# Diffusion-Weighted Imaging in Neonatal Cerebral Infarction: Clinical Utility and Follow-Up

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# ABSTRACT

We describe the clinical utility of echo-planar diffusion-weighted imaging in neonatal cerebral infarction. Eight full-term neonates aged 1 to 8 days referred for neonatal seizures were studied. Patients were followed for a mean of 17 months with detailed neurologic examinations at regular intervals. Head computed tomography (CT) and conventional magnetic resonance (MRI) and diffusion-weighted images were obtained. Percent lesion contrast was evaluated for 19 lesions on  $T_2$ -weighted and diffusion-weighted images. Follow-up conventional MRIs were obtained in seven patients. The findings on diffusion-weighted images. Follow-up conventional MRIs were obtained in seven patients. The findings on diffusion-weighted imaging were correlated with CT and conventional MRI findings as well as with short-term neuro-developmental outcome. Four patients had focal cerebral infarctions. Four patients had diffuse injury consistent with hypoxic-ischemic encephalopathy. Percent lesion contrast of all 19 lesions was significantly higher on diffusion-weighted images. In five patients, there were lesions visualized only with diffusion-weighted imaging. In all patients, there was increased lesion conspicuity and better definition of lesion extent on the diffusion-weighted imaging scans for all patients. Diffusion-weighted imaging is useful in the extent of injury seen on the initial diffusion-weighted imaging scans for all patients. In the acute setting, diffusion-weighted imaging provides information not available on CT and conventional MRI. This information correlates with short-term clinical outcome. (*J Child Neurol* 2000;15:592–602).

Echo-planar diffusion-weighted imaging uses a technique by which, with strong gradient pulses, images sensitive chiefly to the molecular diffusion of water can be generated.<sup>1</sup> It has been shown that with stroke (infarction), as cytotoxic edema develops, diffusion of water molecules decreases.<sup>2–6</sup> Regions with cytotoxic edema demonstrate markedly increased signal (hyperintense) relative to normal gray and white matter. In the adult population, diffusion-weighted imaging has proven highly sensitive and specific for the detection of acute stroke with reported sensitivities ranging from 88% to 100% and reported specificities ranging from 86% to 100%.<sup>7-9</sup> Consequently, this technique has become part of our routine stroke magnetic resonance imaging (MRI) protocol and has profoundly affected the management of adult stroke patients at our hospital.

Several recent animal studies have used diffusionweighted imaging in understanding the pathophysiology of hypoxic-ischemic injury in newborns.<sup>10,11</sup> These studies have demonstrated restricted diffusion in different regions of brain tissue as they become ischemic. Furthermore, Inder et al<sup>12</sup> have demonstrated the utility of diffusion-weighted imaging in identifying early diffuse white-matter injury in periventricular leukomalacia that was not visualized on conventional MRI. Cowan et al<sup>13</sup> reported that diffusionweighted imaging demonstrated increased lesion extent in patients with hypoxic-ischemic encephalopathy compared with conventional MRI.

Since diffusion-weighted imaging has proven valuable in the assessment of adult patients with acute stroke and recent animal and human studies suggest that diffusionweighted imaging is useful in the evaluation of neonatal ischemia, we have used this technique to study eight neonates referred to us for evaluation of seizures. We

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describe the findings on diffusion-weighted imaging in correlation with initial computed tomographic (CT), routine MR, and follow-up MR images. We discuss the implications of initial diffusion-weighted imaging in terms of short-term neurodevelopmental outcome.

# METHODS

# Patient Data

Between 1996 and 1998, 1247 infants were admitted to the Massachusetts General Hospital neonatal intensive care unit, of whom 69 were seen for an evaluation of neonatal seizures. Eight infants who underwent CT, MRI, and diffusion-weighted imaging studies showed different patterns of cerebral infarctions and are the subjects of this report. The Institutional Review Board of the Massachusetts General Hospital has reviewed and approved the diffusion-weighted imaging-MRI study in adult and pediatric patients.

The hospital records of these infants were reviewed for information regarding the patient's gestational age, growth parameters, perinatal history, intrapartum events, labor and delivery, presenting illness (seizures), neurologic examination, laboratory studies, and treatment. These data are summarized in Table 1.

All infants were prospectively evaluated in the High-Risk Newborn Follow-Up clinic at regular intervals. They underwent general physical, detailed neurologic and developmental evaluations based on the methods described by Pretchl and Berntema,<sup>14</sup> Andre et al,<sup>15</sup> and Paine.<sup>16</sup> The detailed neurologic examination consisted of standardized items that included head circumference; visual alertness; cranial nerve examination; muscle tone; primitive and postural reflexes; deep tendon reflexes; ankle clonus; motor asymmetries such as early handedness, cortical thumb, fisting, and mild hemiparesis; and specific spastic deficits such as hemiplegia, diplegia, and quadriplegia. Developmental evaluations were assessed for age-appropriate norms in gross motor, fine motor-adaptive, and speech and language functions.

Neurodevelopmental outcome at the most recent evaluation was categorized as (1) normal: no neurologic abnormality, (2) mildly abnormal: mild neurologic abnormalities such as mild hypotonia, hypertonia, ill-sustained ankle clonus, mild hemiparesis, fall in head circumference by more than 1 SD, motor asymmetry, abnormal handedness, mild gross motor delay, or speech and language delay, or (3) moderate to severely abnormal: significant neurologic deficit such as microcephaly; definite spastic deficits such as hemiplegia, diplegia, or quadriplegia; severe hypotonia; or significant gross motor delay.

### Neuroradiology

MRI was performed on a 1.5-Tesla whole-body scanner (GE Signa, Waukesha, WI) with echo-planar capabilities (Advanced NMR Systems, Wilmington, MA). Diffusion-weighted images and apparent diffusion coefficients were obtained using single-shot, echo-planar imaging with a repetition time (TR) of 6000 ms, a time to echo (TE) of 118 ms, a field of view (FOV) of 40 cm  $\times$  20 cm, image matrix of 256  $\times$  128 pixels, slice thickness of 6 mm with 1 mm gap, and 20 axial slices. The effective gradient strength was 14 mT/M, and b-values were 1221 s/mm<sup>2</sup> and 47 s/mm<sup>2</sup> with six gradient directions and three signal averages. The trace of the diffusion tensor was

	Table 1. Neonatal Clinical Data						
Patient	Perinatal History, Birthweight	Apgar Scores	Seizures	Neurologic Examination	Electroencephalogram	Placenta	
1	Term, 3.5 kg, fetal distress	3; 5	12 hours, generalized tonic-clonic	Hypertonia and L hemiparesis	Seizure activity R temporal	Chorioamnionitis (Listeria infection)	
2	Term, 3.1 kg, meconium present	5; 8	48 hours, R focal	Hypertonia, high- pitched cry	L central spikes and sharp waves	Chorioamnionitis	
3	Term, 4.5 kg, meconium present, decreased fetal movements	2;9	7.5 hours, L focal	High-pitched cry	Frequent bilateral frontal and temporal sharp waves	Meconium vasospasm	
4	Term, 3.3 kg	8; <del>9</del>	8th day, L focal	Nonfocal	R central sharp transients	Not available	
5	Term, 4.3 kg, meconium present	4; 8	27 hours, R focal	Bilateral ankle clonus, axial hypotonia	Bilateral temporal sharp waves	Not available	
6	Term, 3.7 kg, maternal hypotension, meconium present, decreased fetal movements	3; 7	5 hours, L focal	L hemiparesis	Seizure activity-R frontal; sharp transients, R frontal and scattered sharp waves	Villous edema and necrosis	
7	Term, 3.5 kg, meconium present decreased fetal movements	5; 8	6 hours, multifocal, and L clonic	Hypotonia	Bilateral temporal and frontal sharp waves	Not available	
8	Term, tight nuchal cord, apnea, bradycardia	Not avail- able	4–6 hours, generalize tonic-clonic	d Lankle clonus, absent gag, hypotonia	Burst suppression	Not available	



Figure 1. *A*, Axial computed tomographic scan demonstrates right temporoparietal hypodensity (arrow). *B*, Axial echo planar $T_2$ -weighted magnetic resonance image demonstrates subtle hyperintensity of the lesion. *C*, Axial diffusion-weighted image demonstrates marked hyperintensity of the lesion. *D*, Follow-up $T_2$ -weighted image at 2.5 years demonstrates persistent right temporoparietal hyperintensity and tissue loss, consistent with a focal middle cerebral artery infarction.

calculated to produce isotropic diffusion-weighted images and apparent diffusion coefficient maps. This methodology has been described previously in detail.<sup>17,18</sup>

Fast spin echo  $T_2$ -weighted images were acquired with TR = 4200 ms, TE = 102 ms, FOV = 20 cm, acquisition matrix of  $256 \times 256$  pixels, slice thickness of 5 mm with 1-mm gap, and one signal average.

CT of the head was performed on a GE Advantage helical scanner (Waukesha, WI) with 5-mm contiguous axial slices with 140 kVp, 340 mAs, and 1-second scan time.

All images were reviewed by a neuroradiologist and two pediatric neurologists. We performed a quantitative region of interest percent lesion contrast analysis in 19 abnormal regions in our eight patients. A region of interest was drawn in the center of each selected abnormal region. A second region of interest was then drawn close to the lesion but included only unaffected tissue. For both the  $T_{2}$ - and diffusion-weighted images, the mean signal intensity was obtained for each region of interest and percent lesion contrast was calculated for each lesion. The percent lesion contrast was calculated as follows:  $100 \times (SL - SN)/SN$  where SL is signal intensity in the region of ischemia and SN the signal intensity of the normal adjacent brain parenchyma.<sup>19</sup> If the lesion was not identifiable on the T<sub>2</sub>-weighted images, then the location of the lesion was anatomically matched to the visible lesion seen on the matching diffusion-weighted images were compared with means of percent lesion contrast seen on T<sub>2</sub>-weighted images were diffusion-weighted imaging using a paired two-tailed Student's *t*-test.

# Case Illustrations Patient 1 (Figure 1)

J.B. was a 3.5-kg term infant with Apgar scores of 3, 5, and 6 at 1, 5, and 10 minutes, respectively, born by cesarean section because of fetal distress and bradycardia. At 12 hours of life he had tonic clonic seizures of all four extremities. Mild left hemiparesis and diffuse hypertonia were present on neurologic examination. Metabolic



Figure 2. *A*, Axial computed tomographic scan demonstrates no definite abnormality. *B*,  $AxialT_2$ -weighted magnetic resonance image demonstrates left temporal hyperintensity (short arrow). *C*, Axial diffusion-weighted image demonstrates left temporal tip (short arrow) and left thalamic (long arrow) hyperintensity. Follow-up T<sub>2</sub>-weighted image demonstrates persistent left temporal and thalamic hyperintense lesions, consistent with focal infarctions.



Figure 3. *A, E,* Axial computed tomographic scans demonstrate right occipital and right frontal hypodense lesions (arrows). *B, F,* AxialT<sub>2</sub>-weighted magnetic resonance images demonstrate that the lesions are hyperintense. *C, G,* Axial diffusion-weighted images demonstrate that the lesions are hyperintense. *D, F,* Follow-up axialT<sub>2</sub>-weighted images demonstrate hyperintensity and tissue loss in both locations consistent with focal infarctions.

and septic work-ups, including spinal tap, were negative. A CT scan obtained on day 1 of life demonstrated right posterior temporoparietal hypodensity. On day 6 of life, routine MRI could not be obtained because the patient was moving. Echo planar  $T_2$ -weighted and diffusion-weighted images demonstrated hyperintensity in the region of CT hypodensity. The patient's seizures were controlled with phenobarbital and phenytoin on day 3 of life. Electroencephalogram (EEG) revealed multiple areas of seizure activity originating in the right temporal area. Placental pathology revealed *Listeria* infection. At 30 months of age, he has mild left hemiparesis and has had a single seizure recurrence; follow-up  $T_2$ -weighted images at this time demonstrated persistent hyperintensity and tissue loss in the right temporal areary infarction.

## Patient 2 (Figure 2)

J.C. was a 3.1-kg infant, born vaginally, with Apgar scores of 5 and 8 at 1 and 5 minutes, respectively. His birth was complicated by maternal temperature of 101°F and passage of meconium at delivery. At approximately 48 hours of life he was noted to have right leg twitching. A few hours later he had a generalized tonic-clonic seizure. On examination there was diffusely increased tone, a high-pitched cry, and poor suck. The cerebrospinal fluid had 16 white blood cells/ $\mu$ L and 345 red blood cells/ $\mu$ L. Cerebrospinal fluid protein was 77 mg/ $\mu$ L, glucose was 48 mg/ $\mu$ L, and cultures were negative. His EEG showed a left central spike and sharp waves.

Unenhanced CT scan on day 1 of life demonstrated a left frontotemporal hypodensity. The lesion was hyperintense on T<sub>2</sub>- and diffusion-weighted images obtained the same day. Diffusion-weighted images also demonstrated a hyperintense focus in the left thalamus. The seizures were controlled with phenobarbital and phenytoin. Placental pathology revealed evidence of chorioamnionitis. Follow-up T<sub>2</sub>-weighted images 10 months later demonstrated persistent hyperintensity in the left frontotemporal and thalamic lesions, consistent with focal infarctions. At 21 months' follow-up he is left handed with mild asymmetry of right-hand use.

### Patient 3 (Figure 3)

P.F. was a 4.5-kg infant born at full term by cesarean section because of decreased fetal movements and a poor biophysical profile. Apgar scores were 2, 5, and 9 at 1, 5, and 10 minutes, respectively. The patient's initial neonatal course was complicated by hypoglycemia and right ventricular hypertrophy. On day 2 of life the infant developed left-sided focal clonic seizures. Routine laboratory studies were normal. On examination, she was irritable with a high-pitched cry. Unenhanced CT on day 3 demonstrated hypodense regions in the right frontal and occipital lobes. The lesions were hyperintense on  $T_2$ -weighted and diffusion-weighted images obtained the same day. The seizures were controlled with phenobarbital. EEG revealed frequent bilateral frontal and temporal sharp waves. No cardiac or coagulation abnormalities were found. Placental pathology revealed meconium-stained vasospasm.



Figure 4. *A*, Axial T<sub>2</sub>-weighted magnetic resonance image demonstrates a right frontal hyperintense lesion (arrow). *B*, Axial diffusion-weighted image demonstrates that the lesion is hyperintense, consistent with acute infarction. No follow-up images were obtained.

Follow-up  $T_2$ -weighted images 13 months later demonstrated persistent  $T_2$  hyperintensity in the right frontal and occipital lobes consistent with focal middle cerebral artery infarctions. At 24 months' follow-up the child shows evidence of mild speech and language delay and decline in head circumference of more than 1 SD.

## Patient 4 (Figure 4)

A.M. was a 3.3-kg term infant born vaginally. He presented to another hospital at 8 days of life with left clonic seizures. Head CT scan was reported to be within normal limits. Initial work-up included normal blood and cerebrospinal fluid examination. He was treated with antibiotics and acyclovir prior to his transfer to our neonatal intensive care unit. En route to the hospital he developed left-sided focal motor seizures lasting 4 minutes. Upon arrival at our neonatal intensive care unit he was awake, alert, and had a normal neurologic examination. He was treated with phenobarbital. No cardiac or coagulation abnormalities were detected.  $T_2$ -weighted images on the day of admission demonstrated a right frontal hyperintense lesion. On diffusion-weighted imaging, the lesion was hyperintense. At 17 months' follow-up he had a normal neurologic examination. Follow-up images have not been obtained.

#### Patient 5 (Figure 5)

B.W. was a 4.3-kg term infant with Apgar scores of 4 and 8 at 1 and 5 minutes, respectively, who was born by spontaneous vaginal delivery with a prolonged second stage of labor. He was transferred to the neonatal intensive care unit because of respiratory distress on day 2 of life when he was noted to have brief right-sided clonic seizures. Examination was notable for moderate head lag, axial hypotonia and bilateral ankle clonus. Electrolytes, calcium, and glucose and cerebrospinal fluid were normal. Unenhanced CT on day 2 of life revealed a small subarachnoid hemorrhage; no infarctions were reported initially. Upon review, left thalamic and superior temporal hypodensities were noted. On  $T_g$ -weighted MRI obtained the same day, no



Figure 5. *A, E,* Axial computed tomographic images demonstrate left superotemporal hypodensity (arrow). *B, F,* Axial  $T_2$ -weighted magnetic resonance images demonstrate no definite abnormality. *C, G,* Axial diffusion-weighted images demonstrate marked hyperintensity in the left superotemporal region (short arrow) and in the bilateral frontal subcortical white matter (long arrows). *D, H,* Follow-up $T_2$ -weighted images demonstrate persistent hyperintensity and tissue loss in the left superotemporal lobe and persistent hyperintensity in the bilateral frontal white matter. These findings are consistent with parasagittal hypoxic-ischemic encephalopathy.



Figure 6. *A*, Axial computed tomographic image demonstrates bilateral parieto-occiptal hypodense regions as well as hypodensity in the right caudate head (arrows). *B*, AxialT<sub>2</sub>-weighted magnetic resonance image demonstrates hyperintensity in the CT hypodense regions. *C*, Axial diffusion-weighted image demonstrates marked hyperintensity in the bilateral parieto-occipital regions and the right caudate head, as well as the bilateral frontal white matter (long arrows). *D*, Follow-upT<sub>2</sub>-weighted image demonstrates hyperintensity and tissue loss in the diffusion-weighted hyperintense regions. This pattern is consistent with parasagittal hypoxic-ischemic injury.

definite abnormality was seen. Diffusion-weighted images demonstrated left thalamic and left temporal hyperintensity and hyperintense lesions in the bilateral frontal subcortical white matter. These lesions suggested multifocal hypoxic-ischemic encephalopathy rather than focal infarctions. The patient's seizures were controlled by day 3 with phenobarbital. EEG showed bilateral temporal sharp waves. No cardiac or coagulation abnormalities were detected. On T<sub>2</sub>-weighted images obtained 12 weeks later, all lesions identified on initial diffusion-weighted imaging were hyperintense. These findings were consistent with hypoxic-ischemic injury. At 12 months' follow-up this infant remains seizure free with mild hypotonia and mild gross motor delay on neurologic examination.

# Patient 6 (Figure 6)

A.G. was a 3.7-kg term infant with Apgar scores of 3, 7, and 8 at 1, 5, and 10 minutes, respectively, who was born by cesarean section because of fetal bradycardia and passage of thick meconium. Perinatal history was notable for maternal hypotension due to splenic artery rupture. The newborn had poor respiratory effort and was initially hypotonic. She was admitted to the level II nursery for observation. At 5 hours of life she developed a focal seizure involving the left arm and leg. Routine laboratory studies were within normal limits. Spinal tap revealed 54 red blood cells/µL, 8 white blood cells/µL, protein of 80 mg/µL, glucose of 45 mg/µL, and negative cultures. Unenhanced CT on day 1 of life demonstrated hypodensity in the posterotemporal and occipital lobes and the right caudate head. T<sub>2</sub>-weighted images obtained the same day demonstrated hyperintensity in the CT hypodense regions as well as in the right putamen and the right middle frontal gyrus. Diffusion-weighted imaging demonstrated hyperintensity in the T, hyperintense regions as well as in white matter in a parasagittal distribution suggestive of hypoxic-ischemic encephalopathy rather than focal infarctions. Initial EEG revealed electrographic seizure activity and scattered and right frontal sharp-wave transients. The patient's seizures were controlled by day 3 of life with phenobarbital. Her follow-up EEG at age 3 months was normal. No cardiac or coagulation abnormalities were found. At age 4 months the infant showed mild hypertonia, which had resolved by age 13 months. Follow-up  $T_2$ -weighted images obtained 12 months later demonstrated persistent hyperintensity in all of the regions previously characterized by diffusion hyperintensity. These findings are consistent with hypoxic-ischemic injury. She had a brief seizure at age 21 months. She exhibits mild delay in speech and language development and decline in head circumference of more than 1 SD.

## Patient 7 (Figure 7)

N.G. was a 3.5-kg term infant with Apgar scores of 5 and 8 at 1 and 5 minutes, respectively, who was born by forceps-assisted vaginal delivery. Decreased fetal movements were present for about 10 hours prior to delivery with fetal decelerations and meconium staining at birth. At 6 hours of age he was noted to have left-arm twitching followed by multifocal clonic seizures. On examination he had generalized hypotonia with decreased movement of the left arm and leg and poor suck. Electrolytes and cerebrospinal fluid studies were unremarkable. Unenhanced CT images obtained on day 1 of life were degraded by motion artifact, but no abnormality was identified. T2-weighted MR images obtained on day 2 demonstrated hyperintensity in the frontal, parietal, and temporal lobes in a parasagittal distribution. Diffusion-weighted imaging demonstrated hyperintensity in all of the regions characterized by T<sub>2</sub> hyperintensity. There was also hyperintensity in deep and subcortical white matter and there were hyperintense lesions in the bilateral thalami. The patient's seizures were controlled with phenobarbital and phenytoin. The EEG showed bitemporal (left greater than right) and bifrontal sharp waves. No cardiac or coagulation abnormalities were found. The infant developed elevated liver enzymes, disseminated intravascular coagulation, and necrotizing enterocolitis secondary to bowel ischemia in the first week of life and underwent total colectomy. Phenobarbital was continued because of seizure recurrence at age 3 months. Follow-up T<sub>2</sub>-weighted images at age 3 months demonstrated hyperintensity



Figure 7. *A, E,* Axial computed tomographic images demonstrate no definite abnormality. *B, F,* Axial $T_2$ -weighted magnetic resonance images demonstrate hyperintensity in the bilateral temporal and frontal cortex (short arrows). *C, G,* Axial diffusion-weighted images demonstrate hyperintensity in the bilateral frontal and temporal regions in a parasagittal distribution as well as hyperintensity in deep white matter (thin arrows) as well as the pulvinar of the thalami (arrowheads). Follow-up $T_2$ -weighted images demonstrate hyperintensity or tissue loss in the diffusion-weighted hyperintense regions. Dilation of the lateral ventricles marks the profound white-matter tissue loss. These findings are consistent with severe hypoxic-ischemic encephalopathy.

in the regions appearing abnormal on diffusion-weighted imaging. There was also extensive tissue loss. These findings were consistent with hypoxic-ischemic injury. At 18 months' follow-up, right hemiparesis, moderate gross motor delay, and microcephaly were present. Phenobarbital was stopped at age 12 months after a normal EEG was obtained.

## Patient 8 (Figure 8)

R.N. was born at full term and was delivered at home by a midwife. At birth he was noted to be pale with a tight nuchal cord. Cardiopulmonary resuscitation was initiated by paramedics. He was noted to have multifocal seizures at 4 hours of life, was treated with phenobarbital, and was transferred to the neonatal intensive care unit. Examination revealed generalized hypotonia, absent gag reflex, left ankle clonus, and absence of any spontaneous movements. Routine blood counts, electrolytes, and cerebrospinal fluid were all normal. CT scan on day 1 of life was unremarkable. T<sub>2</sub>-weighted MR images obtained the following day demonstrated hyperintensity in the bilateral frontal cortex as well as the bilateral thalami and posterior putamens. Diffusion-weighted imaging demonstrated hyperintensity in the  $T_{\scriptscriptstyle 2}$  hyperintense regions as well as in the corticospinal tracts and much of the subcortical white matter. Initial EEG revealed a burst-suppression pattern. The seizures initially resolved with phenobarbital. Subsequently, the patient continued to have frequent seizure activity and he was continued on phenobarbital. Follow-up MRI 6 weeks later demonstrated persistent hyperintensity in the diffusion-weighted imaging hyperintense regions as well as marked diffuse tissue loss. These findings were consistent with severe hypoxic-ischemic injury. On follow-up at age 3 months he was cortically blind and quadriparetic with significant lag in motor development and microcephaly.

#### RESULTS

### Follow-Up Neurodevelopmental Status (Table 2)

Mean follow-up age was 17 months (range, 3 to 30 months). All eight infants have survived and were seen in follow-up. Neurologic abnormalities were present in seven infants, five of whom showed only mild neurologic abnormality at the most recent follow-up. One infant demonstrated moderate disability and one had severe neurologic abnormality, while one was normal. Three infants had shown a decline in head circumference greater than 1 SD (two of them had mild neurologic abnormalities and one had severe neurologic abnormality). All infants had abnormal EEG findings neonatally; six normalized in follow-up recordings. Anticonvulsants were discontinued in six of these infants before age 12

Patient	Age at Follow-Up, months	Neurodevelopmental Status	Follow-Up EEG	Seizure Recurrence
1	30	Mild; left hemiparesis	Abnormal	Yes
2	17	Mild; prominent left-hand preference	Normal	No
3	24	Mild; expressive speech delay	Normal	No
4	17	Normal	Normal	No
5	12	Mild; hypotonia, gross motor delay	Normal	No
6	23	Mild; expressive speech delay	Normal	Yes
7	12	Moderate; diffuse spasticity, gross motor delay	Normal	Yes
8	3	Severe; cortical blindness, spastic quadriparesis	Abnormal	Yes

Table 2. Clinical Follow-Up

EEG = electroencephalogram.

weeks. Seizures recurred in three patients, two of whom were restarted on anticonvulsants.

# Neuroradiologic Data (Table 3)

Of the four patients (cases 1 to 4) ultimately diagnosed with focal middle cerebral artery infarctions, one had a normal CT scan and three had hypodense cortical areas. All four patients had cortical lesions hyperintense on  $T_2$ -weighted images. The diffusion-weighted images demonstrated hyperintensity of all of the lesions seen on  $T_2$ -weighted images as a well as a left thalamic lesion in one patient (case 2).

Of the two patients (cases 5 and 6) ultimately diagnosed with less severe hypoxic-ischemic encephalopathy with a parasagittal distribution, both had cortical and deep gray nuclei hypodensities seen on CT. One had a normal  $T_2$ -weighted MRI (case 5). One had a  $T_2$ -weighted MRI that showed additional lesions in the right putamen and right frontal lobe (case 6). In both patients, diffusion-weighted imaging demonstrated all of the lesions seen on CT and conventional  $T_2$ -weighted images as well as white-matter lesions that were not seen on conventional imaging. In one patient (case 5), this additional information confirmed hypoxic-ischemic encephalopathy rather than focal infarctions.

Two patients (patients 7 and 8) were ultimately diagnosed with severe hypoxic-ischemic encephalopathy, and both had normal CT scans.  $T_{9}$ -weighted images demonstrated areas of cortical hyperintensity in both patients and deep gray nuclei hyperintensity in one patient (case 8). Diffusion-weighted imaging demonstrated hyperintensity in all of the lesions seen on conventional images as well as extensive white-matter hyperintensity throughout much of the white matter in both patients.

In all patients, there was increased lesion conspicuity and better definition of lesion extent on the diffusion-weighted images compared with the CT and  $T_2$ -weighted MR images. Follow-up MRI demonstrated hyperintensity and tissue loss in all of the areas characterized initially by diffusion-weighted imaging hyperintensity, consistent with infarction.

Percent lesion contrast was evaluated for 19 lesions seen on  $T_2$ -weighted and diffusion-weighted images. These data are summarized in Table 4. Percentage lesion contrast on diffusion-weighted imaging ranged between 37 and 264. Percent lesion contrast on  $T_2$ -weighted images ranged between 0.03 and 19.26. Percent lesion contrast ratio ranged from 5.4 to 2210. Percent lesion contrast was statistically significantly higher on diffusion-weighted imaging compared to  $T_2$  weighted images (P < .001).

# DISCUSSION

Seizures in the newborn are often a dramatic manifestation of several possible etiologies, of which hypoxic-ischemic encephalopathy remains the foremost. Both CT and MRI



Figure 8. *A*, Axial computed tomographic scan demonstrates no definite abnormality. *B*, Axial T<sub>2</sub>-weighted resonance image demonstrates no definite abnormality. *C*, Axial diffusion-weighted image demonstrates hyperintensity throughout most of the superficial and deep white matter. The most hyperintense signal abnormality is seen in the bilateral corticospinal tracts (arrows). *D*, Follow-up axialT<sub>2</sub>-weighted image demonstrates hyperintensity and severe white-matter tissue loss. These findings are consistent with severe hypoxic-ischemic encephalopathy.

				Follow-Up I <sub>2</sub> MRI	
Patient	Initial CT Scan*	Initial T <sub>2</sub> MRI <sup>†</sup>	Diffusion-Weighted Imaging	Age, months	Findings
1	R posterotemporal, parietal hypodensity	R posterotemporal, parietal hyper- intensity	R posterotemporal, parietal hyperintensity	30	Persistent R postero- temporal, parietal hyperintensity
2	L frontotemporal hypodensity	L frontotemporal hyperintensity	L frontotemporal hyperintensity, small left thalamic hyperintensity	10	Persistent L frontal, temporal, and thalamic hyperintensity
3	R occipital and frontal hypodensity	R occipital and frontal hyperintensity	R occipital and frontal hyperintensity	13	Persistent R frontal and occipital hyperintensity
4	Unremarkable	R frontal hyperintensity	R frontal hyperintensity		Not obtained
5	L superior temporal and L thalamic hypodensity	Unremarkable	L thalamic, superotemporal, bifrontal hyperintensity in watershed pattern	3	L thalamic, supero- temporal, bifrontal hyperintensity
6	Bilateral posterior, temporo-occipital, and R caudate head hypodensity	Bilateral temporo- occipital, R caudate, R putamen, R frontal hyperintensity	Bilateral temporo-occipital R caudate, R putamen, R frontal hyperintensity, multiple white- matter hyperintensities in watershed pattern	12	Persistent bilateral temporo-occipital, R caudate, R putamen, R frontal, and white-matter hyperintensities
7	Unremarkable	Bilateral frontal, temporal, and parietal hyperintensity in a watershed distribution	Bilateral frontal, temporal, parietal hyperintensity, bilateral thalamic and deep white-matter hyperintensity	5	Persistent bilateral frontal, temporal, parietal, thalamic, and deep white-matter hyperintensity with extensive tissue loss, enlarged ventricles
8 .	Unremarkable	Bilateral frontal, thalamic, and putamen hyperintensity	Bilateral frontal, thalamic, putamen, subcortical white matter and corticospinal tract hyperintensity	1	Persistent frontal, thalamic, putamen, and deep white-matter hyperintensity with extensive tissue loss, enlarged ventricles

#### Table 3. Neuroradiologic Data

\*At less than 24 hours of age.

<sup>+</sup>At age 2 to 8 days.

CT = computed tomographic; MRI = magnetic resonance imaging.

brain scans provide useful and important information and have remained the mainstay of investigation to delineate the etiology of the seizures and the extent of hypoxic-ischemic brain injury. Previous reports of CT and MRI in the acute setting of hypoxic-ischemic injury have demonstrated radiologic abnormalities in the cerebral cortex, white matter, and basal ganglia.<sup>20,21</sup> However, unmyelinated white matter and infarctions are relatively CT hypodense,  $T_1$  hypointense, and  $T_2$  hyperintense. They cannot always be well differentiated, especially in the acute stage.

In our experience, in this group of eight neonates with seizures, diffusion-weighted imaging has demonstrated cerebral infarctions better than traditional CT scans and  $T_2$ -weighted MRI sequences and has enabled us to confidently identify a seizure etiology in the acute to subacute setting. We identified cerebral infarctions that can be divided into two categories: (1) those that are multifocal and involve cerebral cortex, white matter, and basal ganglia (presumably related to a global hypoxic-ischemic process) and (2) those with distinct focal infarctions in the distribution of the middle cerebral artery (neonatal stroke, presumably

of embolic origin). Diffusion-weighted imaging demonstrated many acute infarctions, which were not seen on routine CT or  $T_2$ -weighted sequences. Other lesions were seen on CT and  $T_2$ -weighted sequences, but lesion contrast was increased on diffusion-weighted imaging and lesion extent was better delineated. Furthermore, seven infants in our group had follow-up MRI scans. All lesions that were hyperintense on the initial diffusion-weighted imaging scans were visualized on follow-up  $T_2$ -weighted images; the lesions were hyperintense with evidence of tissue loss. This confirmed that the lesions seen with diffusion-weighted imaging represented infarctions rather than transient abnormalities. This correlates with adult studies, which have demonstrated a high specificity for diffusion-weighted imaging in the detection of acute infarction. <sup>7-9</sup>

In four cases, diffusion-weighted imaging demonstrated focal infarctions in the distribution of the middle cerebral artery. All four patients presented with focal clonic seizures, which are typical of neonatal embolic cerebral infarctions and have been emphasized previously.<sup>22,23</sup> Barmada and Moosy<sup>24</sup> demonstrated that 5.42% of 592 neonatal brains

Table 4. Percentage Lesion Contrast of Ischemic Lesions

Defined	Lesion	% Lesion Contrast/	% Lesion Contrast/	% Lesion Contrast
Patient	Location	DVVI	12	Ratio (DVVI/1 <sub>2</sub> )
1	R parietal	52.97	0.66	80.16
2	L frontal	164.12	19.26	8.52
2	L thalamus	36.77	10.44	3.52
3	R frontal	90.47	1.28	70.57
3	R occipital	263.6	10.99	24.00
4	R frontal	162.37	17.25	9.42
5	R frontal	42.38	0.03	1632.74
5	L frontal	36.97	3.36	11.00
5	L temporal	124.32	1.94	64.25
6	R frontal	40.5	7.00	5.78
6	R putamen	43.88	4.12	10.65
6	R frontal	98.73	6.49	15.21
6	R occipital	122.62	7.77	15.79
7	R temporal	48.22	3.95	12.21
7	L temporal	82.23	14.76	5.57
8	R thalamus	58.99	9.27	6.36
8	L thalamus	63.22	0.03	2209.84
8	R frontal	110.27	17.37	6.35
8	L frontal	65.86	17.85	3.69

 $DWI = diffusion-weighted imaging; T_2 = T_2$ -weighted magnetic resonance images.

examined at autopsy showed a focal cerebral infarction due to embolism in a major arterial territory. There was a high incidence of sepsis and disseminated intravascular coagulation. Placental infarcts, placental thrombi, villitis, chorioamnionitis, hematologic disorders, and specific inherited disorders of defects in naturally occurring anticoagulant proteins are thought to contribute to the formation of emboli.<sup>25-27</sup> Placental analysis revealed chorioamnionitis in two of our patients, vasospasm in another patient, and villous edema and necrosis in a third patient. None of our patients showed evidence of defects in hypercoagulable factors or hematologic disorders. A large number of focal neonatal infarctions fall under the broad category of "perinatal asphyxia" without a known cause.28 One of our patients fell under this category. All four of our patients with focal infarctions had favorable short-term outcomes. One patient had a normal neurologic examination at short-term followup (case 4) and three had mild neurologic abnormalities (cases 1, 2, and 3).

In the four remaining cases, diffusion-weighted imaging demonstrated diffuse multifocal infarctions in distributions consistent with hypoxic-ischemic encephalopathy. Of these patients, two who presented with focal seizures (cases 5 and 6) had only border-zone infarctions. This pattern correlates with the well-described neuropathologic changes of parasagittal cerebral injury that occurs primarily related to hypotension and lack of perfusion to the arterial border zone (watershed) of the anterior, middle, and posterior cerebral arteries. These patients had fairly good neurologic outcomes, with mild hypotonia in one (case 5) and mild speech and language delay in the other (case 6). Two other patients, who presented with generalized seizures (cases 7 and 8), had ischemic changes in the deep gray nuclei and deep white matter, including the corticospinal tracts, in addition to cortical injury. This pattern correlates with the well-described neuropathologic change of more severe hypoxic-ischemic encephalopathy secondary to profound hypotension and hypoxia. The regions of injury correspond to those thought to be most metabolically active.28 The neurologic outcome of these patients was poor, with diffuse spasticity and significant gross motor delay (case 7) and spastic quadriparesis, microcephaly, and cortical blindness in the other (case 8). Thus, short-term neurologic outcome correlated with the extent of injury seen on the initial diffusion-weighted imaging scans for our patients with hypoxicischemic encephalopathy as well as for our patients with focal infarctions. The exact cause of hypoxic-ischemic encephalopathy in our cases could not be determined accurately. However, all four infants had abnormal late gestational or intrapartum events that are commonly associated with a risk for hypoxic-ischemic encephalopathy. Despite a favorable short-term outcome in six of our patients, we caution that the risk for long-term developmental disabilities; speech and language dysfunction; cognitive, attentional, and behavioral problems; and the risk for epilepsy should not be underestimated.

We considered other causes of decreased diffusion and hyperintense diffusion-weighted signal abnormalities in our patients. Diffusion-weighted imaging in animal models of prolonged seizures has demonstrated decreased diffusion, which reverses once the seizure activity ceases.<sup>29</sup> None of our patients had prolonged seizures; they were brief and easily controlled with anticonvulsants. Furthermore, follow-up scans in seven patients demonstrated that none of the lesions was reversible. In adults, herpes virus meningoencephalitis has been associated with restricted diffusion,<sup>30</sup> but none of our patients had clinical or laboratory evidence of meningoencephalitis. Other rarer causes of diffusionweighted imaging hyperintensity such as pyogenic abscess, tumor, and acute demyelination were not diagnostic considerations in our patients. Diffusion-weighted images have a T2 component and occasionally hyperintensity on diffusionweighted imaging results from the  $T_2$  component rather than from decreased diffusion. In all cases, we reviewed the apparent diffusion coefficient maps, which are only diffusion weighted. They demonstrated hypointensity in all diffusion-weighted hyperintense regions, consistent with decreased diffusion secondary to acute infarction.

Technical factors merit a few comments. Diffusionweighted imaging was safe and uncomplicated in all eight patients studied. The images are acquired in a very short time—2 minutes and 6 seconds—which is favorable compared with conventional CT and MRI for imaging unstable neonates. Furthermore, since the images are obtained by a single-shot technique, individual images have no motion artifact. When a patient moves, the source images can be reregistered to create isotropic diffusion-weighted images without degradation caused by patient motion.

In conclusion, diffusion-weighted imaging appears to be a useful adjunct that complements the use of both CT and MRI in the evaluation of neonatal brain injury. This technique demonstrates greater extent of injury compared with CT and conventional MRI in the acute setting and correlates well with short-term clinical outcome. In recent years, many of the cellular and vascular mechanisms of neonatal hypoxicischemic encephalopathy as well as mechanism-based therapies for hypoxic-ischemic encephalopathy have been areas of intense investigation in experimental animal models.<sup>31</sup> While the application of experimental therapies to the asphyxiated newborn has not been well established, diffusion-weighted imaging could, in the future, be valuable in the evaluation of neuroprotective agents for hypoxicischemic encephalopathy and could greatly affect patient management. Further investigation is needed to determine whether early abnormalities seen on diffusion-weighted imaging are predictive of long-term neurologic outcome and higher cortical functional deficits.

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