Proton Spectroscopy and Diffusion Imaging on the First Day of Life after Perinatal Asphyxia: Preliminary Report

A. James Barkovich, Kaye D. Westmark, Harvinder S. Bedi, J. Colin Partridge, Donna M. Ferriero, and Daniel B. Vigneron

BACKGROUND AND PURPOSE: MR techniques have proved useful in assessing brain injury from perinatal asphyxia when the injury is subacute or chronic. Recent advances in understanding the molecular mechanisms of brain injury have made medical intervention plausible, creating a need for assessment of the brain within the first few hours of life. We report the results of early (first 24 hours after birth) MR imaging in seven patients, including proton MR spectroscopy in six.

METHODS: MR studies were performed within the first 24 hours of life in seven consecutive patients who were encephalopathic after complicated deliveries. Standard T1-, T2-, and diffusion-weighted sequences were performed in all patients; single-voxel MR spectroscopy was performed in two locations in six of the seven patients. Follow-up MR studies were performed in four patients at ages 7, 8, 9, and 15 days, respectively.

RESULTS: T1-weighted images were normal in all seven patients. T2-weighted images were normal in three patients and showed T2 prolongation in the basal ganglia or white matter in the other four. Diffusion images showed small abnormalities in the lateral thalami or internal capsules in all seven patients. Comparison with clinical course in all seven patients and with follow-up MR studies in four showed that the diffusion images underestimated the extent of brain injury. Proton MR spectroscopy showed substantial lactate elevation in all six of the patients studied. Two patients died in the neonatal period and the other five were left with clinically significant neurologic impairment.

CONCLUSION: MR spectroscopy performed in the first 24 hours after birth is sensitive to the presence of hypoxic-ischemic brain injury, whereas diffusion imaging may help identify but underestimate the extent of the injury. Further studies are ongoing in an attempt to expand upon this observation.

MR techniques have had a considerable effect on the diagnosis of brain injury in the neonate. It has been demonstrated that standard MR imaging (1–7) and, more recently, MR diffusion imaging (8–11) and MR spectroscopy (12–19) enable identification of abnormalities that correspond with outcome. As techniques have improved, the goal of imaging studies has changed from merely identifying damage to identifying it at an early stage, when medical intervention might still be helpful. Diffusion imaging and MR spectroscopy are considered to have the greatest potential in this regard, yet to our knowledge the relative value of these techniques has not been studied. We recently had the opportunity to study seven encephalopathic neonates in the first 24 hours after birth; all seven were studied with diffusion imaging and six were studied with MR spectroscopy (patient 6 did not have MR spectroscopy because of a staff error). The results of those studies are reported in this article.

Methods

Seven patients at two institutions had clinically significant encephalopathy in the neonatal period after complicated deliveries; all seven neonates were admitted to our institutions over a period of 6 months. All were assessed while in the neonatal intensive care unit by experienced neonatologists and child neurologists who cared for or were consulted on the care of the infants. Apgar scores, initial umbilical cord blood gases,
TABLE 1: Clinical data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gestational Age (weeks)</th>
<th>Apgars (1, 5, 10 min)</th>
<th>Arterial Blood Values</th>
<th>Other Organs</th>
<th>Findings of Neurologic Examination</th>
<th>Birth History</th>
<th>Seizures/EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>3, 4, 4</td>
<td>pH = 7.08 BD = −12</td>
<td>Hematuria, normal hepatic function</td>
<td>Hypotonia, decreased spontaneous movements</td>
<td>Spontaneous vaginal delivery (Pitocin augmentation), fetal tachycardia</td>
<td>Seizures at 12 hr EEG: multifocal spikes with voltage suppression</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>0, 0, 0</td>
<td>pH = 6.9 BD = −25</td>
<td>Hepatic and renal failure, coagulopathy, hypoglycemia</td>
<td>Poor gag reflex, pupils dilated and nonresponsive to light, doll’s eyes, no spontaneous movements, hypotonia, no response to painful stimulation</td>
<td>Abruptio placentae, emergency C-section</td>
<td>Seizures at 36 hr EEG: depressed background</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>3, 4, 4</td>
<td>pH = 7.08 BD = −12</td>
<td>Hematuria, normal hepatic function</td>
<td>Hypotonia, decreased spontaneous movements</td>
<td>Spontaneous vaginal delivery (Pitocin augmentation), fetal tachycardia</td>
<td>Seizures at 12 hr EEG: multifocal spikes with voltage suppression</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>0, 0, 0</td>
<td>pH = 6.9 BD = −11</td>
<td>Hematuria</td>
<td>Hypotonia, decreased spontaneous movements</td>
<td>Spontaneous vaginal delivery with Pitocin augmentation</td>
<td>No clinical seizures, EEG-voltage suppression</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>0, 3, 5</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Seizures at 12 hr EEG: multifocal spikes with voltage suppression</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>0, 2, 3</td>
<td>pH = 6.9 BD = −11</td>
<td>Hematuria</td>
<td>Hypotonia, decreased spontaneous movements</td>
<td>Spontaneous vaginal delivery with Pitocin augmentation</td>
<td>No clinical seizures, EEG-voltage suppression</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>2, 2, 2</td>
<td>pH = 7.2 BD = 12 (age 2 hr)</td>
<td>Elevated hepatic enzymes, hematuria</td>
<td>Hypotonia, decreased spontaneous movements, absent gag reflex</td>
<td>Vaginal delivery (Pitocin augmented)</td>
<td>No clinical seizures EEG: nearly total absence of electrical activity</td>
</tr>
</tbody>
</table>

TABLE 1: Clinical data

The proton spectrum for each location considerably affecting ADC values (personal communications, Petra Hüppi, Jeff Neil). The proton spectrum for each location was acquired using the GE PROton Brain Exam sequence with parameters of 2000/288 and 128 acquisitions. Voxel size was 5 cm³. The MR spectroscopy parameters and voxel locations were chosen to maximize the detection of lactate (20) and to minimize the spectral contamination from extracranial adipose tissue. The two spectra were obtained with the same parameters and voxel size; the first voxel was centered on the deep gray matter (lentiform nucleus or thalamus) and the second in the anterior watershed white matter. The spectra, diffusion images, ADC values (from the diffusion images), and imaging studies were compared with our database of more than 150 neonates of gestational ages ranging from 26 to 42 weeks postconceptual age and with published norms (13, 21–26).

Patients 4, 5, 6, and 7 underwent follow-up MR studies at ages 9, 15, 8, and 7 days, respectively. Imaging parameters were identical to those of the initial imaging study. Again, patient 6 was not studied with MR spectroscopy, and diffusion images were not obtained at the follow-up study of patient 6.

All imaging studies were reviewed by two neuroradiologists with extensive experience in imaging of neonates. Both authors independently reviewed the SE imaging studies, the spectra, and the diffusion images and were in agreement as to the presence or absence of every abnormality, the location of the abnormalities, and their severity. In addition, the spectra and diffusion data were reviewed by an MR scientist with more than 10 years’ experience in in vivo MR spectroscopy (focusing particularly on neonates in the last 4 years). This author concurred with the findings on the MR spectra and diffusion studies as interpreted by the neuroradiologists.

Limited clinical follow-up was available in all seven patients, obtained from the neonatologists who last examined the infants.

Results

Initial MR Studies

Results are listed in Table 2. Routine T1-weighted images were normal for age in all patients. T2-
### TABLE 2: MR imaging data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>T1-Weighted Images</th>
<th>T2-Weighted Images</th>
<th>Diffusion-Weighted Images</th>
<th>Spectroscopy*</th>
<th>Follow-up MR Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Slight T2 prolongation of WM and deep GM</td>
<td>Reduced diffusion in lateral thalami</td>
<td>Lac/NAA &gt; 1 in BG, Lac/NAA ~ 0.3 in WS, NAA/Cr = 0.7 BG, NAA/Cr = 1.1 WS, Lac/Cr = 1.0 BG, Lac/Cr = 0.6 WS, Lac/Ch = 0.8 BG, Lac/Ch = 0.4 WS</td>
<td>Not performed</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>Slight T2 prolongation of WM; GM normal</td>
<td>Visually normal, ADC calculations showed slightly reduced diffusion everywhere</td>
<td>Lac/NAA &gt; 3 in BG, Lac/NAA &gt; 2 in WS, NAA/Cr = 0.7 BG, NAA/Cr = 0.7 WS</td>
<td>Not performed</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Slight T2 prolongation in basal ganglia</td>
<td>Slightly reduced diffusion in lateral thalami</td>
<td>Lac/NAA &gt; 3 in BG, Lac/NAA &gt; 3 in WS, NAA/Cr = 1.0 BG, NAA/Cr = 1.1 WS, Lac/Cr &gt; 3 BG, Lac/Cr &gt; 3 WS, Lac/Ch = 0.2 BG, Lac/Ch = 0.2 WS</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Slight motion degradation, possible T2 prolongation in basal ganglia</td>
<td>Minimal area of reduced diffusion in PLICs</td>
<td>Lac/NAA = 0.6 in BG, Lac/NAA = 0.5 in WS, NAA/Cr = 1.4 BG, NAA/Cr = 1.5 WS, Lac/Cr = 0.8 BG, Lac/Cr = 0.8 WS, Lac/Ch = 0.34 BG, Lac/Ch = 0.30 WS</td>
<td>At age 9 days, globular T1 shortening in ventral and lateral thalami and in posterior and lateral putamina and in depths of perirolandic cortex; T2 prolongation in lateral thalami and posterior putamina</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal, Slight motion degradation</td>
<td>Minimal area of reduced diffusion in PLICs and possibly in most lateral thalami</td>
<td>Lac/NAA &gt; 0.8 in BG, Lac/NAA &gt; 0.6 in WS, NAA/Cr = 1.3 BG, NAA/Cr = 1.3 WS, Lac/Cr = 1.0 BG, Lac/Cr = 0.8 WS, Lac/Ch = 0.5 BG, Lac/Ch = 034 WS</td>
<td>At age 15 days, globular T1 shortening in ventral and lateral thalami and in posterior and lateral putamina; T2 changes in posterior putamina, T2 prolongation diffusely in thalami; diffusion normal</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>Normal</td>
<td>Minimal area of reduced diffusion in ventrolateral thalamic nuclei</td>
<td>Lac/NAA = 1.8 BG, Lac/NAA = 3 WS, Lac/Cr = 1.1 BG, Lac/Ch = 2 WS, NAA/Cr = 1.2 BG, NAA/Cr = 2 WS, Lac/Cr = 1.6 BG, Lac/Cr = 5 WS</td>
<td>At 8 days, T1 and T2 shortening in the entire BG and lateral thalami; MRS shows marked reduction of NAA and persistent, moderate Lac elevation in both BG and WS voxels</td>
</tr>
<tr>
<td>7</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced diffusion in ventrolateral thalamic nuclei</td>
<td>Not done</td>
<td>At age 7 days, T1 shortening in lateral thalami, putamina and perirolandic cortex; reduced diffusion in dorsal brain stem, entire thalami, corticospinal tract</td>
</tr>
</tbody>
</table>

Note: NAA = N-acetylaspartate, Cr = creatine, Ch = choline, PLIC = posterior limb of internal capsule, WM = white matter, GM = gray matter, WS = watershed region, BG = basal ganglia.

* Normal levels: NAA/Cr = 1.4–1.7 in the basal ganglia (BG) and 1.6–2.0 in the watershed region (WS).
Findings at MR spectroscopy were abnormal in the six patients in whom it was performed. All had significant (>0.3) elevation of lactate/N-acetylaspartate (NAA) ratios in both voxels sampled (17, 27). In addition, the NAA appeared reduced, as the NAA/creatine (Cr) ratios were substantially lower than normal (our normal values in neonates range from 1.4 to 1.7 in the basal ganglia and from 1.6 to 2.0 in the frontal watershed white matter).

Follow-up MR Studies

All follow-up studies in the four patients in whom they were obtained showed definite brain injury (Table 2). All had much more extensive brain injury among the six patients studied and the extent of injury was determined by diffusion-weighted images, which were normal in four and showed mild edema (T2 prolongation) in the basal ganglia or cortex in the other three; no focal areas of T1 or T2 abnormality were present. Of interest, the diffusion-weighted images did not appear dramatically abnormal in any of the patients. The only area of reduced diffusion was in the posterior limb of the internal capsule (PLIC, Fig 1) in two patients and in the lateral thalamic nuclei and, perhaps, in the PLIC (Fig 2) in three patients. One patient had an apparently normal initial study (Fig 3) but further analysis showed a decrease of 15% to 20% in ADCs throughout the brain compared with that of healthy neonates imaged on our unit (unpublished results) and with published values (26).
Injury than was apparent on the initial diffusion images. In patients 4, 5, and 6, who initially had diffusion abnormality in only small regions of the PLIC, the follow-up studies at 9, 15, and 8 days, respectively, showed involvement of most of the thalami, the posterior putamina, and the depth of the perirolandic cortex, respectively (Fig 2). The diffusion abnormalities had resolved in the two in whom follow-up diffusion studies were obtained (patients 4 and 5), and the amount of lactate was definitely reduced at MR spectroscopy. NAA/Cr was further decreased in the basal ganglia. Patient 7, who initially had reduced diffusion in the ventrolateral thalamic nuclei (and possibly in the PLIC), had abnormal T1 shortening and reduced diffusion throughout the dorsal brain stem, basal ganglia, and corticospinal tracts at 7 days (Fig 2).

Clinical Follow-up
Limited follow-up was available in these infants. Two of the patients (patients 2 and 3) died after mechanical ventilation was discontinued, owing to persistent profound neurologic impairment. The other five were hypotonic, with feeding difficulties and poor airway protection at discharge from the hospital; their long-term prognosis is considered poor. Indeed, patients 1 and 7 had abnormal tone and impaired gag reflexes at their 5-month follow-up examinations.

Discussion
Over the past decade, a number of publications have described the utility of MR techniques in the assessment of hypoxic-ischemic brain injury in ne-

Fig 2. Patient 7.
A and B, Diffusion-weighted images (b = 700 s/mm²) at age 18 hours shows reduced diffusion, manifest as high signal intensity (arrows), in the lateral thalami and possibly in the posterior limbs of the internal capsules. No significant reduction in diffusion is seen in the centra semiovale (in B).
C and D, Follow-up diffusion-weighted images (b = 700, s/mm²) at age 7 days at the same levels show reduced diffusion (hyperintensity, arrows) within a much larger area, including the lentiform nuclei and thalami (in C) and along the corticospinal tracts (in D).
E, Axial SE (516/8) image through the basal ganglia shows T1 shortening in the lateral thalami (open arrows) and lentiform nuclei (solid arrows), confirming the injury seen in C.
onates (4–7, 10, 13, 14, 16, 19, 27–37). These studies have shown that the subsequent clinical deficit is related to the severity of brain injury, as assessed by imaging or metabolic assessment (spectroscopy). Recent work has suggested that, in the near future, the extent of hypoxic-ischemic brain injury may be reduced by a variety of new strategies (38, 39). For the purposes of such therapy, the ability to detect subacute or chronic injury and prognosticate outcome becomes less important than the ability to detect damage in the early postnatal period, at a time when therapy may be effective. A few publications have addressed the detection of acute neonatal hypoxic-ischemic injury in the early postnatal period, using both diffusion imaging (8, 9, 10, 11) and proton MR spectroscopy (14, 40). This is the first study, to our knowledge, to compare diffusion imaging and spectroscopy in the first 24 hours after birth.

Although the diffusion-weighted images were at least slightly abnormal in all of our patients, the discrepancy between the extent of the abnormality on the first set of images and the second set of images was striking; clearly, the topologic extent of injury was underestimated on the initial studies. In all four patients in whom follow-up MR imaging was obtained, tissue damage was substantially more extensive than was suggested by the initial images (Figs 1 and 2). A similar underestimation of damage in asphyxiated neonates by early diffusion-weighted imaging has been noted by others (10, 41). This underestimation could have serious consequences if therapy were withheld because minimal or relatively minor injury was suspected. In patients 4, 5, 6, and 7, the images obtained on day 1 suggested minor injury when, in fact, subsequent studies on days 9, 15, 8, and 7, respectively, showed much more extensive injury. The reason for this underestimation is not clear. In embolic and thrombotic stroke, both in adults and children, diffusion imaging seems to be sensitive to the early detection of ischemic injury. In adults with embolic or thrombotic infarctions, the enlargement of strokes is often seen and is attributed to an ischemic penumbra that is hypoperfused but viable at the time of diffusion imaging (42–44). It is generally accepted that the penumbra suffers definitive infarction after the initial diffusion image has been acquired. However, neonatal injury is neither thrombotic nor embolic. The brain is hypoperfused, then reperfused. No classical penumbra exists in this situation. How, then, do we explain this discrepancy between the day 1 diffusion study and the final injured territory? Could it result from the same processes that caused false-negative diffusion-weighted imaging findings in the study by Robertson et al (10). In all likelihood, both are the result of delayed energy failure (also called biphasic energy failure), a well-known phenomenon in neonatal hypoxic-ischemic injury (45–48). In biphasic energy failure, an initial reduction of energy substrate results in an initial impairment of cell metabolism. Reperfusion results in a transient return to apparently normal cell metabolism that lasts for a variable period of time, generally in the range of 24 hours (45–47), after which the cell dies. The delay in cell death is postulated to result from the duration of a cascade of intracellular molecular events that lead to mitochondrial dysfunction (38, 39). Imaging confirmation of this delay was iden-
tified by Rumpel et al (45), who found a biphasic function for the evolution of cytotoxic edema, as determined by ADC maps and histologic examination, after hypoxic-ischemic injury in neonatal rats. At the end of hypoxia-ischemia, these authors found the ADC in the ipsilateral cortex to be substantially decreased. Upon reoxygenation, it returned transiently to normal, followed by a secondary, although less pronounced, decline after 8 to 48 hours. After this, the ADC rose steadily. After 8 hours of recovery, the proportion of vasogenic edema steadily increased, as indicated by the T2 prolongation; at 21 hours, the majority of glial cells were enlarged, whereas the neurons were apoptotic. These results indicate that delayed cerebral injury is accompanied by late glial swelling in conjunction with an enlarged interstitial space due to cell damage; they also help to explain why findings on diffusion-weighted studies may be falsely negative when performed in the first hours after neonatal hypoxic-ischemic injury.

Our results suggest that proton MR spectroscopy depicts the severity of injury more accurately than does diffusion-weighted imaging. MR spectroscopy performed within minutes of the diffusion-weighted studies showed abnormally elevated lactate and diminished NAA in all patients in our series. We obviously cannot state that there was no diminution in lactate during the interval between the first and second phases of energy failure. If cell function and, in particular, mitochondrial function normalized during reperfusion, we would expect a resumption of adenosine triphosphate production via the tricarboxylic acid cycle and a decrease in lactate production. Indeed, Penrice et al (49) showed in a pig model that lactate levels decrease after an initial increase, with a nadir at about 24 hours after birth, before beginning to rise again. However, it appears that mitochondrial function does not completely normalize, as lactate levels remain elevated. More important from an imaging perspective, it seems that any reduction of lactate is less significant than, or occurs later than, the normalization of diffusion, as all six patients in our study in whom MR spectroscopy was performed had lactate levels predictive of moderate to severe injury, according to the work of Hanrahan et al (14) and Amess et al (40). The clinical outcome and the follow-up MR studies indicate that the predictions based on these measurements were accurate.

We compared the topologic extent of the diffusion abnormality, as assessed by diffusion imaging, with the degree of biochemical change in specified topological sites, as assessed by MR spectroscopy. This comparison was made because these are currently the means by which studies are evaluated in the literature (7, 10, 13, 14, 15, 36, 40) and by which norms are established. A comparison of diffusion imaging with spectroscopic imaging might be useful in the future, as spectroscopic imaging is now commercially available on some MR units. Another important point is that diffuse injury might not be initially apparent on diffusion images. As Figure 3A illustrates, a diffusion image of a patient with reduction of diffusion fairly equally throughout the brain looks nearly normal. Thus, ADCs must be calculated and compared with those of age-matched control subjects before a study can be definitively read as normal or abnormal.

An understanding of these MR spectroscopic and diffusion imaging findings is difficult with the limited knowledge available about the temporal evolution of neonatal hypoxic-ischemic injury. The generation of spectra with more accurate lactate peaks, obtained by using the technique of lactate editing, which eliminates contributions from other protons that might resonate at the same frequency as lactate, would help to increase our accuracy in assessing these patients. Our understanding could be further improved by the generation of ADC-versus-time and lactate-versus-time curves that would show when ADC values and lactate levels reach their highest and lowest levels with respect to the injury. Such curves could be useful for determining the reliability of lactate and diffusion levels at a particular postnatal time for predicting the severity of injury. Forbes et al (8) recently published data indicating that proton diffusion normalizes more quickly in the basal nuclei of the asphyxiated neonate than in the cortex. However, their patients were all imaged at least 2 days after birth, and their analysis dealt with timing in days rather than hours. For our analyses of images obtained during the first day of life, the difficulty in determining precisely when an injury occurred with respect to the time of delivery can substantially alter the temporal analysis. Therefore, we believe it is more useful, at present, to rely on time-independent values and ratios, such as those generated by Hanrahan et al (14) and Amess et al (40) for lactate levels, rather than on time-dependent numbers.

What, then, is the optimal MR examination for an encephalopathic, possibly asphyxiated, neonate who is only a few hours old? Until more information is available, it appears that proton MR spectroscopy, performed with a long TE to maximize sensitivity to lactate (20), is the single most useful study. Regarding the location of the voxel, we found the highest levels of lactate in the thalamic/basal ganglia voxel in this study. Amess et al (40) and Hanrahan et al (14) also used voxels centered over the deep gray nuclei for their studies and found a good correlation between metabolite ratios and outcome. These results most likely reflect the fact that acute, profound diminution of blood flow in the neonate seems to severely affect the deep gray nuclei (30, 50–52). Therefore, it seems that if a single voxel is to be sampled, the thalamus/pu-tamen is the best location. Keeping in mind that patients with watershed injury may have higher lactate levels in the intervascular boundary zones (13), it is probably reasonable to sample a second voxel in the watershed region if time permits. The optimal solution may be to perform a spectroscopic...
imaging sequence, if available, that allows multiple smaller regions to be sampled individually. We continue to perform diffusion imaging because it is fast and supplies confirmatory information. Also, we continue to perform standard T1- and T2-weighted SE sequences to look for underlying hemorrhage, malformations, and patterns of injury that suggest metabolic disorders or infection, as disorders other than hypoxia-ischemia can cause neonatal encephalopathy.

Conclusion

This small series suggests that MR spectroscopy performed in the first 24 hours after birth is sensitive to the severity of hypoxic-ischemic brain injury, whereas diffusion imaging depicts and localizes, but underestimates, the extent of the injury. If MR imaging is to contribute to decisions regarding medical intervention in encephalopathic neonates, it is critical to better understand the optimal time at which the MR studies should be performed.

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