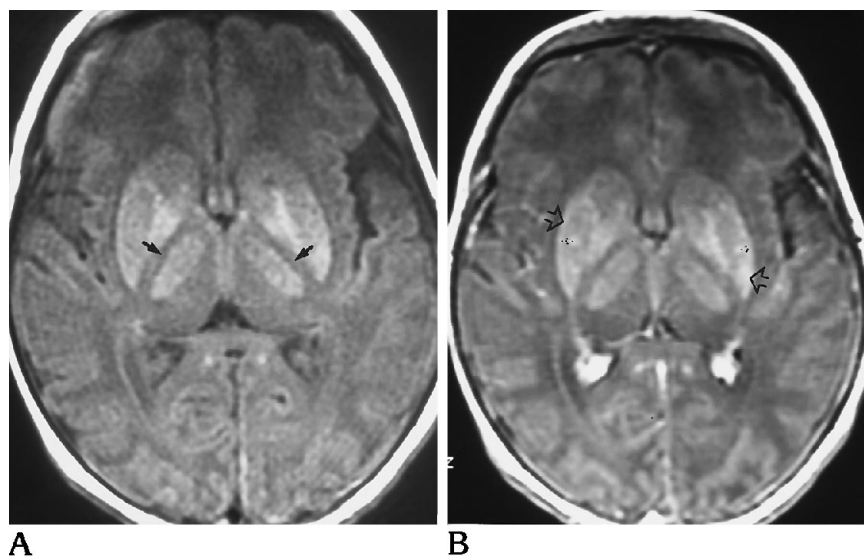


Fig 1. Patient 1.

A, Areas of T1 shortening before contrast administration. Note the loss of normal high T1 signal intensity in the posterior limb of the internal capsule (arrows).

B, Focal and diffuse enhancement (arrows) in the putamina that have enhanced to become nearly isointense with the globi pallidi.

were precontrast T1 shortening within the basal ganglia that determination of the enhancement was difficult. However, definite focal and diffuse enhancement of the putamen and perirolandic cortex was detected (Fig 1). Patient 4, imaged on day 3, had no detectable enhancement.

Group 2. Patients 5 and 6, imaged on days 7 and 8, respectively, had subtly decreased gray-white differentiation in the parasagittal cortex, but no abnormality in the basal ganglia or brain stem on noncontrast images (Fig 2A and B). Patient 5 also had punctate areas of T1 shortening within the centrum semiovale, consistent with small foci of hemorrhage or calcification. Postcontrast images revealed minimal focal enhancement within the peritrigonal white matter bilaterally (Fig 2C and D). Patient 6 similarly had loss of gray-white differentiation within the cortex but also had thrombosis of the superior sagittal sinus, raising the possibility of venous hypertension and subsequent edema as a cause for the abnormalities. Enhancement was present only within the left frontal parasagittal area, a region of possible venous infarction or arterial boundary-zone infarction.

Group 3. On noncontrast images, patients 7, 8, and 9 had T1 or T2 shortening within the brain stem, basal ganglia, and/or perirolandic cortex, in addition to loss of gray-white differentiation in other regions of the cerebral cortex. Postcontrast images of patient 7, scanned on day 10, showed prominent enhancement within the dorsal midbrain, cervicomedullary junction, tectal plate, anterior hypothalamus, and the base of sulci within the perirolandic sulcus re-

gion (Fig 3A-D). Postcontrast images of patient 8, scanned on day 7, showed marked contrast enhancement within the periventricular and perirolandic regions, anterior hypothalamus, fornices, and brain stem. Postcontrast images of patient 9, scanned on day 2, did not show definite areas of enhancement after contrast administration.

Group 4. Patients 2 and 10, imaged on days 5 and 3, respectively, were placed in a separate group because, although clinical parameters and birth history were similar to infants in groups 2 and 3, precontrast and postcontrast MR did not reveal any abnormality.

Clinical Birth History and Follow-Up

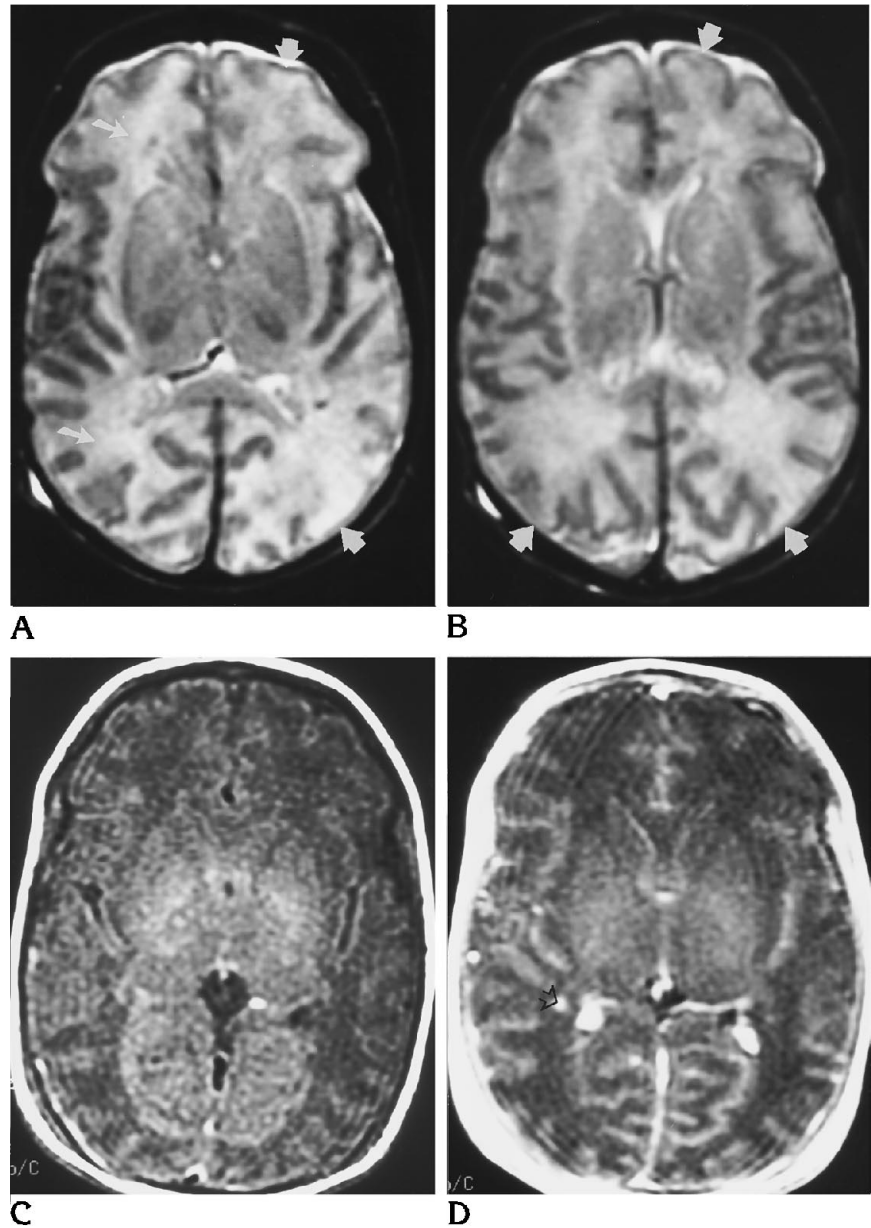
Group 1 (Patients 1, 3, and 4). The birth histories of these patients were similar in that two of the three had documented cardiopulmonary arrest, very low cord blood pH, and high base deficit. All had documented profound (fewer than 40 beats per minute) bradycardia. Patient 1 had transient oliguria that resolved after 1 day. Patients 1 and 3 had seizures documented in the first 2 days of life and severe neurologic abnormalities at a 3-month follow-up examination. Patient 4 has no evidence of seizures, central hypotonia, or spasticity at age 10 months, and is attaining age-appropriate milestones.

Group 2 (Patients 5 and 6). Patient 6 had a clinical history similar to group 1 patients, with low Apgar scores, low umbilical cord blood pH, high base deficit, and transient oliguria that resolved in the first 2 days; however, no seizures

Fig 2. Patient 5.

A and B, Contiguous axial T2-weighted images without contrast reveal subtle cortical and subcortical hyperintensity (arrows), with loss of gray-white differentiation within the parasagittal cortex.

C and D, Axial T1-weighted images pre-contrast and postcontrast reveal focal area of contrast enhancement (arrow) in the peritrigonal white matter. The basal ganglia are normal.



were noted. At age 3 months, the patient has normal tone with mild developmental delay. Patient 5 had a complicated delivery at 35 weeks, with mildly depressed Apgar scores (5 and 7) and early, transient hypotonia. Three-month follow-up revealed mild developmental delay with poor visual tracking.

Group 3 (Patients 7, 8, and 9). These patients uniformly had the most severe perinatal insult, with documented cardiopulmonary arrest, low Apgar scores, and very low umbilical cord blood gas pH in two of the three. All had seizures on the first day of life. Patient 9 was in status epilepticus shortly after birth and throughout the

time of imaging. Two of the three have died. The third has severe neurologic deficits at age 2 years.

Group 4 (Patients 2 and 10). Patient 10 had a history of meconium aspiration after failed induction and prolonged latent phase, resulting in an emergency cesarean section. Initial Apgar scores were depressed (3, 5, and 8) and arterial blood gas revealed an acidosis with a base deficit of 15. There was no evidence of central hypotonia nor spasticity of the extremities at age 4 months. Patient 2 was delivered by emergency cesarean section after failed forceps delivery. Fetal bradycardia, low 1-minute Apgar

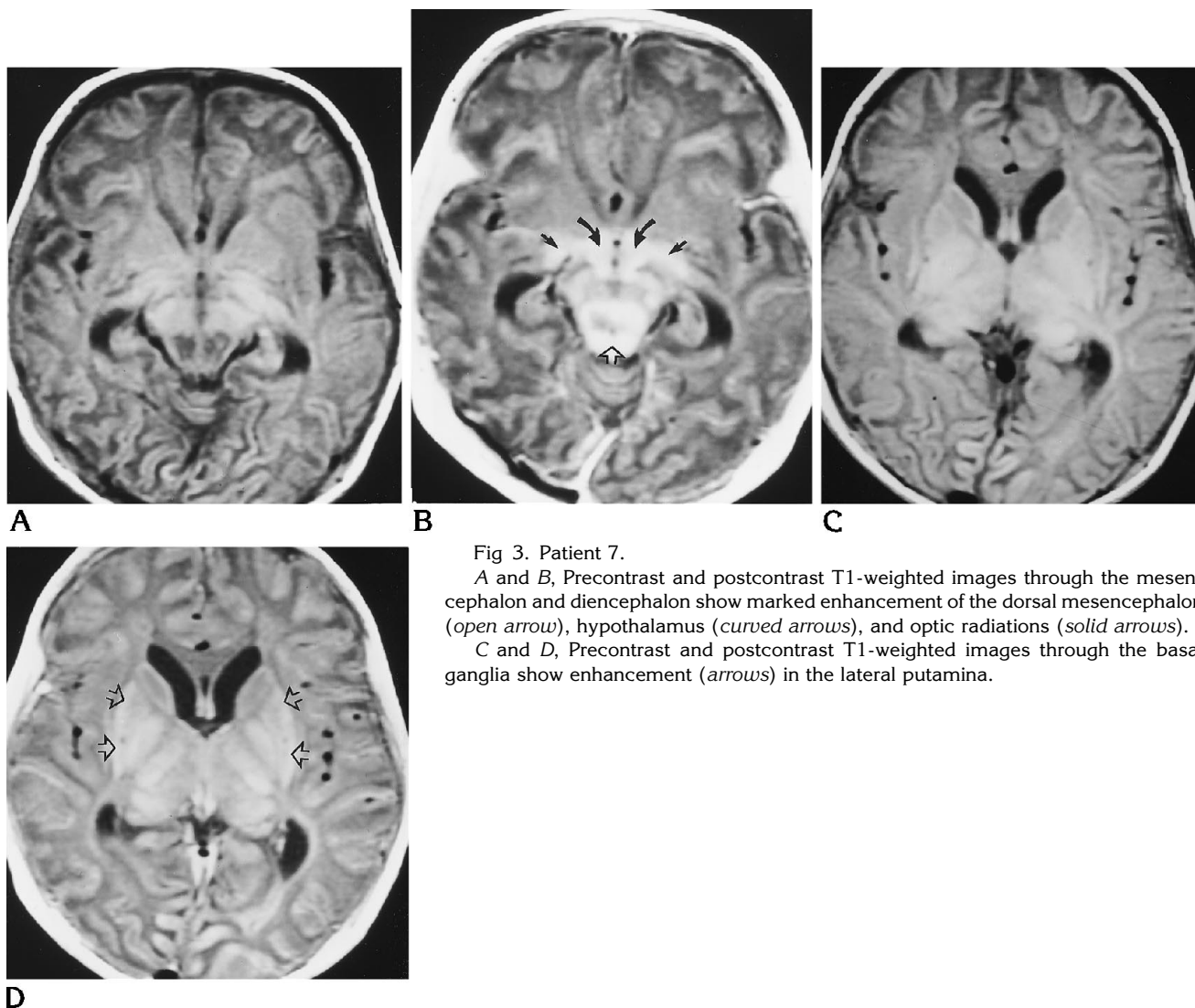


Fig 3. Patient 7.

A and B, Precontrast and postcontrast T1-weighted images through the mesencephalon and diencephalon show marked enhancement of the dorsal mesencephalon (open arrow), hypothalamus (curved arrows), and optic radiations (solid arrows).

C and D, Precontrast and postcontrast T1-weighted images through the basal ganglia show enhancement (arrows) in the lateral putamina.

score, and low cord blood pH were recorded. No seizures, hypotonia, lethargy, nor depressed neonatal reflexes were noted in the neonatal period; this is the neonate who has not had a 3-month exam.

Discussion

In evaluating contrast enhancement in asphyxiated neonates, several factors must be considered. Among these are the location of enhancement, degree of enhancement, and the timing of the scan with respect to the hypoxic-ischemic event. Because contrast enhancement is largely a reflection of breakdown of the blood-brain barrier (11, 12), optimal interpretation of these factors requires knowledge of the pathophysiology of the blood-brain barrier and its breakdown.

The temporal evolution and location of contrast enhancement after ischemic blood-brain barrier breakdown depend on the duration and the nature of the ischemia. Two temporal patterns of enhancement have been described after ischemic brain injury, one relating to vascular occlusive ischemic injury and the other to non-occlusive ischemic injury (9, 13). In either case, histologic evidence of breakdown of the blood-brain barrier occurs within hours of the ischemic event. In occlusive infarction, however, blood is not delivered to the infarcted tissue, so that this early deficiency in the blood-brain barrier cannot be detected by imaging studies. Histologically, extravasation of serum proteins is seen on day 2, followed on day 3 or 4 by proliferation of capillaries from pial vessels into the margins of the infarcted tissue (14). This network of new

vessels becomes dense by the end of the first week. Because the capillaries are not mature and the glial footplates have not yet formed fully around them, they do not have an intact blood-brain barrier; thus, intravascular contrast (and other proteins) can extravasate into the extracellular space, and contrast enhancement will be detected by imaging studies. In occlusive infarction, this enhancement is first noted typically at day 5 or 6, secondary to this new vessel proliferation. Contrast enhancement will be seen in these areas on imaging studies until the blood-brain barrier is reestablished, a process that usually takes approximately 6 weeks.

In nonocclusive infarcts, blood is delivered to damaged capillaries as soon as flow with sufficient capillary perfusion pressure is restored, thus allowing contrast enhancement to be seen earlier than with occlusive infarction. This "re-flow" of blood results in a reactive hyperemia that contributes to blood-brain barrier disruption within the first few hours. At 5 to 72 hours, a second phase of blood-brain barrier opening has been described; this process results from release of various substances from ischemic neurons (12, 15). Thus, one would expect early extravasation of contrast through the damaged capillary endothelium into the extracellular space; this is, in fact, what is seen *in vivo*. Crain et al showed that watershed and noncortical infarcts tend to enhance earlier (in less than 3 days), and enhancement resolves earlier (in 3 to 5 days) than cortical infarcts (9). They postulated that the numerous collaterals to the basal ganglia and the fact that watershed infarcts are typically nonocclusive resulted in preservation of blood flow to the infarcted regions; as a consequence, contrast was delivered to the injured capillaries and extravasated into the extracellular space (9). This hypothesis was supported by the work of Mathews et al, who showed early enhancement of nonocclusive infarcts, but delayed enhancement of occlusive infarcts in an animal model (8). Other factors that influence the degree of contrast enhancement in infarcted tissue include dose of contrast (16), capillary perfusion pressure (17), and the severity and length of the ischemic event (18, 19). We hypothesize that asphyxiated neonates suffer primarily nonocclusive ischemia; thus, we expect to see contrast enhancement early in the postnatal course of these patients.

The location of contrast enhancement occurred in areas with precontrast T1 shortening

in the basal ganglia, brain stem, and perirolandic cortex (groups 1 and 3), or in the subcortical white matter in infants with T2 signal abnormality involving the parasagittal cortex (group 2). Thus, the pattern of contrast enhancement reflected patterns of ischemic damage that have been described with varying types and severity of hypoxic-ischemic injury (3, 10).

Although the number of patients in our study is small, our data suggest that presence or absence of contrast enhancement might be helpful in differentiating patients with moderate brain injury from those with severe injury. Although precontrast MRs of all group 1 patients had a similar pattern of damage, the presence of enhancement on the postcontrast MR suggested that two of the patients suffered more severe damage than the third. Furthermore, both of the patients whose postcontrast images showed enhancement manifested seizures in the first 24 hours of life and were found to have severe neurologic abnormalities at follow-up visits after discharge. Patient 4, with no enhancement, had no early seizure activity and is without abnormal neurologic signs or symptoms at 10 months. It is unlikely that the seizures caused the enhancement in the basal ganglia, because patient 8, who had neonatal seizures, showed enhancement only in other regions (Table). The fact that patient 4 is developing normally also suggests that the presence of abnormal T1 shortening alone is not adequate to predict a poor outcome, at least in the short term.

The presence of contrast enhancement also was helpful in verifying that the subtle loss of gray matter-white matter distinction in the parasagittal region in patient 5 was truly abnormal (Fig 2). This focal enhancement within the peritrigonal white matter may be an ischemic injury that results because the peritrigonal white matter is a relative "watershed zone" of a preterm infant (3, 20, 21). It is of interest that the infant with enhancement in the region of the optic radiations had difficulty in visual tracking noted at age 3 months.

The issue of the safety of administering gadolinium chelate complexes such as gadoteridol to neonates must be discussed. Multicenter trials have confirmed that gadolinium complexes are safe contrast agents with significantly fewer adverse effects than traditional iodinated contrast media. There has been no *in vivo* evidence of release of free gadolinium ions; chemotoxicity is considered to be absent or

minimal (22). Data from prospective trials in neonates and children have not revealed any special problems in the pediatric age group (22). Although possible toxicity has been suggested in an *in vitro* experiment and a single animal study (23, 24), several clinical trials have been performed in which high-dose gadolinium had been administered without adverse events (25–28). Even in patients with renal failure, serum creatinine levels have shown no appreciable change after administration of gadolinium complexes (22). Nonetheless, we monitored creatinine values and urine output in patients in our study; imaging studies were performed only after renal function had returned to normal, minimizing any possible toxicity.

Patient 6 illustrates that laboratory data and Apgar scores can sometimes be misleading. This patient had a pH of 6.78, base deficit of 22, and low Apgar scores, a clinical scenario that was similar to that of the patients in group 3. However, no seizure activity was identified. Although MR revealed subtle loss of gray-white differentiation in the parasagittal region and a sagittal sinus thrombosis, there was no evidence of basal ganglia, perirolandic, nor brain stem abnormality. At age 3 months, this patient is essentially normal, with questionable developmental delay. Although the cortical damage sustained by this patient may manifest itself in neurologic or neuropsychologic deficiencies in the future, the difference between early outcome in this patient and the patients in group 3 is striking.

Patients 2 and 10 were unique in this series in that their initial MR studies were normal; both patients are clinically normal after relatively short postnatal periods. Two aspects of these patients are worthy of discussion. The first is that both patients had significant acidosis, large base deficits, and low Apgar scores that were not very different from the other patients in the study. Thus, once again, we found that the initial laboratory (blood gas) and clinical (Apgar scores) parameters were not useful in predicting outcome. MR findings were more useful, as was the information that neither of these patients had signs or symptoms of hypoxic-ischemic encephalopathy (lethargy, seizures, hypotonia, increased tendon reflexes, abnormal neonatal reflexes (1, 29)). The absence of seizures was the clinical finding that had the best correlation with short-term clinical outcome in our series.

The second important concept is that the absence of neurodevelopmental abnormalities in the early postnatal period does not guarantee normal subsequent development. Patients with relatively mild brain injury may have normal neonatal courses but develop motor deficits during the second or third year of life or manifest difficulty in abstract thinking in school (1). Thus, long-term follow-up with periodic neurodevelopmental examinations is of great importance in assessing the predictive value of any diagnostic modality in the evaluation of asphyxiated neonates.

The imaging results for patient 9 were somewhat confounding in that he had a birth history and clinical course consistent with severe hypoxic-ischemic event but had no contrast enhancement. We believe the lack of enhancement may have been related to the fact that the infant was in status epilepticus at the time of imaging. Status epilepticus can cause vasospasm that, in conjunction with postasphyxial cytotoxic swelling, would result in decreased delivery of contrast to the affected tissues (30). In support of this explanation, an MR perfusion examination (not a part of the study reported in this work) showed a lack of perfusion of the cerebral cortex in this infant. An alternative explanation is that this patient was scanned on day 2 after injury, perhaps too early for us to detect contrast enhancement from the second phase of breakdown in the blood-brain barrier.

In summary, our preliminary results suggest that contrast-enhanced MR imaging may be useful in the evaluation of asphyxiated neonates. In particular, the presence of contrast enhancement seems to correlate with tissue necrosis from hypoxic-ischemic brain injury. Enhancement may be seen as early as 3 days after injury. Patients in whom contrast enhancement was demonstrated in the basal ganglia all manifested signs and symptoms of moderate to severe hypoxic-ischemic encephalopathy and had poor neurodevelopmental outcome. Those with enhancement restricted to the cerebral cortex or subcortical white matter showed less severe clinical manifestations. Other than patient 9, who was scanned early and while in status epilepticus, those with no enhancement are developmentally and neurologically healthy on early clinical follow-up. A large-scale prospective study is underway to correlate conclusively enhancement with outcome and to understand better the consequences of normal neonatal MR

findings and abnormal neonatal MR findings without enhancement.

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