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Cerebral Structure and Metabolism and Long-Term Outcome in Small-for-Gestational-Age Preterm Neonates

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ABSTRACT

In the present study, we compared brain development and metabolism of small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants using proton magnetic resonance spectroscopy (^{1}H-MRS). We tested the hypothesis that intrauterine growth retardation caused by placental insufficiency is associated with changes in cerebral metabolism and is followed by an adverse neurodevelopmental outcome at the age of 2 y. Twenty-six AGA and 14 SGA (birth weight <P 2.3) preterm infants with no major ultrasound abnormalities were enrolled prospectively. At 32 and 41 wk postmenstrual age, ^{1}H-MRS and magnetic resonance imaging were performed. For ^{1}H-MRS, a volume of interest was placed in the basal ganglia and in the periventricular white matter. Using echo times of 31 and 144 ms N-acetylaspartate/choline (NAA/Cho), lactate/Cho, *myo*-inositol/Cho (mI/Cho), and glutamate-glutamine-γ-aminobutyric acid/Cho (Glx/Cho) ratios were compared between AGA and SGA groups. Griffiths' developmental quotient (DQ) values were assessed at 24 mo corrected age. Griffiths' DQ (AGA, 104 ± 10; SGA, 99 ± 9) and brain development assessed using magnetic resonance imaging showed no significant differences between both AGA and SGA groups, and NAA/Cho, Lac/Cho, mI/Cho, and Glx/Cho ratios were not significantly different between the groups. NAA/Cho ratios increased from 32 to 41 wk, whereas mI/Cho ratios decreased in both groups. No differences in cerebral metabolism, brain development, and DQ values between AGA and severely SGA infants could be demonstrated. **(*Pediatr Res* 56: 285–290, 2004)**

Abbreviations
AGA, appropriate for gestational age
BG, basal ganglia
Cho, choline
DQ, developmental quotient
Glx, glutamate/glutamine/γ-aminobutyric acid
^{1}H-MRS, proton magnetic resonance spectroscopy
Lac, lactate
mI, *myo*-inositol
MRI, magnetic resonance imaging
NAA, N-acetylaspartate
NAAG, N-acetylaspartylglutamate
PVWM, periventricular white matter
SGA, small for gestational age
TE, echo time
TI, inversion time
TR, repetition time
VOI, volume of interest

Preterm infants who are small for gestational age (SGA) as a result of placental insufficiency are at increased risk for adverse neurodevelopmental outcome in comparison with age-matched appropriate-for-gestational-age (AGA) neonates (1–4). Placental insufficiency can be demonstrated in these pregnancies using Doppler ultrasonography of the umbilical artery (5). Most of these pregnancies are terminated by cesarean section because of severe fetal compromise with impending hypoxia-ischemia (6).

During the past decade, it was demonstrated that perinatal hypoxia-ischemia may have long-lasting effects on cerebral metabolism as has been demonstrated using *in vivo* cerebral proton magnetic resonance spectroscopy (^{1}H-MRS) (7,8). A decrease of the N-acetylaspartate/choline (NAA/Cho) ratio in asphyxiated full-term neonates predicts an adverse neurodevelopmental outcome (7,9–11). Elevated levels of lactate (Lac) in the brain of asphyxiated neonates, even months after the hypoxic-ischemic insult, have been shown to be predictive of neurodevelopmental delay (7,8,10,12). *Myo*-inositol (mI),

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which is one of the osmoregulators of the brain, can be found in astrocytes and is considered a glial cell marker (13). It increases in the early phase after hypoxia-ischemia and decreases during the perinatal period (14,15). Related metabolites such as glutamate, glutamine, and γ-aminobutyric acid are collectively known as Glx, the peak patterns of which are difficult to separate at 1.5 T. Glutamate, which is the main constituent of the Glx peak, is an excitatory amino acid, and its concentration increases after hypoxia-ischemia (16,17). Moreover, glutamate may play a role in brain development, by influencing neurite sprouting, synaptogenesis, and dendrite pruning (18).

The aim of the present study was to compare brain metabolism and imaging in a group of SGA and AGA preterm infants at 32 wk postmenstrual age and at term. We hypothesized that SGA and AGA infants have different ^{1}H-MRS findings at both time points and that abnormal metabolite ratios in SGA preterm infants precede an abnormal neurodevelopmental outcome at the age of 2 y.

METHODS

Patients. All neonates in this study were born between March 1, 1999, and December 31, 2001, and were admitted to the neonatal unit of the Wilhelmina Children's Hospital/University Medical Center Utrecht because of a gestational age of <32 wk and/or a birth weight of <1500 g. The study was approved by the Medical Ethical Committee of the Wilhelmina Children's Hospital, and informed parental consent was obtained in all cases. Inclusion criteria were *1*) absence of fetal infections, congenital malformations, and metabolic and chromosomal disorders; *2*) intraventricular hemorrhage grade ≤IIa according to the criteria of Levene *et al.* (19); *3*) periventricular leukomalacia ≤grade I according to the criteria of de Vries *et al.* (20); and *4*) stable clinical condition.

Twenty-six AGA and 14 SGA infants were eligible for this study. SGA was defined as a birth weight <p 2.3 according to Dutch national birth weight centiles (21). Placental insufficiency was diagnosed by abnormal Doppler flow patterns of the umbilical artery as described previously (5,6). Patients were examined at a postmenstrual age of 32 wk [early magnetic resonance imaging (MRI)] and/or 41 wk (late MRI). Of the 26 AGA neonates examined at 32 wk, 24 also had a second scan at term, and MRS data could be obtained in 21 of them. Of the 14 SGA newborns included, 7 had both an early and a late MRI, 2 had only an early MRI, and 5 had only a late MRI examination. In 2 AGA infants, parental permission was not obtained for the second MRI. Of the SGA infants, one infant was not examined at term because of episodes of hypoxia-ischemia at 39 wk. Another infant was not examined because of referral to another hospital at the time of the second MRI. Of the five SGA neonates who had a scan at term only, two were born at 33 and 34 wk, respectively, and were included for the examination at term because of their extreme growth retardation, and three others were studied at term only because they were not clinically stable at the time of the early MRI, *i.e.* at 32 wk gestational age. Patient characteristics are listed in Table 1.

Neurodevelopmental follow-up was performed at regular intervals up to the age of 24 mo as reported previously (7). Assessment of outcome was made using items from Amiel-Tison and from Grenier and Touwen and the Griffiths' mental developmental scale. The developmental quotient (DQ) of the Griffiths' test at 24 mo was calculated (22).

The MRI examinations were performed in unsedated neonates, using vacuum pillows (Med-Tec, Orange City, IA, U.S.A.) to avoid movements of the patient's head. Patients with a weight of <1500 g at the time of the MRI studies were examined using an MRI-compatible incubator (Dräger, Lübeck, Germany) (23). Heart rate and transcutaneous oxygen saturation were monitored using pulse oxymetry (Nonin, Minneapolis, MN, U.S.A.), and respiratory rate was monitored using an abdominal transducer (Philips Gyroscan ACS-NT, Best, the Netherlands).

MRI. Standard MRI was performed for localization of the volume of interest (VOI) for ^{1}H-MRS, using a 1.5 Tesla Philips ACS-NT system. MRI included sagittal T1 [repetition time

Table 1. *Patient characteristics*

	AGA	SGA
No. of patients		
Total	26	14
Early MRI/^{1}H-MRS	26/26	9/9
Late MRI/^{1}H-MRS	24/21	12/12
Early + late MRI/^{1}H-MRS	21/21	7/7
Birth weight (mean ± SD)	1200 ± 425	675 ± 150
Postmenstrual age at birth (wk; mean ± SD)	29.2 ± 2.3	30.1 ± 2.7
Apgar score 1 min (median)	7	6
Apgar score 5 min (median)	9	9
Arterial lactate on admission (mmol/L)	4.4 ± 3.4	6.5 ± 4.1
Postmenstrual age at early MRI/^{1}H-MRS (median, range)	32.1 (31.1–33.7)	32.9 (31.6–33.3)
Postmenstrual age at late MRI/^{1}H-MRS (median, range)	40.6 (39.3–42.6)	41.3 (39.3–42.6)
IRDS		
Grade 1 or 2	10	3
Grade 3 or 4	1	2
PDA	6	2
NEC	1	1
Sepsis (coagulase-negative Staphylococcus)	10	8

IRDS, idiopathic respiratory distress syndrome; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis.

(TR)/echo time (TE) 512/15 ms], axial turbo spin-echo T2 (TR/TE 5912/90 ms), and inversion recovery [IR; TR/inversion time (TI)/TE 3500/950/32 ms for preterm infants or 4021/600/30 ms for term infants]; the slice thickness was 4 mm with a gap of 0.4 mm (T1- and T2-weighted images) or 0.8 mm (IR images). The MRIs were observed as described by Battin and Rutherford (24) for white matter abnormalities, cortical folding, and germinal matrix at both time points and in addition for signs of abnormal myelination of the internal capsule at term age.

^{1}H-MRS. For the ^{1}H-MRS examination, a VOI of ~4 cm^3 was placed in the basal ganglia (BG) of both hemispheres for the early examination. Both BG were included to optimize signal to noise. At term, the VOI was placed in the left BG as in our previous studies (11). A second VOI included the left periventricular white matter (PVWM; Fig. 1). Contact with the lateral ventricle and the cortex was avoided, including as much PVWM as possible to optimize signal to noise. A PRESS sequence with a TR of 2000 ms was used. The TEs were 31 and 144 ms. For the BG, 64 measurements were averaged, and for the PVWM, 128 measurements at the early examination and 64 measurements at the late examination were averaged. Total ^{1}H-MRS examination time was ~20 min for the early and 15 min for the late measurement.

NAA, creatinine, Cho, and Lac peaks were identified in the spectra obtained with a TE of 144 ms at, respectively, 2.02, 3.02, 3.24, and 1.33 ppm, whereas Glx and mI were identified at 2.10–2.25 and 3.56 ppm, respectively, using a TE of 31 ms. Lac was identified as an inverted doublet with a TE of 144 ms. Curve fitting was performed using MRUI software, including VARPRO/AMARES (EC Human Capital & Mobility/Networks program) (25). Previous knowledge included the position of the inverted doublet of Lac at 1.33 ppm, with an interpeak distance of 7 Hz. Line width was set at a maximum of 7 Hz. Previous knowledge of the Glx peak was a line width of 7 Hz. No further previous knowledge was entered. NAA/Cho, Lac/Cho (TE 144 ms) and Glx/Cho, and mI/Cho (TE 31 ms) were calculated. In case of coupled resonances (Lac), the combined area under both peaks was used for calculations. Children were examined as close as possible to 32 and 41 wk of postmenstrual age.

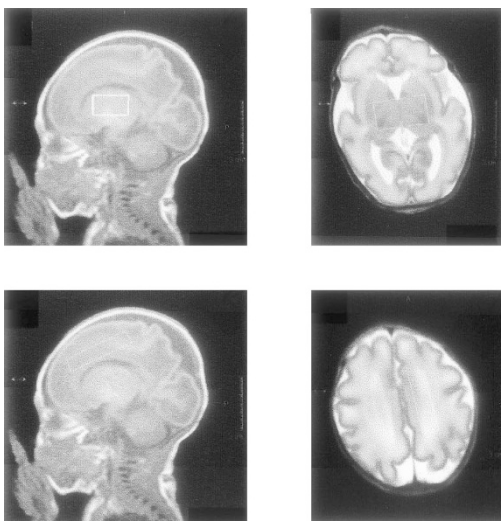

Figure 1. Location of the VOI (T1-weighted sagittal and T2-weighted axial images) at 32 wk in the area of the BG (top) and the PVWM (bottom).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 9.0 (SPSS, Chicago, IL, U.S.A.). Mann-Whitney *U* tests or *t* tests were used to compare the ratios between SGA and AGA groups at 32 and 41 wk, depending on the distribution of the data. Mann-Whitney *U* tests were performed to compare the ratios within each group at the two time points. $P < 0.05$ was considered significant. Power analysis demonstrated that with an expected 15% difference between the AGA and SGA groups in NAA/Cho or Lac/Cho ratios and an expected variation coefficient of 10%, a group size of 11 would be sufficient to demonstrate differences with $P = 0.05$ and a power of 0.90.

RESULTS

There were no significant differences between the AGA and SGA infants in clinical variables (Table 1), except for birth weight and a postmenstrual age difference of 5 d at the time of the first examination. Eleven SGA infants had a head circumference <2.3rd centile, two between the 2.3rd and 10th centiles, and one at the 25th centile. All infants were normoglycemic during examinations, and blood gas values, including base deficit, were within the normal range.

MRI. MRI was in concordance with cranial ultrasound findings and did not show major brain pathology. No differences in cerebral development (cortical folding, germinal matrix, white matter, and myelination) were observed between the SGA and AGA groups at both time points.

^{1}H-MRS. An example of spectra of the BG using TEs of both 31 and 144 ms at 32 and 41 wk is presented in Fig. 2. The NAA/Cho, Lac/Cho, mI/Cho, and Glx/Cho ratios (mean ± SD) of the BG and PVWM at 32 and 41 wk are presented in Fig. 3. No significant differences were found between the AGA and SGA groups at both time points. Effects of age were demonstrated on NAA/Cho and mI/Cho ratios: NAA/Cho increased between 32 and 41 wk, whereas mI/Cho decreased. Changes in Lac/Cho and Glx/Cho were not significant. Three of the SGA infants showed an increase in Lac/Cho, compared with none of the AGA infants. No differences were demonstrated between SGA infants with a head circumference above or below the 2.3rd centile (data not shown).

Neurodevelopmental outcome. No significant differences in DQ between the AGA (104 ± 10) and SGA (99 ± 9) infants were found at the age of 2 y. One infant in each group had a DQ below 85.

DISCUSSION

The present study compared brain metabolism of the BG and PVWM in 26 preterm AGA infants with 14 preterm SGA infants, studied at 32 and 41 wk postmenstrual age using ^{1}H-MRS. In contrast with previous observations that SGA infants, as a result of placental insufficiency, carry a high risk

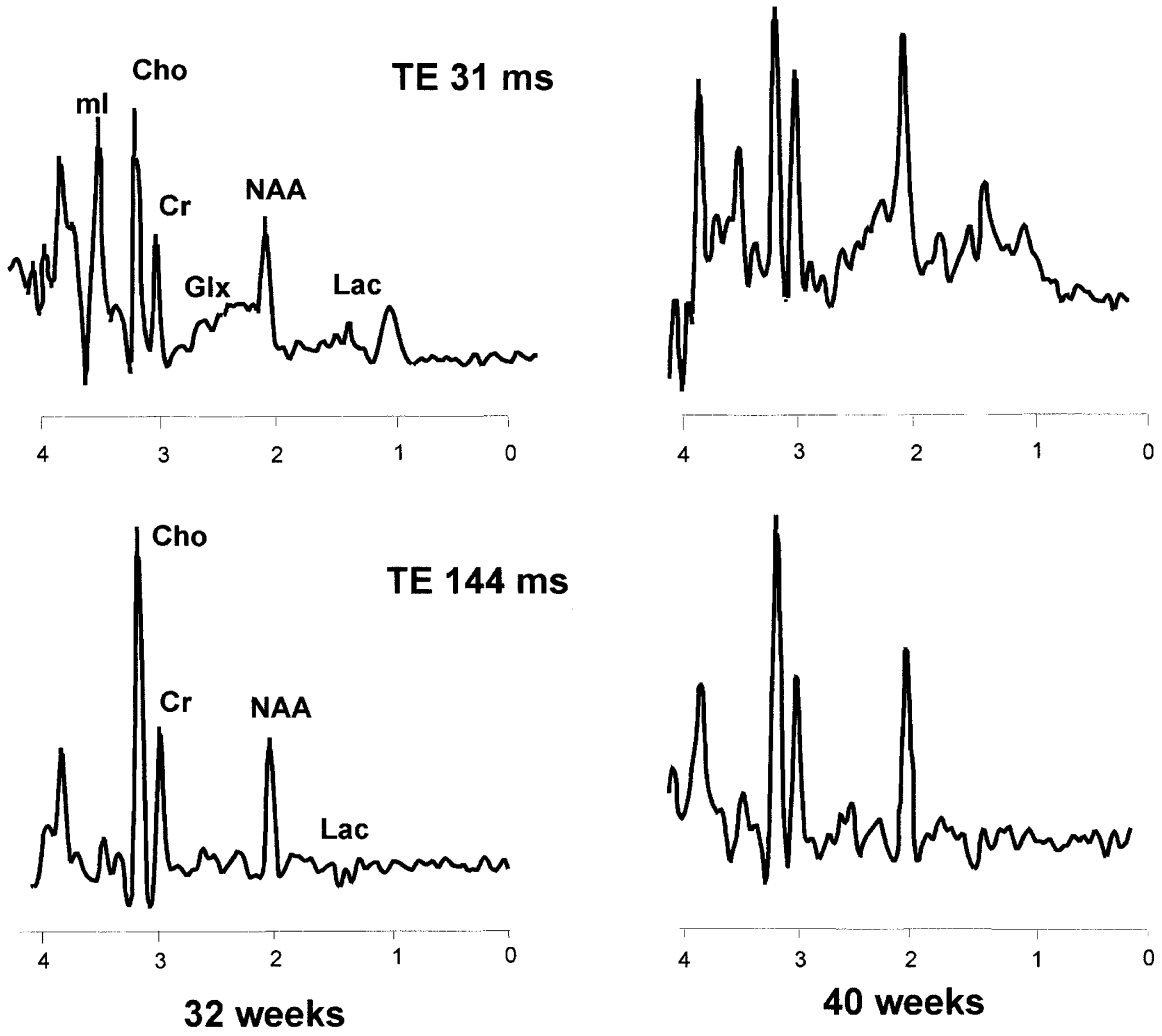

Figure 2. ^{1}H-MR spectra of an SGA infant at 32 wk (left) and 41 wk (right) using TEs of 31 (top) and 144 ms (bottom). Identified resonances are mI (3.56 ppm), Cho (3.24 ppm), creatine (Cr, 3.02 ppm), Glx (2.10 - 2.25 ppm), NAA (2.02 ppm), and Lac (1.33 ppm).

of an abnormal neuromotor development (1–4), Griffiths' DQ values in the present study at 24 mo (corrected age) did not differ between the SGA and AGA infants. Although differences in neurodevelopment might be demonstrated at a later age, the present SGA group performed just as well as the AGA group at the corrected age of 2 y. It could be that subtle changes in medical care over the last 5 y may have improved outcome of these extremely SGA neonates, which explains the difference with the aforementioned older studies (1,2). Furthermore, the neonates selected for the study had no abnormalities in the PVWM on MRI and had a gestational age of at least 25 wk and therefore may be considered a selected group of patients. Cerebral development assessed with MRI according to Battin and Rutherford (24) showed no differences between the two groups.

^{1}H-MRS findings showed that NAA/Cho ratios were not significantly different between SGA and AGA infants. The NAA signal reflects tissue concentrations of both NAA and N-acetylaspartylglutamate (NAAG). NAA has been reported to reflect the presence of neurons, oligodendroglial lineage cells, and axons in the CNS (26–28). It has been suggested that NAA(G) may be an acetyl-group carrier between mitochondria and cytoplasm in neuronal cells (29,30). A decrease of the NAA signal is usually interpreted as a reduction in the number of neurons, but it may also reflect altered function of neuronal mitochondria. The finding that no differences in NAA/Cho could be demonstrated between SGA and AGA infants seems to indicate that no differences in neuronal density or function are present between the two groups, despite fetal compromise in SGA infants. The increase of NAA/Cho ratios in cerebral tissue as a result of maturation was previously described in detail and is confirmed in the present study (14,31–34).

mI is a crucial constituent of living cells and participates in several physiologic functions. It is a major osmolyte and also serves as the precursor to phosphatidylinositol. mI has been used as a glial cell marker (13). The decrease in mI/Cho ratios between 32 and 41 wk found in the present study was described before by Kreis *et al.* (14), who suggested that the concentration of mI was associated with postnatal life rather than with gestational age. Because we did not find an effect of postnatal age on mI/Cho (data not shown), our study does not support this suggestion. The decline of mI/Cho between 32 and 41 wk might be due to the decrease in water content of the human

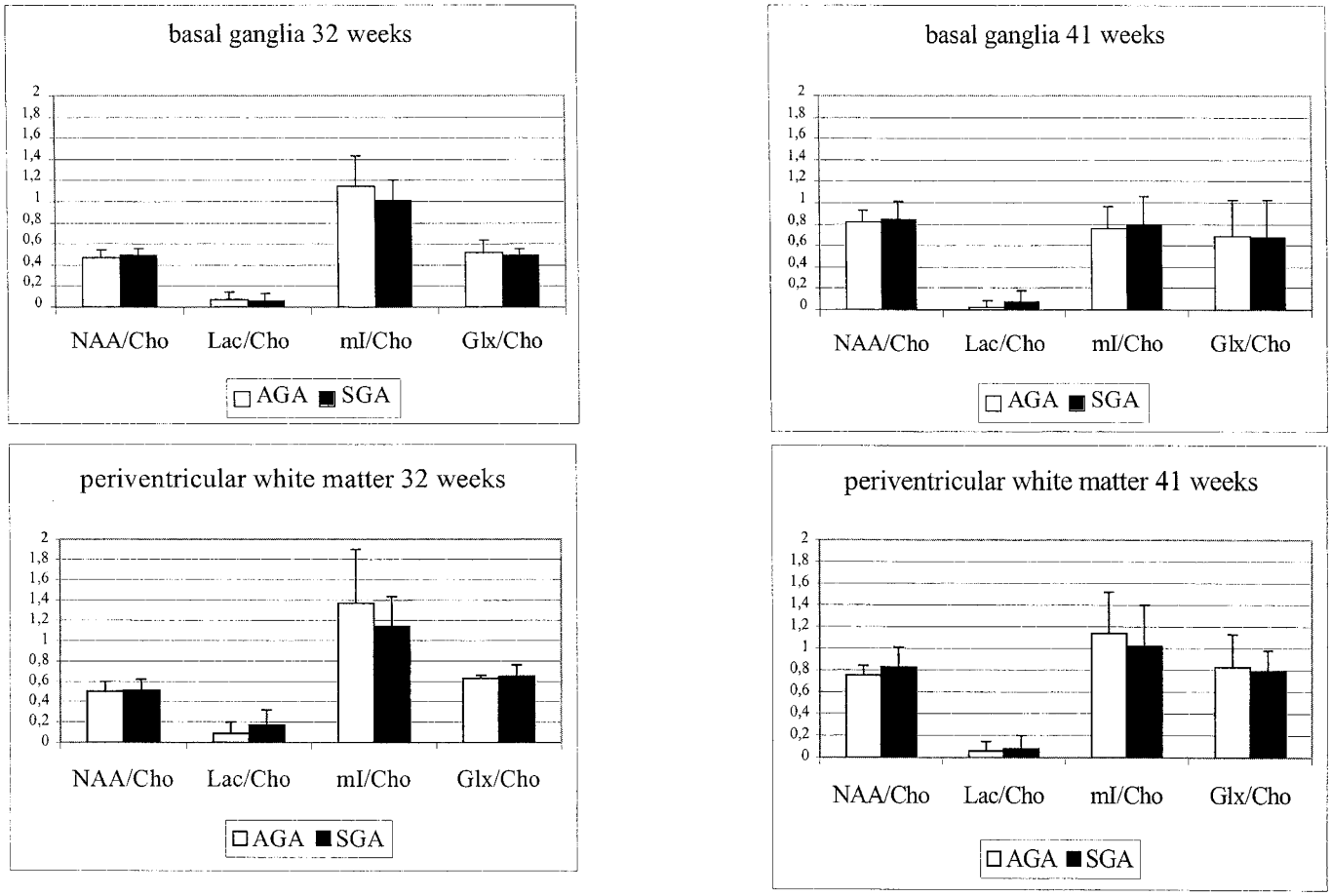

Figure 3. Ratios of different metabolites (mean ± SD) of the AGA and SGA groups in the BG and PVWM at 32 and 41 wk.

brain during this time period with accompanying changes in osmoregulation of the brain (13). No significant differences in mI/Cho ratios were found between the groups, indicating that there was no significant difference in cerebral osmoregulation.

Glx plays a major role in the cascade resulting in cellular brain injury after hypoxia-ischemia, and concentrations may be elevated if measured within the first week of postnatal life after perinatal asphyxia (17,35). Glx/Cho ratios were not elevated in the SGA infants in the present study. It is possible that Glx normalized in the 2.5 wk between birth and the first MRI examination, a period during which the infants were normoxic.

Of the 7 SGA infants who were tested longitudinally, 3 had an increase in Lac/Cho ratios between 32 and 41 wk, compared with none of the 21 AGA infants tested longitudinally. It should be realized that the relatively low Lac resonance may be a potential source of inaccurate measurements of Lac/Cho ratios. Further studies are necessary to confirm these findings. The role of Lac as a source of high-energy substrate for the preterm brain has been suggested before. Leth *et al.* (36) described the presence of Lac in 10 of 10 preterm SGA neonates and in 10 of 13 preterm AGA infants, whereas it was not detected in 7 term infants. They suggested that Lac might be produced locally or in peripheral tissues and that it may play a role in brain metabolism. Cady *et al.* (37) found a decreasing Lac concentration with increasing gestational age in the thalamus and occipital-parietal region, indicating a changing glycolytic activity in the immature brain of AGA infants. Lac may be used as fuel for the brain but also for the synthesis of myelin (38). No differences in the degree of myelination of the internal capsule between AGA and SGA groups were found in the present study, supporting the similarity of the AGA and SGA groups. Because the present study focused only on differences between the AGA and SGA groups, detailed discussion of differences in ^{1}H-MRS between the BG and PVWM, previously also reported by others (32), are beyond the scope of this article.

There are a few limitations of this study. First, the group of SGA infants is small. On the basis of the findings of the present study, a new power analysis reveals that group sizes of at least 110 would be necessary to demonstrate differences in NAA/Cho. Second, metabolite ratios were calculated, not absolute concentrations. Because measurements of absolute concentrations are often based on assumptions of the concentration of water in the brain (32), we decided to study ratios of metabolites in these neonates, who show a very rapid brain development and possibly a rapidly changing water content of the brain.

From the present study, we conclude that NAA/Cho, Lac/Cho, mI/Cho, and Glx/Cho ratios were not significantly different in SGA infants compared with AGA infants at 32 and 41 wk postmenstrual age. Effects of postmenstrual age on NAA/Cho (increase between 32 and 41 wk) and mI/Cho ratios

(decrease) could be demonstrated. Griffiths' DQ at 24 mo and cerebral maturation as assessed with MRI were not different between the SGA and AGA infants selected for the present study.

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