0031-3998/01/4903-0356
PEDIATRIC RESEARCH

Vol. 49, No. 3, 2001
Printed in U.S.A.

Value of ^{1}H-MRS Using Different Echo Times in Neonates with Cerebral Hypoxia-Ischemia

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ABSTRACT

Previous studies have shown altered brain metabolism after cerebral hypoxia-ischemia, using magnetic resonance spectroscopy with echo times (TE) of 272 and 136 ms, based on peak-area or peak-height ratios. The present study examined the additional value of proton magnetic resonance spectroscopy with a short TE (31 ms) to predict a poor outcome in neonates with brain hypoxia-ischemia. Studies were performed in 21 full-term neonates with perinatal asphyxia in a 1.5 tesla magnetic field. Proton magnetic resonance spectroscopy was performed in a single volume of interest including the basal ganglia. TE of 272, 136 and 31 ms were used. After curve-fitting procedures, peak-areas as well as peak-height ratios of different brain metabolites were calculated, comparing patients with a poor *versus* a good outcome. Seven neonates out of 21 had a poor outcome. Neonates with a poor outcome showed a significantly lower *N*-acetylaspartate/choline (NAA/Cho) and a significantly raised lactate/NAA (Lac/NAA) ratio using TE of 272 and 136 ms. Using a TE of 31 ms, no differences were found in glutamate/NAA (Glx/NAA), Glx/Cho, myo-inositol/NAA (mI/NAA), and mI/Cho ratios between neonates with a good and those with a poor outcome. Highest predictive values could be achieved for NAA/Cho with a TE of 136 ms. We conclude that low NAA/Cho and high Lac/NAA ratios predict a poor outcome in neonates with cerebral hypoxia-ischemia. TE of 272 and 136 ms have a better predictive value than a TE of 31 ms. **(*Pediatr Res* 49: 356–362, 2001)**

Abbreviations:

Cho, total choline
Cr, phosphocreatine and creatine
DQ, developmental quotient
Glx, glutamate, glutamine and GABA
^{1}H-MRS, proton magnetic resonance spectroscopy
IR, inversion recovery
Lac, lactate
mI, myo-inositol
MRI, magnetic resonance imaging
NAA, *N*-acetylaspartate
NPV, negative predictive value
PPV, positive predictive value
PRESS, point-resolved spectroscopy
TE, echo time
TI, time to inversion
TR, repetition time

Previous studies have shown changes in the cerebral metabolism of human neonates and of animals following hypoxia-ischemia (1–5). Using ^{1}H-MRS, decreases in NAA/Cho and NAA/Cr ratios were noted to predict poor neurodevelopment (1). An increased brain Lac, which, under normal circumstances, is present in only very small amounts in the neonatal brain and is hardly detectable by ^{1}H-MRS at term age, also predicts a poor outcome (3, 6). These studies used TE of 272 or 136 ms (1, 2, 4, 6). Using a TE of 272 ms, the peak at 1.33 ppm represents Lac. Using a TE of 136 ms, the Lac peak will be inverted, thereby distinguishing between Lac and lipids or macromolecules. Due to coupling effects, the amplitude of the Lac peak is expected to be smaller at TE 136 ms compared with TE 272 ms (7). Secondly, T2 values for NAA, Cho, and Cr differ (8, 9), and thereby differences in NAA/Cho or NAA/Cr ratios between good outcome and poor outcome groups might be more prominent at certain TE. In addition, T2 values may change following cerebral hypoxia-ischemia (10). Therefore, differences in metabolite ratios might be more prominent at longer TE. In fact, a recent study demonstrated a better predictive value for a long TE (270 ms) *versus* a short TE (20 ms) in occipital gray matter of young children (11).

With shorter TE, *e.g.* 30 ms, lipids and macromolecules can be identified. Especially in ischemic brain areas, these metabolites with resonances of 0.9–1.3 ppm will be elevated massively, thereby complicating the detection of lactate at 1.33 ppm (12). Elevated lipid signal in adults with stroke may result

Received November 9, 1999; accepted June 8, 2000.
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Supported by a donation (Sterproject) of the University Medical Center Utrecht, the Netherlands [A.M.R.].

from myelin breakdown. Its importance in the far less myelinated brain of the neonate is uncertain.

Animal experiments have emphasized the role of the excitotoxic amino acid Glx in causing progression of neurologic damage following brain hypoxia-ischemia (13, 14). Levels of Glx were also raised in the cerebrospinal fluid of asphyxiated human neonates, and correlated with the severity of hypoxic-ischemic encephalopathy (15). At short TE, *e.g.* 31 ms, Glx can be detected *in vivo* in cerebral tissue with ^{1}H-MRS (16, 17), but cannot be discriminated from glutamine and gamma-aminobutyric acid, which have similar resonances. A recent paper by Pu *et al.* (18) suggested that ^{1}H-MRS detectable levels of Glx were elevated in neonates with severe hypoxic-ischemic encephalopathy.

mI is a very prominent compound of neonatal spectroscopy. This molecule is thought to play a role in osmoregulation, cell nutrition, detoxification, and surfactant production and as a second messenger (8). mI is thought to be a glial cell marker (19), although this has been debated in a recent abstract (20). Brain mI levels are decreased during hepatic encephalopathy and hypoosmolarity (21). As cerebral water shifts take place in the acute phases of brain hypoxia-ischemia (22, 23), mI levels may be changed during the acute phase of brain hypoxia-ischemia. Elevated levels of mI/Cr ratios have been found in neonates with cerebral hypoxia during the first week of life (24). No changes in mI have been seen in children with chronic cerebral ischemia, suggesting relative resistance of glial cells to ischemia (25).

The present study examined the predictive value of ^{1}H-MRS with different TE in neonates with cerebral hypoxia-ischemia. Secondly, the hypothesis was tested whether Glx and mI were increased in neonates with cerebral hypoxia-ischemia and a poor neurodevelopment.

PATIENTS AND METHODS

Patients

Studies were performed in 21 full-term neonates (mean gestational age 40.5 wk) with perinatal asphyxia. Patients were diagnosed as having perinatal asphyxia when at least three of the following criteria were met: abnormal fetal heart rate patterns, need for resuscitation at birth with Apgar scores <5 at 5 min, meconium stained amniotic fluid, and pH of the umbilical artery <7.10. All infants were admitted to the Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital between 1995 and 1997. Cranial ultrasound was performed as soon as possible after admission and at least once a week until discharge. Patient characteristics are shown in Table 1.

MRI and ^{1}H-MRS studies were performed at a mean age of 8 d after birth, *i.e.* after the hypoxic-ischemic insult. MRI examinations were performed for clinical reasons, and ^{1}H-MRS was added to the scan protocol following informed parental consent. The study was approved by the Medical Ethical Committee of the Wilhelmina Children's Hospital/University Medical Center Utrecht.

The patients were transferred from the Neonatology Intensive Care Unit to the MR unit in a transport incubator. If considered necessary, the infants were sedated for the examination with a combination of i.m. pethidine (2 mg/kg body weight), chlorpromazine (0.5 mg/kg body weight), and promethazine (0.5 mg/kg body weight). Previously, we have demonstrated this to be safe and effective (1). During the MR studies, heart rate and transcutaneous oxygen saturation were monitored using standard equipment (Nonin, Minneapolis, MN, U.S.A.) as well as respiratory rate (Philips ACS-NT, Best, The Netherlands).

Table 1. *Patient characteristics*

Gestational age (wk) [mean (95% confidence interval)]	40.5 (39.9–41.1)
Birthweight (g) [mean (95% confidence interval)]	3490 (3200–3780)
Gestational age at test (wk) [mean (95% confidence interval)]	41.6 (40.8–42.4)
Male/female	14/7
Sarnat*	
1	6
2	12
3	3

* Sarnat HB, Sarnat MS 1976 Neonatal encephalopathy following fetal distress. A clincal and electroencephalographic study. Arch Neurol 33: 696–705 (ref. 25a).

The 18 surviving infants were seen in the follow-up clinic at 3, 9, 18, and 24 mo of age. Assessment of neuromotor outcome was made using items from Amiel-Tison, and Grenier and Touwen during the first year of life, and applying the Griffiths Mental Developmental Scale during the second year of life (26–28). Cerebral palsy was classified according to the criteria of Hagberg *et al.* (29). A DQ below 85 on the Griffiths scale was considered abnormal.

Methods

MRI and ^{1}H-MRS. Studies were performed in a 1.5 tesla Philips ACS-NT system (Best, Netherlands). MRI included spin echo sagittal T1 (TR/TE: 450/30 ms), and axial T2 (TR/TE: 3000/50,150 ms) and IR weighted (TR/TI/TE: 2500/800/30 ms) scans. Thereafter, one volume of interest was selected using a PRESS sequence, including the left basal ganglia. The size of the volume was dependent on the size of the basal ganglia, but was mostly $20 \times 20 \times 20$ mm^3 (anteroposterior, left-to-right, and feet-to-head directions). Contact with the periventricular white matter and the lateral ventricle was avoided. For ^{1}H-MRS, 64 signals were averaged, 512 data points, and a bandwidth of 1000 Hz were used. TR/TE were 2000/31,136,272 ms. The data were processed by applying Lorenz-Gaussian windowing in the time domain (Gaussian broadening 6 Hz, exponential narrowing 4 Hz) for noise reduction and spectral resolution enhancement, followed by zero-filling to 4096 data points.

Curve fitting was performed using MRUI software, including VARPRO/AMARES (EC Human Capital & Mobility/Networks program, Universitat Autonoma, Barcelona, Spain). Peaks were identified by the operator. Time-domain-algorithm ratios of peak areas were calculated and included NAA/Cho, NAA/Cr, and Cho/Cr, Lac/NAA (TE 272,136 ms) and Glx/NAA, Glx/Cho, Glx/Cr, mI/NAA, mI/Cho, and mI/Cr (TE 31 ms). In case of coupled resonances (Lac) the combined area under both peaks was used for calculations. (See Figure 1).

Statistical analysis. A Mann-Whitney *U* test was used to compare metabolite ratios of patients with a normal *versus* an

abnormal outcome. The correlation between peak height *versus* time-domain-algorithm peak area ratios was analyzed. Analysis was done using SPSS version 8.0 for Windows software. A p value of <0.05 was considered statistically significant.

Receiver operator characteristics (ROC) curves were calculated using MedCalc software (MedCalc Software, v4.16A, Mariakerke, Belgium) and the areas under the ROC curve were used to determine the optimum test parameters. This optimum test parameter was used as a cutoff level. PPV and NPV were calculated, based on the NAA/Cho and Lac/NAA ratio with optimum sensitivity and positivity.

RESULTS

MRI

Results of MRI and follow-up are listed in Table 2. Twelve infants showed normal development (DQ >85). Two of these infants however had an Erb's paresis. Seven newborns had a poor outcome, three of whom died. Six of these seven infants showed severe lesions of the basal ganglia. One infant with a normal MRI had a DQ <85, but no motor impairment. This child had also dysmorphic features, but no syndrome has been found so far.

In the 12 neonates with a normal development, MRI showed minor lesions in six infants. Both children with the Erb's paresis had normal MRI and a normal developmental quotient.

^{1}H-MRS

Figures 1*A* and *B* are an example of ^{1}H-MRS of an individual patient. Table 3 shows NAA/Cho, NAA/Cr, Cho/Cr, and Lac/NAA ratios using a TE of 272 ms. In Table 4, the same ratios are listed as in Table 3, but here a TE of 136 ms was used. In Figures 2 and 3, individual data of NAA/Cho and Lac/NAA ratios with TE 136 ms are presented *versus* postnatal age. NAA/Cho was significantly lower in neonates with a poor outcome compared with the patients with a good outcome. NAA/Cr was also decreased, but not significantly. Lac/NAA ratios were significantly higher in children with a poor outcome. Using a TE of 31 ms, NAA/Cho and Lac/NAA ratios did not differ significantly between the groups with a good or a poor outcome.

Glx and mI ratios are listed in Table 5, using a TE of 31 ms. Individual data *versus* postnatal age are presented in Figures 4 and 5. Glx ratios of 11 infants with normal follow-up were compared with 6 newborns with abnormal follow-up. Glx ratios appeared to be higher in children who died or had a poor neurodevelopment, but none of these ratios were significantly higher in these patients. Increased ratios of mI/NAA and mI/Cho were found, but none of these differed significantly.

Table 6 shows the areas under the ROC curves and predictive values for TE 272 and 136 ms. The areas under the ROC curves of both TE did not differ significantly. Using a TE of 272 ms, the PPV of NAA/Cho was higher than using a TE of 136 ms, using a cutoff value of 0.79 for a TE of 272 ms and 0.62 for a TE of 136 ms. The PPV for Lac/NAA was equal for both TE, using cutoff values of 0.44 for a TE of 272 ms and 0.09 for a TE of 136 ms. The NPV of NAA/Cho was higher using a TE of 136 ms, and almost equal for Lac/NAA.

PPV and NPV of Glx and mI ratios were not calculated because no significant differences were found between patients with a poor *versus* a good outcome.

Table 2. *Sarnat, MRI, and follow-up*

Patient	Sarnat	Age at MRI (d)	MRI	Follow-up	DQ	Age at DQ (mo)
1	1	1	Normal	Erb's paresis	x	
2	1	1	Signal change BG	Normal	x	
3	1	1	Normal	Normal	95	12*
4	1	4	Normal	Erb's paresis	91	26
5	1	3	Normal	Mental retardation	70	25
6	1	30	Small thalamic lesion	Normal	104	16*
7	2	8	Normal	Normal	97	15.5*
8	2	4	Normal	Normal	96	22
9	2	13	Normal	Normal	88	23
10	2	13	Small PV hemorrhage	Normal	90	17.5*
11	2	2	Normal	Normal	102	18*
12	2	6	Motion artefacts	Athetoid CP	84	23.5
13	2	14	Abn signal BG/PLIC	Athetoid CP	76	24
14	2	9	Abn signal putamen	Normal	95	11.5
15	2	10	↑↑ Signal intensity T2; petechial hemorrhages	Normal	114	18*
16	2	11	VD, small abn signal thalamus	Normal	120	18*
17	2	3	Normal	Normal	111	24.5
18	2	7	Abn signal BG/PLIC	Quadriplegia, CVI	x	15
19	3	1	Abn PLIC, cortical highlighting	Died	x	
20	3	2	Abn thalamus	Died	x	
21	3	3	Abn BG + ↑↑ signal intensity T2	Died	x	

Patients 1 and 2 not seen at our outpatient clinic; patient 18 had a severe quadriplegia; patients 19, 20, and 21 died. *VD*, ventricular dilatation; *abn*, abnormal; *PLIC*, posterior limb of the internal capsule; *CP*, cerebral palsy; *PV*, periventricular; *occ*, occipital; *BG*, basal ganglia; ↑↑, increased; *CVI*, cortical visual impairment; *x*, no (*DQ*) calculated.

* No further follow-up visits because of normal development.

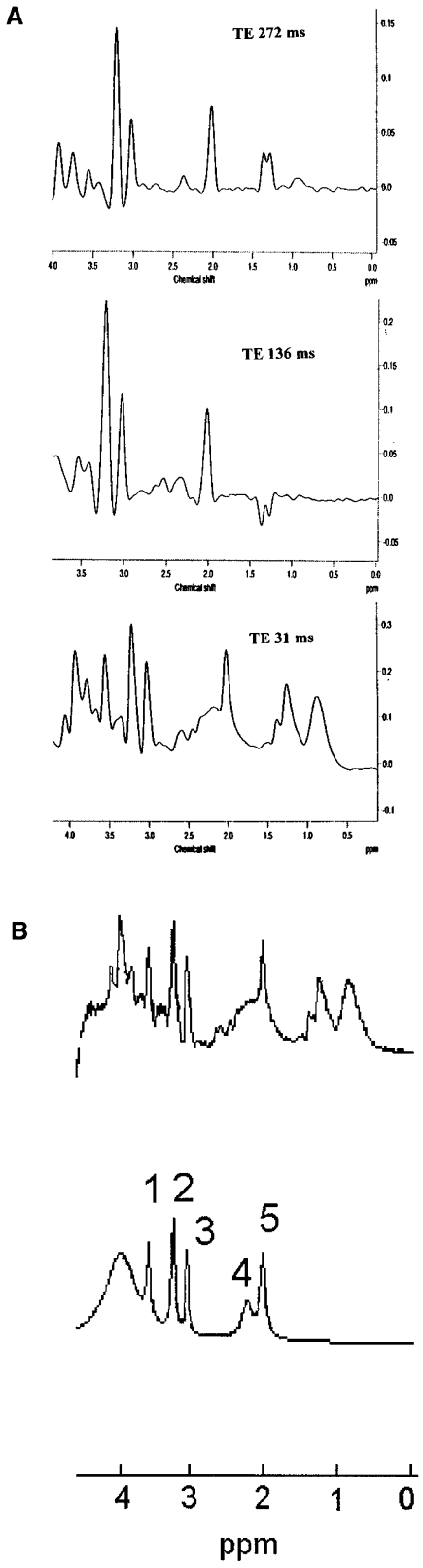

Figure 1. (*A*) Proton MR spectra from the brain of a neonate following severe asphyxia (case 18). Using TE of 136 and 272 ms, a prominent Lac doublet is demonstrated at 1.33 ppm. Using a TE of 31 ms, Glx is shown at 2.0–2.3 ppm and mI at 3.5–3.6 ppm. (*B*) Proton MR spectra from case 13, using a TE of 31 ms (*top*). Using curve fitting, five peaks were identified for further calculations (*bottom*). *1*: mI; *2*: Cho; *3*: Cr; *4*: Glx; *5*: NAA. Resonances at 0.8–1.3 ppm were not fitted deliberately, as they contained a major contribution from mobile lipids and macromolecules.

DISCUSSION

The aim of our study was to examine the prognostic value of an adverse outcome of different TE in neonates with cerebral hypoxia-ischemia. In children with a good *versus* a poor outcome, the NAA/Cho, NAA/Cr, Lac/NAA, Glx/NAA, and mI/NAA ratios were compared using TE of 272, 136, and 31 ms. Our results showed that for TE of 272 and 136, NAA/Cho was significantly decreased in children with a poor outcome compared with patients with a normal neurodevelopment. NAA/Cho and NAA/Cr ratios obtained at a TE of 31 ms showed too wide a range to be used for prediction. Recently, this has also been observed by others (11). Lac/NAA was raised in children with a poor outcome at TE of 272 ms and 136 ms. Glx and mI ratios were not altered. The predictive value of TE 136 ms was slightly better than using a TE of 272 ms. Differences in T2 values of metabolites and the effects of brain hypoxia-ischemia on these T2 values might change metabolite ratios (9, 10). Therefore, differences in ratios between neonates with a good or a poor outcome may be more prominent at certain TE.

Although NAA appears to be present in precursors of oligodendrocytes (30, 31), NAA is still considered a neuronal marker, whereas Cho and Cr are present in all types of cells (30). In accordance with previous studies (1, 4, 32–34), we found decreased NAA/Cho ratios for TE of 272 and 136 ms, indicating a more severe neuronal loss in the children with an abnormal follow-up. In newborns with a poor outcome, the NAA/Cr tended to be decreased, but differences were not significant. Although others have described a decrease in Cr simultaneous with the decrease in NAA (35), this is unlikely in our study, as Cho/Cr ranges did not change at all. Others have described persisting decreases of NAA/Cr in neonates following perinatal brain hypoxia-ischemia (36). Lac is produced in the acute stage as an end product of the anaerobic glycolysis. Following resuscitation, it decreases, but due to the secondary energy failure it increases again after 24 h (5, 37). Elevated Lac levels have been shown until months after the hypoxia-ischemia, probably due to an influx of Lac-producing macrophages in the damaged tissue or an altered redox state (36, 38, 39). Lac/NAA was significantly elevated in the group with abnormal outcome, as in previous reports (1, 6, 32, 40, 41). Only three neonates were examined during the first day of life, so most of the Lac found is probably due to secondary energy failure and influx of macrophages (42).

Amplitude of the area under the Lac peak was higher at TE 272 ms compared with TE 136 ms. This may be caused by coupling effects at TE 136 ms (7), causing signal loss at TE 136 ms. Introduction of a correction factor would be justified on a theoretical basis. However, we did not do so because it would affect Lac/NAA ratios similarly in both good and poor outcome groups, and therefore would not influence further statistical analysis. Although the ROC curve for Lac/NAA had a larger area under the curve at TE 272 ms than at TE 136 ms, the PPV and NPV were not affected by this loss of signal.

Glx is an important neurotransmitter in the cascade leading to neuronal cell damage following hypoxia-ischemia (43). It activates postsynaptic receptors resulting in opening of the

Table 3. *Metabolite ratios at TE 272*

Outcome	NAA/Cho mean (95% CI)	NAA/Cr mean (95% CI)	Cho/Cr mean (95% CI)	Lac/NAA mean (95% CI)
Good	0.87 (0.80–0.95)	1.67 (1.46–1.89)	1.96 (1.62–2.29)	0.35 (0.27–0.44)
Poor	0.71* (0.58–0.84)	1.41 (1.14–1.68)	2.00 (1.74–2.26)	1.01* (0.31–1.72)

* $p < 0.05$; *95% CI*, 95% confidence interval.

Table 4. *Metabolite ratios at TE 136*

Outcome	NAA/Cho mean (95% CI)	NAA/Cr mean (95% CI)	Cho/Cr mean (95% CI)	Lac/NAA mean (95% CI)
Good	0.71 (0.65–0.76)	1.42 (1.11 –1.73)	2.01 (1.58 –2.44)	0.10 (0.03 –0.17)
Poor	0.55* (0.42–0.69)	1.14 (0.93 –1.35)	2.18 (1.36 –3.00)	0.89* (−0.44 –2.23)

* $p < 0.05$; *95% CI*, 95% confidence interval.

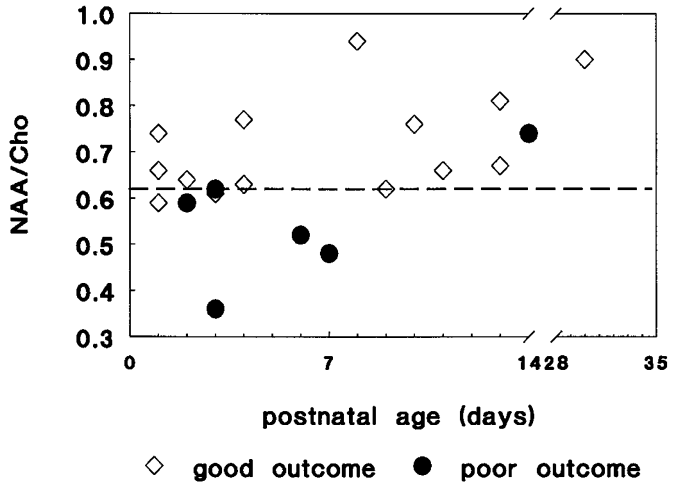

Figure 2. NAA/Cho ratios of individual patients, obtained with TE 136 ms, *vs* postnatal age. The *dotted line* indicates the cutoff value (0.62) as obtained through ROC analysis.

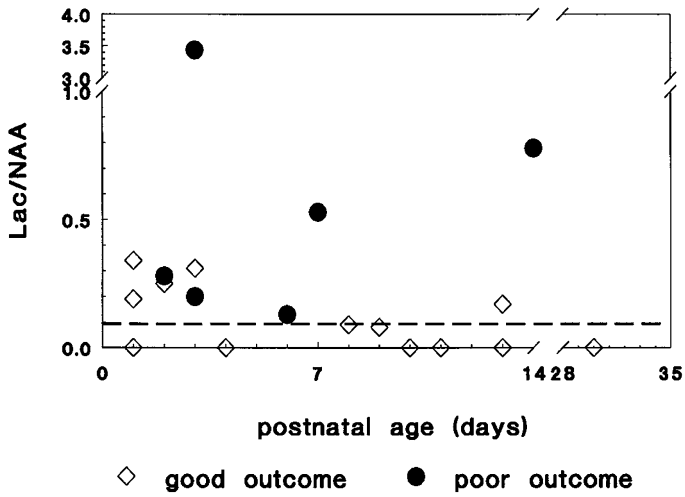

Figure 3. Lac/NAA ratios of individual patients, obtained with TE 136 ms, *vs* postnatal age. The *dotted line* indicates the cutoff value (0.09) as obtained through ROC analysis.

Table 5. *Metabolite ratios at a TE 31 ms*

Outcome	Glx/NAA mean (95% CI)	Glx/Ch mean (95% CI)	Glx/Cr mean (95% CI)	mI/NAA mean (95% CI)	mI/Cho mean (95% CI)	mI/Cr mean (95% CI)
Good	0.96 (0.79–1.13)	1.27 (0.95–1.58)	3.53 (1.97–5.08)	1.28 (1.00–1.56)	1.65 (1.14–2.17)	4.55 (2.57–6.54)
Poor	1.28 (0.51–2.04)	1.34 (0.53–2.15)	5.14 (−2.10–12.38)	2.05 (0.14–3.97)	1.93 (0.58–3.28)	4.86 (1.35–8.38)

95% CI, 95% confidence interval.

Ca^{2+} channels (44, 45). Calcium plays a crucial role in the formation of oxygen free radicals and neuronal damage (46, 47). Ischemia decreases the availability of glucose. During ischemia, glutamine is also used as an alternative substrate to glucose for neuronal cells, and Glx and GABA for the glial compartment (48). In our study, Glx ratios tended to be elevated in patients with a poor neurodevelopment, but were not significantly higher when compared with patients with a normal follow-up. Also, in cerebral fluid of newborn infants with hypoxic-ischemic encephalopathy, Glx levels were only elevated during the first two days of life (15). This is also the period when patients with hypoxic-ischemic encephalopathy may show severe seizures. Our patients were examined at a mean postnatal age of 8 d (range 1–30 d), which may be too late to detect a significantly raised amount of Glx. It is possible that Glx levels had decreased due to normalization of Glx uptake and synthesis after a period of hypoxia. Another explanation may be that it is used as alternative fuel for neuronal and glial cells during the ischemia. Thirdly, Glx is excreted outside the cell so Glx levels are raised in the extracellular space (49), whereas MRS detects mainly intracellular metabolites. Pu *et al.* (18) reported raised peaks of α-glutamate at 3.75 ppm, using a

TE of 135 ms. However, these α-Glx resonances in their publication are very small. In our experience, the α-Glx peak at a TE of 136 ms was too small for reliable curve fitting.

mI levels are high after birth, followed by a rapid fall during the first year of life (8). It is a precursor of the inositol phosphates, which are active in releasing Ca^{2+} (50). They also act as osmoregulators in astrocytes (19, 51), and in addition, they may act as a storage pool for glucose (50). During recovery of hypoxia-ischemia it is raised (52).

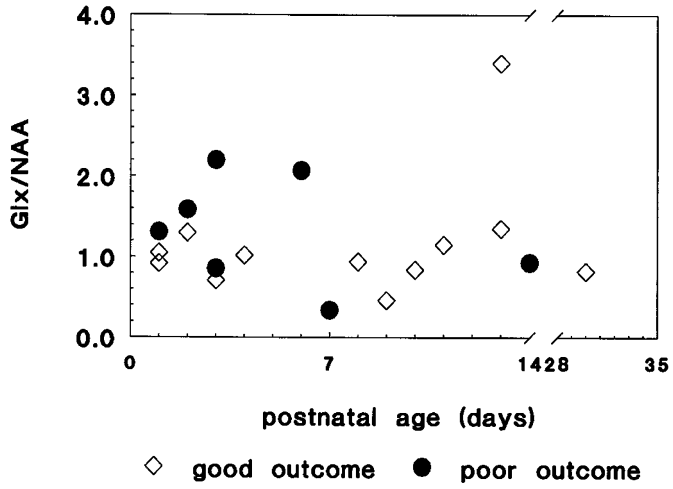

Figure 4. Glx/NAA ratios of individual patients, obtained with TE 31 ms, *vs* postnatal age.

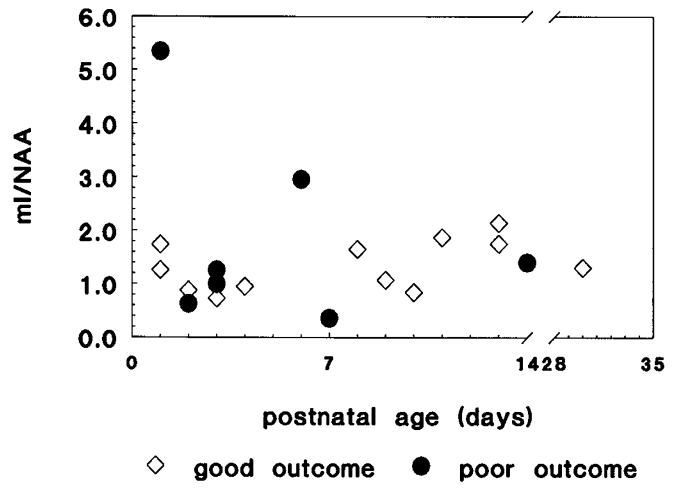

Figure 5. mI/NAA ratios of individual patients, obtained with TE 31 ms, *vs* postnatal age.

Levels of mI/NAA, mI/Cho, and mI/Cr were not significantly different between the good and poor outcome groups. This may be due to the fact that most of our patients were examined a few days after the acute period of hypoxia-ischemia. At that time, initial changes in brain osmolarity and thereby changes in levels of mI may have subsided at the time of MRS.

It would be preferable for all metabolites to use absolute concentrations instead of metabolite ratios. However, this would include T1 and T2 measurements in all individual patients. As measuring time is limited in these neonates to approximately 1 h, absolute concentrations could not be measured.

Predictive values of ^{1}H-MRS using a TE of 136 ms are good and comparable with those of cerebral function monitor (CFM) (PPV 86%, NPV 91%) (53) and somatosensory evoked potentials (PPV 82%, NPV 92%) at an age of 6 h (54). At the end of the first week, CFM and evoked potentials normalize in most asphyxiated patients, even if they will develop a neurodevelopmental delay. This is in contrast with ^{1}H-MRS, which is predictive at an early time point after perinatal asphyxia (55), and retains its prognostic value throughout the first month after hypoxia-ischemia.

Peak-height ratios and time-domain algorithms producing peak-area ratios correlated well (Pearson correlation 0.915, $p < 0.001$, data not shown). Both peak-height as well as time-domain algorithms can therefore be used for prognostic ends (1). As reference values are dependent on the hardware and software used, local reference values need to be acquired for prognostic purposes.

We conclude that low NAA/Cho and elevated Lac/NAA ratios during the first month of life predict a poor outcome after perinatal hypoxia-ischemia. Predictive values of ^{1}H-MRS are comparable with neurophysiological examinations, but ^{1}H-MRS can be performed at a later time point after the hypoxic-ischemic moment without a decrease of its predictive values. Glx/NAA and mI/NAA ratios do not significantly differ between children with a good or poor outcome and therefore a TE of 31 ms has no additional predictive value in neonates tested at a mean posthypoxia age of 8 d. For prognostic purposes, ^{1}H-MRS with a TE of 136 ms has slight advantages over a TE of 272 ms.

Acknowledgments. The authors thank Marco Nijenhuis and all other technicians of the MR institute for their enthusiastic cooperation.

Table 6. *Area under ROC curves, PPV, and NPV for TE 272 and 136 ms*

	NAA/Cho			Lac/NAA		
TE	Area under ROC curve (95% CI)	PPV (%)	NPV (%)	Area under ROC curve (95% CI)	PPV (%)	NPV (%)
272	0.86 (0.64–0.97)	91	61	0.89 (0.66–0.98)	89	75
136	0.90 (0.68–0.98)	85	100	0.67 (0.42–0.86)	89	72

95% CI, 95% confidence interval.

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