CORRELATION OF BASAL GANGLIA MAGNETIC RESONANCE SPECTROSCOPY WITH APGAR SCORE IN PERINATAL ASPHYXIA

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Background: Brain metabolite levels are measured by proton magnetic resonance spectroscopy (1H MRS) and include N-acetylaspartate (NAA), creatine (Cr), choline (Cho), and lactate and the ratios NAA to Cho and Cr (NAA-ChoCr), NAA-Cr, NAA-Cho, and Cho-Cr. Brain metabolite levels may correlate with the degree of neonatal asphyxia.

Objective: To determine which brain metabolite ratios have the strongest correlation with the Apgar scores in infants with possible asphyxia; whether the correlation is stronger with basal ganglia (BG) or anterior border-zone metabolites; and whether a combined approach using routine MR imaging (MRI), diffusion-weighted MRI, and MRS can be used to evaluate the severity of neonatal asphyxia.

Methods: Twenty infants with 1-minute Apgar scores of 6 or less were studied at 2 to 28 days of age. The MRS variables were compared with routine and diffusion-weighted brain MRI. Clinical variables and MRS findings were subjected to factor analysis and stepwise multiple regressions to determine interrelationships.

Results: The BG region NAA-Cho and NAA-ChoCr ratios correlated with the 1-minute (P<.001) and 5-minute (P = .01 for NAA-Cho; P = .006 for NAA-ChoCr). There was no correlation between metabolite levels and the 10-minute Apgar scores. The strongest predictions exist between the 1-minute Apgar scores and the NAA-Cho and NAA-ChoCr ratios. In the anterior border zone, the only correlation was between the 1-minute Apgar score and the NAA-Cho ratio, but there was a strong age effect in these data. Lactate was found in the BG of 3 infants, all of whom had 5-minute Apgar scores of 6 or less. Three patients had focal lesions on MRI; 2 of these had elevated lactate levels in the abnormal region; and the third, who had an intrauterine stroke, had no lactate in the region.

Conclusions: Correlations between NAA-Cho and NAA-ChoCr ratios and the 1- and 5-minute Apgar scores are stronger in the BG region than in the frontal border zone. The presence or absence of lactate may indicate the severity of the brain insult, and the combination of MRS, MRI, and diffusion-weighted MRI may assist in localizing and predicting a long-term brain injury.

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PATIENTS AND METHODS

Twenty infants, all 37 to 42 weeks' gestation and with a 1-minute Apgar score of 6 or less, were enrolled. Infants were excluded if they had a known metabolic disease or brain structure abnormalities. Ten of the 20 infants had acidosis (pH < 7.2) and/or a perinatal event such as abruptio placentae, preeclampsia, or fetal bradycardia. The MRI examination was performed as soon as possible after birth (mean age, 8 days; range, 2-28 days). Informed consent was obtained from parents after the procedure was explained fully. Sedation was not necessary for any study. Routine brain MRI included T1-weighted sagittal images and T1-weighted, T2-weighted, and fluid-attenuated inversion-recovery axial images. Ten infants also underwent diffusion-weighted imaging with contiguous slices 3.3 mm thick and a diffusion factor of b = 1000 s/mm².

All infants underwent routine clinical examination and were given Apgar scores by the treating neonatologist. (Unless otherwise indicated, data are given as mean ± SD.) Mean Apgar scores were 2.4 ± 1.8 at 1 minute, 6.0 ± 2.1 at 5 minutes, and 7.9 ± 1.9 at 10 minutes (10-minute scores were available in 17 infants).

After the MRI examination, single-voxel proton MR spectra were acquired from the BG region in all patients (4.9 ± 1.3 mL, including all BG and parts of the thalamus) and the anterior border zone (4.9 ± 1.2 mL, between the anterior and middle cerebral artery distribution) in 13 of the 20 patients (Figure 1). In addition, if the infant had a focal area of ischemia as determined by routine or diffusion-weighted MRI, MRS was performed in that region.

Single-voxel spectra were acquired with a double spin-echo technique with repetition time of 1600 milliseconds and echo time (TE) of 144 milliseconds. At this TE, the lactate peak appears negative because 144 milliseconds equals 1/J, where J is the spin-spin coupling constant between the methine (CH) and methyl (CH₃) protons in lactate.²⁶ If lactate was present, an additional spectrum was often acquired with a TE of 288 milliseconds to confirm and better define the lactate peak. An automated single-voxel proton spectroscopy technique (PROBE/SV; GE Medical Systems, Milwaukee, Wis) was used. Magnetic resonance spectral processing included a negative Lorentzian filter (half the Cr line width) and an 8-Hz Gaussian filter to improve the signal-to-noise ratio, zero-filling from 2048 to 8192 data points, Fourier transformation, and automatic phasing with manual fine-tuning of the zero-order phase. The intensity of the residual water signal was decreased by a low-frequency filter, and the peaks were fitted with a combined Lorentzian and Gaussian fit with a baseline that was chosen manually. The Cho and Cr peaks were fitted with a combined 2-peak fit. Although the Cr peak area often is used as a reference for metabolite ratios, the Cr signal was sometimes very low, producing artificially high NAA-Cr ratios. In addition, it is sometimes difficult to get accurate peak areas for Cho and Cr separately because of peak overlap. Therefore the metabolite signal ratios NAA to Cho and Cr (NAA-ChoCr), NAA-Cr, NAA-Cho, and Cho-Cr were calculated from the peak areas. In addition, relative metabolite levels were estimated by adjusting the signal intensities for the voxel volumes.

Data were analyzed with single regressions for exploratory purposes (any P < .05 was deemed statistically significant), then with stepwise multiple regression, with a minimum of F = 4.00 to enter and F = 3.99 to remove. For each region of interest (BG or anterior border zone), data were analyzed with age and Apgar scores as independent variables and metabolite levels or ratios as dependent variables.

Figure 1. Typical regions of interest shown on T2-weighted magnetic resonance images (repetition time, 3000 milliseconds; effective echo time, 96 milliseconds) for the basal ganglia (A) and the frontal border zone (B).
level. However, results with NAA-metabolite ratios have been inconclusive. Low NAA-Cr and NAA-Cho ratios were reported to correlate with bad outcome, but neither of these correlations was found in another study. A high Cho-Cr ratio may or may not be correlated with bad outcome. Spectra of the basal ganglia (BG) correlated with outcome in only a single study. One study found no correlation between Apgar scores and "3P MRS data, but there seem to have been no attempts to correlate Apgar scores with "H MRS data, even when both types of data were acquired. We investigated the relationship between Apgar score and "H MRS metabolite ratios in patients with possible mild to marked perinatal asphyxia. Special attention was paid to the BG region, which may be most vulnerable in asphyxia.

RESULTS
Spectra recorded from the BG showed varying levels of NAA and occasionally of lactate (Figure 2). In 1 patient, a signal from propylene glycol near 1.1 parts per million prevented accurate quantitation of the nearby lactate peaks. Regression analysis showed that the 1-minute Apgar score correlated with the NAA-Cho and NAA-ChoCr ratios in the BG (Figure 3 and Table 1) and marginally with relative NAA levels (P = .02). The 5-minute Apgar score correlated with the NAA-Cr, NAA-Cho, and NAA-ChoCr ratios (Table 1) and with the relative levels of NAA (P = .009), Cr (P = .04), and ChoCr (P = .04). No significant correlations were found with the

Table 1. Correlations Between Apgar Scores and Metabolite Ratios in the Basal Ganglia

<table>
<thead>
<tr>
<th>Metabolite Ratio</th>
<th>Significance of Apgar Scores, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-Minute</td>
</tr>
<tr>
<td>NAA-Cr</td>
<td>.12</td>
</tr>
<tr>
<td>NAA-Cho</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NAA-ChoCr</td>
<td>&lt;.001</td>
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</tbody>
</table>

*All 20 infants are included in the correlations. No correlations with 10-minute Apgar scores were significant. NAA indicates N-acetylaspartate; Cr, creatine; and Cho, choline.

Table 2. Correlations Between Apgar Scores and Metabolite Ratios in the Anterior Border Zone in a Subset of Patients

<table>
<thead>
<tr>
<th>Metabolite Ratio</th>
<th>Significance of Apgar Scores, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-Minute</td>
</tr>
<tr>
<td>Anterior border zone</td>
<td></td>
</tr>
<tr>
<td>NAA-Cr</td>
<td>.41</td>
</tr>
<tr>
<td>NAA-Cho</td>
<td>.02</td>
</tr>
<tr>
<td>NAA-ChoCr</td>
<td>.05</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>NAA-Cr</td>
<td>.16</td>
</tr>
<tr>
<td>NAA-Cho</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NAA-ChoCr</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Only the 13 infants for whom anterior border-zone data were available are included in the correlations. The significance of basal ganglia correlations in this subset of patients is included for comparison. NAA indicates N-acetylaspartate; Cr, creatine; and Cho, choline.
The correlations with BG metabolite ratios were still significant in this population (Table 2), and the stepwise multiple regression results were very similar, often with even clearer correlation patterns.

For the definitive analysis, the 2 early Apgar scores as well as gestational plus postnatal age (GPA) in weeks and age in days were entered into a stepwise multiple regression as predictors of each of the metabolite ratios. Only the 1-minute Apgar score survived as a significant predictor of the NAA-Cho ratio (r = 0.70; F1,18 = 17.00; P < .001) and the NAA-CrCho ratio. In contrast, only the 5-minute Apgar score survived as a significant predictor of the NAA-Cr ratio (r = 0.49; F1,18 = 5.57; P < .001). Principal component analysis confirmed that 61% of the total variance was accounted for by 1 factor, which showed maximal loading on 1-minute Apgar score, NAA-Cho, and NAA-Chocr, and lowest loading on NAA-Cr ratios. Age and GPA failed to enter any of the multiple regressions.

Spectra were acquired from the anterior border zone in 13 of the 20 infants. The only significant correlation in this region was a weak correlation between 1-minute Apgar scores and the NAA-Cho ratio (Table 2). Stepwise multiple regression analysis showed that much of this correlation was due to age. The correlations with BG metabolite ratios were still significant in this population (Table 2), and the stepwise multiple regression results were very similar, often with even clearer correlation patterns.

Three of the 6 infants with 5-minute Apgar scores of 0 or less showed a large BG lactate signal when examined within 9 days of birth. In the 2 infants without a propylene glycol peak, the lactate-NAA ratios were 0.73 and 0.35 and the lactate-Chocr ratios were 0.17 and 0.11. In the infant with propylene glycol, the estimated metabolite ratios were lactate-NAA of approximately 0.40 and lactate-Chocr of approximately 0.13. No other infants had a lactate signal detectable above the noise. The 3 infants with elevated BG lactate levels also had low NAA-Chocr ratios (0.23, 0.34, and 0.39) compared with the other 17 (mean, 0.41 ± 0.10).

Focal abnormalities were seen on routine brain or diffusion-weighted MRI in 3 infants. Infant 1 had a middle cerebral artery infarct that presumably occurred 1 month before delivery, apparently the result of severe anemia that went untreated. The routine brain MRI did not assist in the timing of the stroke. No lactate or other metabolite signal was detected in the infarct region. An MRI obtained 8 months later showed a large, middle cerebral artery infarct with focal atrophy and no lactate signal in the old stroke region.

Infant 2 had diffusion-weighted abnormalities in the frontal lobes; infant 3 had diffusion-weighted abnormalities in the occipital lobes (Figure 4, A). Both infants showed no focal abnormalities on routine MRI. Both infants had lactate signals in the region with abnormal findings (Figure 4, B), and infant 3 also had a BK lactate peak. At a follow-up investigation 7 weeks later, infant 3 still had a small BK lactate peak. In the occipital region of the previous diffusion-weighted abnormalities, biocapsular atrophy (Figure 4, C) and a persistence of the lactate elevation were seen. Infant 2 did not undergo a follow-up examination.

In previous investigations, decreased brain NAA-metabolite ratios after asphyxia usually correlated with poor neurodevelopmental outcome 3 to 12 months later, and the presence of lactate suggested an even worse prognosis. To our knowledge, no study has shown a correlation between brain metabolites and Apgar score, although it is reasonable to expect such a relationship, and no investigation has used the combination of diffusion-weighted MRI, routine MRI, and MRS to define the extent of a neonatal brain insult.

In our analysis of 2 regions, the BG region metabolites seem more sensitive than anterior border-zone metabolites in correlating with the 1- and 5-minute Apgar scores (Table 2). This is consistent with recent evidence that deep structures might be most vulnerable to as-
If the Apgar score indicates the severity of asphyxia or the proximity of asphyxia to the delivery, our results suggest that there is a correlation between brain metabolite levels and asphyxia. The weak correlations in the anterior border zone may be due partly to difficulty in locating this region accurately. Because this difficulty would be present in a typical clinical environment, measurement of BG region metabolite levels should be more sensitive than that of anterior border zone metabolite levels in clinical studies.

Stronger correlations were found with NAA-Chol and NAA-CholCr ratios than with NAA-Cr ratios (Tables 1 and 2). This is probably the result of low Cr levels in a few cases (eg, Figure 4, B, compared with Figure 2). A low Cr level could lead to normal NAA-Cr ratios, even if the NAA level is decreased. The strong correlation with NAA-CholCr ratios may be useful, because this metabolite ratio can be calculated even if the Cho and Cr peaks are not well resolved, so that only a combined area can be determined. Furthermore, the main factor derived from principal component analysis, which accounted for 61% of the total variance, loaded mainly on the 1-minute Apgar score and NAA-Chol and NAA-CholCr ratios. These 3 variables, therefore, constitute the main substructure in our data.

The 1-minute Apgar score may represent best the degree of asphyxia, since this is determined early in the course of resuscitation efforts. The brain metabolite levels show no correlation with the 10-minute Apgar scores, which were the same or higher than the 5-minute score in all the infants, even when the infant was receiving full life support. At our institution, the 10-minute Apgar score may be substantially higher than the initial score, even if the infant is on a respirator, because effective resuscitation may improve the color, heart rate, and reflex irritability in asphyxia. Although a study showed that the 1-minute Apgar score was a strong predictor of complications after asphyxia, previous investigations have not attempted to correlate proton MRS variables to Apgar scores. Our positive result may be related to our sample, which includes a broad range of asphyxia, since the 1-minute Apgar scores ranged from 0 to 6. Alternatively, there may be regional variations in the United States in assigning Apgar scores. If this is true, the MRS metabolite ratios would be important, since there is no clinical judgment bias in MRS.

Stepwise multiple regression analysis revealed that the variance in our BG NAA-metabolite ratios was due mostly to the Apgar scores, not to age since birth or GPA. However, these metabolite ratios are known to change with age and may complicate some studies. In healthy infants, the NAA-metabolite ratios appear to increase about 10% to 15% in the first month. In our study, 2 observations suggest that a similar or greater increase may occur in asphyxiated infants. First, among the 5 infants with 5-minute Apgar scores of 0 or 9, the NAA-CholCr ratios in the 3 older infants (16–28 days of age) were higher than in the 2 younger infants (5 and 7 days of age) by about 1% per day. Second, in infant 3, the NAA-metabolite ratios in a follow-up study increased by about 1% per day for 7 weeks. Although not definitive, these observations suggest that age must be considered in MRS studies of infants with low NAA-metabolite ratios.

Three of 6 children with 5-minute Apgar scores of less than 6 had a significant BG lactate peak and low NAA-CholCr ratios. These 3 infants are likely at highest risk for poor outcome based on previous findings.

Finally, only 3 patients showed a focal abnormality on routine or diffusion-weighted MRI. Two had a perinatal insult and showed elevated lactate levels in the region of abnormality. One patient did not show lactate in a middle cerebral artery infarct that was presumed to have occurred approximately 1 month before delivery. We speculate that the presence of lactate results from a more recent insult, with the lack of lactate in a stroke region suggesting an earlier process. One infant had a persistent local elevation of lactate level 7 weeks after birth in a region that underwent ischemia at birth. Further studies are needed to elucidate lactate production and washout in the neonatal brain.

First, BG NAA-metabolite ratios are related directly to the 1- and 5-minute Apgar scores, especially the former. Second, the BG seems to be a sensitive region in defining asphyxia-related brain metabolite abnormalities, as anticipated from recent studies suggesting BG-thalamus vulnerability.

Third, the Cho-Cr ratio does not appear to correlate with Apgar scores. Fourth, age since injury must be considered in quantitative MRS studies. Fifth, the use of routine and diffusion-weighted MRI assists in defining focal brain insults. Adding MRS to the imaging may prognosticate and help time the occurrence of the brain insult. In regard to timing an insult, further investigations using a multimodality imaging approach should help determine the type and timing of a brain insult. We need to define the length of time that abnormalities on diffusion-weighted imaging as well as MRS-detected lactate persist after injury, since infants are likely different from adults in these processes.

We speculate that a combined approach using clinical variables, MRS-derived BG metabolite levels, and routine and diffusion-weighted MRI will define an asphyxiated population at high risk for poor neurodevelopmental outcome. Such infants should be targeted for brain resuscitation measures in future treatment trials. Finally, the development of standardized approaches to measure metabolite levels may allow for large, multi-institution studies aimed at improving outcome and reducing the risk for cerebral palsy.

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