PROTON MAGNETIC RESONANCE SPECTROSCOPY IN THE EVALUATION OF CHILDREN WITH CONGENITAL HEART DISEASE AND ACUTE CENTRAL NERVOUS SYSTEM INJURY

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We studied nine infants and children, aged 1 week to 42 months, with severe acute central nervous system injuries associated with cardiac disease or corrective operations by means of single-voxel proton magnetic resonance spectroscopy to determine whether this technique would be useful in predicting neurologic outcome. Proton magnetic resonance spectroscopic data were acquired from the occipital gray and parietal white matter (8 cm³ volume, stimulated echo-acquisition mode sequence with echo time of 20 msec and repetition time of 3.0 seconds) a median of 9 days after operation (range 3 to 42 days). Data were expressed as ratios of areas under metabolite peaks, including *N*-acetylaspartate and *N*-acetyl compounds, choline-containing compounds, creatine and phosphocreatine, and lactate. Four patients had cerebral insults before operation, one had both a preoperative and a perioperative insult, three had perioperative insults, and one had a prolonged cardiac arrest 2 days after operation. Outcomes (Glasgow Outcome Scale scores) were assigned at discharge and 6 to 12 months after injury. Six patients were in a vegetative state or had severe impairment at discharge, and two still had severe impairment at 6- to 12-month follow-up. Proton magnetic resonance spectroscopy showed lactate in these two patients, along with markedly reduced ratios of *N*-acetyl compounds to creatine compounds. The other four patients with severe impairment recovered to a level of mild disability at follow-up. Proton magnetic resonance spectroscopy showed no lactate in these four patients; however, one patient showed moderately reduced ratio of *N*-acetyl compounds to creatine compounds. The three patients who had mild or moderate impairment at discharge showed no lactate and mild or no changes in metabolite ratios; follow-up revealed normal or mild outcomes. Overall, we found that the presence of lactate and markedly reduced ratios of *N*-acetyl compounds to creatine compounds were predictive of severe outcomes at discharge and long-term follow-up, whereas no lactate and mild or no changes in ratios suggested potential for recovery with at least a mild disability. Continuing investigations are in progress to determine the optimal selection of candidates and timing of proton magnetic resonance spectroscopic studies. (J Thorac Cardiovasc Surg 1996;112:403-14)

Of the approximately 10,000 children who annually undergo heart operations, as many as 25% have some form of neurologic morbidity.¹⁻³ Although

many of these insults are caused by perioperative cerebral injury, it is also clear that in a significant number of patients either preoperative cerebral ischemia or subtle developmental central nervous system (CNS) malformations contribute to or are responsible for poor neurodevelopmental outcomes. Perioperative cerebral monitoring, particularly with newer techniques such as near-infrared spectroscopy and transcranial Doppler ultrasonography, offers methods to reduce the prevalence of such insults.⁴⁻⁶ For those infants who do have cerebral injury, however, neurologic evaluation to predict outcome is limited by the lack of specific neurodiagnostic methods.

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Table I. Clinical and CPB data in nine patients with CNS injury

Patient no.	Age at scan (mo)	Cardiac lesion	Etiology of insult	GCS and preoperative neurologic examination
1	0.25	Cardiomyopathy	54 days before operation, out-of-hospital cardiac arrest	3; markedly abnormal, spastic and jittery, no response to pain
2	0.25	Interrupted aortic arch	18 days before operation, prolonged cardiac arrest	12; mildly abnormal, hypotonic with sluggish pupils
3	0.5	Interrupted aortic arch	2 days before operation, cardiac and respiratory failure	15; mildly abnormal, focal seizures during exam
4	1.25	Interrupted aortic arch	Preoperative and perioperative, severe hypoperfusion before operation, divided TCA time increased	3; moderately abnormal, decreased tone, lethargic
5	1	Hypoplastic left heart	Perioperative, intraoperative ventricular fibrillation with open cardiac massage	12; mildly abnormal, generalized hypotonia
6	10	Atrioventricular canal	Perioperative, not determinable	12; mildly abnormal, generalized hypotonia
7	14	Tetralogy of Fallot	Perioperative, four periods of TCA totaling 69 min, low-flow CPB of 102 min	15; normal
8	42	Aortic stenosis	Perioperative, not determinable, Williams syndrome	15; mildly abnormal, developmental delay, hypotonia
9	20	Right ventricular out-flow obstruction	Postoperative, late cardiac tamponade and arrest	15; normal

GCS, Glasgow Coma Scale score; *Te*, esophageal temperature; *Tc*, core temperature; *Unc*, duration of unconsciousness at scan; *hosp*, duration of hospitalization; *N/A*, not applicable.

*For cases 4, 7, and 8, total period of TCA is given with individual periods in parentheses.

We recently showed that single-voxel proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) is useful in predicting outcome in children with serious acute CNS insults.⁷ The ratios of *N*-acetyl compounds (NA), primarily *N*-acetylaspartate, to creatine compounds (Cr), creatine and its precursor phosphocreatine, were significantly lower in patients with poor neurologic outcomes than in patients who had good or moderate recoveries. Moreover, we observed that cerebral lactate was present in most patients with poor but not good outcomes. Our findings suggested that $^1\text{H-MRS}$ might be useful in assessing the prognoses of children with serious neurologic findings associated with cardiac disease or operation. During the past 1½ years, we have evaluated nine such cases. This study reviews data from these cases and discusses the potential use of $^1\text{H-MRS}$ in this clinical situation.

Methods

Patient selection and data collection. Between January 1994 and June 1995, a total of 13,646 infants and children were admitted to Loma Linda University Children's Hospital. Of these, 466 underwent corrective or palliative cardiovascular operations, with an overall survival rate of 95%. Of these survivors, nine had severe CNS insults and were selected to undergo $^1\text{H-MRS}$. Investigation of these

nine patients was approved by the Institutional Review Board of Loma Linda University Medical Center and Children's Hospital. Patient data collected included age, cardiac defect, preoperative and perioperative monitoring variables, preoperative and postoperative neurologic examination findings, and results of postoperative electroencephalography, magnetic resonance imaging (MRI) scans, and $^1\text{H-MRS}$ scans (Tables I and II). The time that the patient had remained in a coma or vegetative state before being scanned or the time that the patient had regained consciousness before being scanned and the duration of hospitalization were also recorded.

Neurologic outcome was assigned according to the Glasgow Outcome Scale score at discharge from the hospital and at follow-up.⁷ Follow-up neurologic examinations were done or scheduled at 6 to 12 months after injury. The Glasgow Outcome Scale score includes the following outcomes: (1) good outcome (resume all activities); (2) mild disability (minor, almost undetectable alteration in function, no assistance required); (3) moderate disability (neurologic deficit, requiring assistance but remaining independent); (4) severe disability (incapable of resuming most activities, limited communication skills and partial or total dependence on others); (5) persistent vegetative state; and (6) death.

$^1\text{H-MRS}$ technique. MRI and $^1\text{H-MRS}$ were performed with a Magnetom SP4000 1.5T whole-body imaging system (Siemens Medical Corp., Iselin, N.J.). After informed consent had been obtained and patients were in a medically stable condition, patients were transported to the MRI scanner and monitored as previously described.⁷

Preoperative ABG (pH/BE)	TCA* (min)	Low-flow (min)	CPB (min)	Temperature °C (Te/Tc)	Cool/rewarm (min)	Unc/hosp (days)
6.93/−14.7	20	32	140	16.6/19.3	19/69	7/28
6.80/−28.0	24	74	160	16.9/19.8	19/67	0/7
6.98/−24.0	NA	NA	No CPB	34.9/—	NA	0/34
7.24/−8.0	102 (27 + 22 + 5 + 48)	123	329	15/19	47/51	5/22
7.42/−5.7	52	0	86	16.8/NA	26/60	8/65
7.41/−4.0	NA	0	100	20.1/24.1	52/48	4/42
7.34/−8.2	69 (9 + 20 + 17 + 23)	102	162	15.9/20.1	12/48	0/30
7.42/−5.0	37 (20 + 17)	19	84	15/20.2	10/55	8/35
7.18/−2.1	38	24	124	19.9/22.6	43/43	5/95

Routine T1- and T2-weighted spin echo images in the transverse, coronal, and sagittal planes were obtained with a circularly polarized head coil and used for localization of the volumes of spectroscopic interest. All spectra were acquired by means of water-suppressed ^1H -MRS with a stimulated echo acquisition mode sequence with the following parameters: echo time, 20 msec; repetition time, 3.0 seconds; middle interval time, 30 msec; and number of acquisitions, 128. After localized shimming, the first proton spectrum was acquired in an 8 cm^3 volume of interest placed in occipital gray matter, followed by a second (7 to 9 cm^3) spectroscopic acquisition in parietal white matter. Food and Drug Administration–approved stimulated echo acquisition mode sequences were supplied in the ^1H -MRS software package (Numaris 2.3; Siemens) on the whole-body scanner used for the study. Total study time averaged 60 minutes.

Metabolites measured with ^1H -MRS include NA (neuronal markers), Cr (bioenergetic metabolites), Ch (choline-containing compounds including free choline, phosphoryl choline, and glycerophosphoryl choline, which are released during membrane disruption), lactate (which accumulates in response to tissue damage and associated anaerobic metabolism), glx (glutamate and immediately formed glutamine), and mI (myoinositol).⁸ Spectral post-processing included zero filling to 4K, apodization (0.8 Hz Gauss broadening), Fourier transformation, and manual zero-order phasing. No baseline correction or automatic curve-fitting routines were applied to spectra. The area under each metabolite peak was calculated by the manual placement of cursors delineating the boundaries for each peak. The software integration routine supplied with the imager then provided the area under the curve within each of those peak boundaries. Peak area metabolite

ratios (NA/Cr, NA/Ch, and Ch/Cr) were then manually calculated for each spectrum. All measurements were taken by the same operator to maintain constancy and reproducibility. The operator also carefully excluded signals from glutamate, glutamine, and γ -aminobutyric acid resonances, which occur around 2.0 ppm and add to the NA peak area when short echo time sequences are used. Peak areas were not corrected for T1 and T2 relaxation time effects because quantitation was not attempted in this study. The presence of lactate was determined by identifying a characteristic peak doublet with 7 Hz splitting at 1.3 ppm relative to NA on the ^1H -MRS spectrum. Overlying lipid and protein resonances often observed with short echo time sequences can complicate the analysis of lactate; however, the operator interpreted lactate to be present only if the signal-to-noise ratio was sufficient and splitting of the doublet could be measured, as seen in Fig. 1.

Interpretation of the ^1H -MRS spectra was done immediately after processing by comparison with normal age-matched control spectra. Visual inspection of the spectra, in conjunction with review of the metabolite ratio data and comparison with age-matched control data, is necessary to accurately interpret the data. Metabolite peaks undergo dramatic changes in the first 2 to 3 years after birth,^{9–12} and the ability to compare a patient's spectrum with normal control spectra is critical to interpretation. Metabolite ratios can also be misleading, because they do not necessarily reflect decreases in the absolute metabolite concentrations. Because of the difficulties in quantitating in vivo metabolites, ratios have been used to describe changes seen in ^1H -MRS spectra. Ratios reflect changes in two metabolites, so if both metabolites increase or decrease by the same amount, the ratio remains

Table II. MRI, ¹H-MRS, and outcome data for nine patients with CNS injury

Patient No.	MRI scan (days to study*)	Occipital				Parietal			
		NA/Cr	NA/Ch	Ch/Cr	Lac	NA/Cr	NA/Ch	Ch/Cr	Lac
1	Cerebral edema (5)	0.89	0.64	1.39	Lac -	0.65	0.50	1.31	Lac -
2	Cerebral edema (3)	NS	NS	NS	NS	0.84	0.66	1.28	Lac -
3	Cerebral edema (17)	0.54	0.50	1.09	Lac -	1.05	0.71	1.47	Lac -
4	Left occipital hemorrhage (42)	0.81	1.02	0.80	Lac -	0.70	0.98	0.72	Lac -
5	Occipital petechial hemorrhage (9)	NS	NS	NS	NS	0.49	0.28	1.78	Lac +
6	Basal ganglia and watershed infarct (12)	1.08	1.94	0.56	Lac -	1.12	1.92	0.59	Lac -
7	Diffuse atrophy (16)	NS	NS	NS	NS	0.71	0.87	0.82	Lac -
8	Basal ganglia and cerebellar infarct (9)	NS	NS	NS	NS	0.95	1.00	0.95	Lac -
9	Diffuse ischemic insult (13)	0.50	0.32	1.55	Lac +	0.31	0.23	1.32	Lac +

Lac, Lactate; NS, spectrum not satisfactory (insufficient quality to obtain data).

*From time of insult to ¹H-MRS scan.

†¹H-MRS data compared with age-matched control data.

normal. Even with these potential problems, we have found that patients who had metabolite ratios reduced more than 1 to 2 standard deviations below the mean of those patients with good or moderate outcomes were likely to have a poor outcome.⁷

More recently, with a linear discriminant analysis of a larger series of 94 children, we confirmed our original findings that a reduced NA/Cr ratio and the presence of lactate were most predictive of a poor outcome.^{7,13} The interpretation of our spectra, emphasizing the change in these two variables, is reported in Table II. A spectrum was considered to predict a poor outcome if lactate was detected and a more than 30% decrease in NA/Cr ratio was seen. The percentage decreases from normal values reported in Table II were determined by comparison with normal values reported in the literature¹⁰ and with normative data collected at our own institution from eight control patients with no CNS injury and 15 additional patients with mild CNS injuries for whom results of neurologic examination were normal.

Bypass and profound hypothermia circulatory arrest methods. The operative and cardiopulmonary bypass (CPB) records were reviewed, and the data are summarized in Table I. Eight of the nine patients determined after operation to have neurologic injuries required CPB assistance during their initial surgical intervention. Profound hypothermia with periods of total circulatory arrest (TCA) was used in seven cases.

While the patient was anesthetized with fentanyl, isoflurane, or both and after anticoagulation with heparin, extracorporeal circulation was established with nonpulsatile perfusion and a membrane oxygenator, as previously described elsewhere.¹⁴ Perfusate consisted of a balanced crystalloid solution supplemented with 25% serum albumin to normalize oncotic pressure. A 25 μ m arterial filter and an in-line monitor of arterial and venous blood gases

(CDI 400) were included in the CPB circuit. Surface cooling was accomplished with a cooling blanket and ice packs on the head. The CPB perfusate temperature was reduced until the core temperature was approximately 18° C, permitting the use of one or more periods of TCA. Blood gas management during CPB was directed at maintaining a pH of 7.40 and an arterial carbon dioxide tension of 35 to 40 mm Hg, uncorrected for body temperature (alpha-stat). Arterial oxygen tension was maintained at greater than 120 mm Hg. CPB flow was established at a rate of approximately 100 ml $\times$ kg⁻¹ $\times$ min⁻¹ and was reduced to approximately 25 to 50 ml $\times$ kg⁻¹ $\times$ min⁻¹ during profound hypothermia. Cooling and rewarming times are listed in Table I. During rewarming, packed erythrocytes were gradually added to the CPB circuit to produce a hematocrit of approximately 30% at 37° C.

Results

Clinical, CPB, and ¹H-MRS data from the nine patients are presented in Tables I and II. The median age of the nine patients was 1.25 months (range 0.25 to 42 months). The median time after CNS insult until ¹H-MRS scan was done was 9 days (range 3 to 42 days). Interpretation of the spectroscopic findings and the discharge and late (6 to 12 months after operation) outcomes of these patients are also included in the table.

Clinical data

Patients in a vegetative state or with severe impairment at discharge. Six patients were considered to be in a vegetative state or to have severe neurologic impairment before or after operation and at dis-

<i>Interpretation of ¹H-MRS data†</i>	<i>Discharge outcome</i>	<i>6- 12-month outcome</i>
Normal spectra, normal NA/Cr ratios, no Lac detected; suggests good outcome	Severe	Normal
Normal spectrum, normal NA/Cr ratio; no Lac detected, peaks around 1.10 ppm are amino acids/proteins; suggests good outcome	Moderate	Mild
Normal spectrum in gray matter, 30% reduction of NA/Cr in white matter only, no Lac detected; suggests good outcome	Mild	Normal
Normal spectra, normal NA/Cr ratios, no Lac detected (however, study was done late after insult); suggests good outcome	Severe	Mild
Very abnormal spectrum, 50% reduction in NA/Cr, Lac detected; suggests poor outcome	Severe	Severe
Normal spectra, normal NA/Cr ratios, no Lac detected; suggests good outcome	Vegetative state	Mild
Mildly abnormal spectrum, 30% reduction in NA/Cr ratio suggests a risk of sequelae; no Lac detected; suggests good outcome	Moderate	Mild
Mildly abnormal spectrum, 25% reduction in NA/Cr suggests sequelae but may be due to William's syndrome, no Lac detected; suggests good outcome	Vegetative state	Mild
Very abnormal spectra, 55%-70% reduction in NA/Cr ratios, prominent Lac peaks detected; suggests poor outcome	Severe	Severe

charge. Two patients (patients 5 and 9) had detectable cerebral lactate and showed little or no recovery (Fig. 1; patient 9). Both also showed marked reductions in NA/Cr ratios. In contrast, the other four patients in a vegetative state or with severe impairment (patients 1, 4, 6, and 8) had spectra that suggested potential for recovery, as indicated by the absence of lactate and milder changes in metabolite ratios. All showed significant improvement at follow-up 6 to 12 months later (one with a normal condition and three with mild disability). One patient (patient 8) in a vegetative state one month after injury had spectra that suggested potential recovery (Fig. 2, A). His condition improved to mild disability, and follow-up ¹H-MRS 9 months later showed increases in the NA/Cr and NA/Ch ratios (Fig. 2, B).

Patients with mild or moderate impairment at discharge. The three patients who had either mild (patient 3) or moderate impairment (patients 2 and 7) at discharge showed no lactate and mild or no changes in metabolite ratios. Follow-up examinations revealed normal or mild outcomes.

Etiologies of the CNS insults. Although the definitive cause of each observed neurologic injury could not be identified, cases 1 through 4 featured severe preoperative asphyxial events in association with either worsening cardiovascular function or prolonged cardiorespiratory arrest (Fig. 3; case 2). The lowest preoperative arterial pH for these four patients averaged 6.99 ± 0.09 . Patient 4 also underwent a lifesaving congenital heart operation 1 day

after birth to treat a complex cardiac lesion. Total duration of TCA at profound hypothermia was prolonged (102 minutes); the four periods of TCA were separated by periods of low-flow CPB (totaling 123 minutes). Moreover, open cardiac massage was required for approximately 3 minutes immediately after separation from CPB.

In cases 5 through 9, operative events may have contributed to or caused the injuries. With the chest open and preparations made to initiate CPB, patient 5 (who was undergoing cardiac transplantation for hypoplastic left heart syndrome) had ventricular fibrillation necessitating open cardiac massage for 12 minutes. The core temperature at arrest was 33° C, and a pulsatile arterial waveform was observed during open cardiac massage. CPB was then initiated without further difficulty. The complex congenital cardiac lesion in case 7 required four periods of TCA at profound hypothermic temperatures (total time 69 minutes) and an extended period of low-flow CPB (102 minutes). Patient 9 underwent emergent mediastinal exploration for late cardiac tamponade on the second postoperative day (Fig. 1). During transfer to the operating room table, the patient had cardiopulmonary arrest. She was immediately intubated, and closed chest compressions were begun. The patient's chest was opened during cardiopulmonary resuscitation, and the tamponade was relieved. The lowest pH at the time of cardiopulmonary resuscitation was 7.18, with an oxygen tension of 53 mm Hg. No further intraoperative complications were noted. Although we suspect that

Fig. 1. ^1H -MRS scan in occipital gray matter of 20-month-old child (patient 9) 13 days after cardiac arrest and postoperative complications. Spectrum suggests a poor prognosis because of significant reductions in the NA metabolite peak and NA/Cr and NA/Ch ratios, increase in Ch/Cr ratio, and prominent lactate (Lac) peak. The patient was severely disabled at discharge and remains unchanged 1 year later.

perioperative CNS injuries occurred in cases 6 and 8, no definitive cause could be identified. After operation, these two patients were in hemodynamically stable condition and did not appear to have compromise.

Discussion

During the past decade, increasing attention has been devoted to risk assessment for long-term neurologic and developmental disorders in children with acquired or congenital heart disease. Hypoxic-ischemic injury as a result of the primary cardiac disease and a wide variety of acute perioperative and postoperative neurologic insults have been reported in approximately 8% (range 2% to 25%) of infants and children who undergo cardiac operations.^{1, 15, 16} Little attention, however, has been paid to the postoperative neurologic assessment of these patients as a means of predicting outcome, for several reasons. (1) Most patients remain critically ill in the immediate postoperative period and are receiving multiple medications that either mimic or obscure neurologic findings. (2) Bedside technical constraints hinder performance of a satisfactory examination. (3) The examination has inherent limitations as a predictor of outcome, particularly in young infants. (4) Some have reservations concerning the use of currently available technologies, including electroencephalography,¹⁷ cranial ultra-

sonography,¹⁸ evoked responses,¹⁹ computed tomographic or MRI scans,^{3, 20} and single-photon emission computed tomographic scanning²¹ to predict outcome. It is not uncommon that any neurologic deficits present are first recognized once the child's cardiovascular status has improved several days after operation. It is at this juncture that objective evaluation of cerebral function would be useful in predicting the risk for long-term neurodevelopmental disorders.

^1H -MRS is now being used to examine a wide variety of acute and chronic disorders of the CNS in children and adults.⁷ Several investigators have also reported on the spectral changes seen during normal development.⁹⁻¹² In recent studies, we showed that ^1H -MRS and clinical data together were useful in predicting outcome after a variety of acute serious CNS injuries.⁷ In 30 children (neonatal to 180 months, studied a mean of 7 days after insult), we found that the NA/Cr ratios were significantly lower in patients with bad outcomes (severe disability, vegetative state, death) than in patients with good outcomes (normal, mild, or moderate disability). In addition, cerebral lactate was present in 80% of cases with bad outcome, versus none of the cases with good outcomes. We also used a linear discriminant analysis and combined four clinical variables (Glasgow Coma Scale score, initial pH, blood glucose, and duration of unconsciousness) with the

Fig. 2. **A**, ^1H -MRS spectrum in parietal white matter of a 42-month-old child with Williams syndrome (patient 8) obtained 9 days after cardiac operation while the child remained in a vegetative state. Spectrum shows a moderately decreased NA/Cr ratio, suggesting a risk of sequelae; however, absence of lactate suggests potential for recovery. Follow-up examination 9 months later revealed mild disabilities. **B**, Follow-up spectrum of same patient obtained 9 months after operation. Spectrum shows recovering NA peak; however, NA/Cr and NA/Ch ratios are below normal values for a 51-month-old child. *ml*, Myoinositol.

^1H -MRS data and were able to correctly classify outcome in 100% of cases. More recently, in a larger series of 94 infants and children, we found that ^1H -MRS was particularly predictive for children older than 18 months 3 to 5 days after insult.²²

Two earlier studies with ^1H -MRS in asphyxiated neonates found that poor neurodevelopmental outcomes correlated with decreases in the NA/Ch ra-

tio.^{23, 24} The presence of cerebral lactate was observed in one of these reports and was also indicative of a poor outcome.²⁴ ^1H -MRS has also been used to evaluate the prognosis of children after near-drowning by correlating outcome with elevations in lactate in combination with a reduction in NA.²⁵ In a more recent study of 78 infants with perinatal or developmental disorders (with long T2

Fig. 3. ^1H -MRS scan in parietal white matter of a 7-day-old infant (patient 2) who had prolonged cardiac arrest at the age of 4 days. Presence of normal spectrum for this age predicts good outcome. Patient subsequently underwent two operations for repair of her cardiac anomalies, at 22 days and 6 months of age. Follow-up examination showed patient to have mild disability.

rather than the short T2 echoes used in our study), it was found that the NA/Ch or NA/Cr ratios were reduced in 17 of 21 children with delayed development and in eight of 23 with minor neurologic abnormalities, but not in any of the 34 patients with normal development.²⁶

Cerebral lactate and poor prognosis. The presence of cerebral lactate as a factor suggesting a poor outcome has been reported in adults with strokes and other forms of hypoxic-ischemic insults²⁷ and in infants with hypoxic-ischemic encephalopathies.²⁴ We also noted this correlation between lactate and poor outcome in other children with acute CNS insults as a result of near-drowning, trauma, and out-of-hospital cardiac arrest. In this study, the presence of lactate was also associated with a poor neurologic outcome. Two patients had lactate peaks, which normally appear as a doublet at 1.3 ppm relative to NA on the ^1H -MRS spectra. Patient 9 had a definite lactate peak 12 days after a postoperative cardiac arrest and has not recovered beyond a level of severe disability even 1 year after her insult. In case 5, the lactate peak was evident although overlaid with lipid resonances. In this patient, limited recovery to a level of severe disability was observed. The only two patients who continued to have severe impairment at 6- to 12-month follow-up were patients who had lactate. All other

patients with initial severe outcomes recovered at least to a level of mild disability.

The presence of lactate also correlated with marked reductions in the NA/Cr and NA/Ch ratios and with increases in the Ch/Cr ratio. This correlation may reflect severity of injury. Severe injuries cause both irreversible neuronal and glial loss, as well as significant alterations in neuronal and glial metabolic function that increase brain lactate formation. Alternatively, brain metabolic injury or altered flow-metabolic relationships may lead to increased lactate formation, which then causes additional neuronal damage. Of interest is a recent study that measured arteriovenous lactate differences and found increased cerebral lactate release after TCA but not after low-flow CPB in children undergoing cardiac operations.²⁸ The higher lactate release seen after TCA is presumably a contributing factor to the higher neurologic morbidity associated with TCA.³ Overall, it is likely that cerebral lactate is both a marker of and a contributor to continued injury. Attempts to reduce lactate formation with sodium dichloroacetate in children with mitochondrial diseases²⁹ and in animal models of global ischemia³⁰ suggest that ^1H -MRS may be of value in determining whether such treatments should be considered in patients with neurologic dysfunction as a result of cardiac disease or operation.

Abnormalities on MRI scan versus spectroscopic data. Spectra are typically obtained from the occipital gray and parietal white matter, on the assumption that the patient has had a diffuse rather than focal cerebral injury and that these areas adequately reflect the results of tissue damage. Case 5 (see appendix) demonstrates the need for comparison of the MRI findings with the spectroscopic results. One of this patient's major neurologic deficits was cortical blindness as a result of extensive mesial occipital lobe petechial hemorrhage. Although this patient did not show significant developmental improvement, the MRI findings were critical in assessing the nature of the long-term neurologic problems of this infant, who had continued cortical blindness as a result of the lesions. In contrast, the other patients with visual impairments all regained visual function; their occipital gray matter spectra suggested the potential for recovery of visual function.

Spectroscopy in occipital gray versus parietal white matter. Several investigators have published normal developmental curves for some of the metabolite ratios in gray matter, and to a lesser extent in white matter.⁹⁻¹² Our previous study also reported normative and pathologic data for occipital gray matter.⁷ We are therefore able with some confidence to interpret the data from the five cases in which occipital gray matter spectra were obtained. Until we are able to collect additional normative data on parietal white matter, we must cautiously interpret our findings in the four cases (cases 2, 5, 7, and 13) in which we were only able to obtain parietal spectra. In cases in which both spectra were obtained, however, the abnormalities were similar in white and gray matter. This suggests that it may be possible to shorten the ¹H-MRS acquisition time by studying only one brain region, depending on whether the insult is diffuse and equally reflected in gray and white matter. If the lesion is focal, obtaining spectra from the specific region of interest as well as other brain regions would be helpful. This is an important issue to consider, because recent studies have shown that 50% of children with postoperative choreoathetosis had perfusion defects in the basal ganglia according to single-photon emission computed tomography, despite normal results of neuroimaging studies.²¹ Spectroscopy may also have the potential to detect subtle abnormalities that are remain undetected with conventional MRI scanning. In addition, spectral abnormalities may first be observable in gray rather than white matter. For

example, in case 9 we observed more lactate and greater reductions in the NA/Cr ratio in gray than in white matter. The ability to determine sequential spectral changes may thus be helpful in designing therapies to reverse injury.

Other potential preoperative and postoperative indications for ¹H-MRS. We have not had the opportunity to extensively study patients whose preoperative or postoperative neurologic examination results were mildly abnormal or normal. This patient population would be interesting to study to determine whether spectroscopy might predict which children would be at risk for subtle neurologic deficits. In fact, it has been suggested that subtle CNS malformations may be a comorbid factor in patients with congenital heart disease.³¹ Developmental delays might therefore be unrelated to acute or subacute hypoxic-ischemic injury. Supporting this concept are several recent autopsy studies of children with congenital heart disease; these studies found a surprisingly high prevalence of developmental abnormalities. In one study, 67.8% of 28 patients without and 75% of 24 patients with systemic anomalies had CNS malformations.³² Another study of 41 infants with hypoplastic left heart syndrome found that 29% had major or minor CNS anomalies and an additional 10% had either agenesis of the corpus callosum or holoprosencephaly.³³ If so, preoperative MRI and ¹H-MRS might determine which infants are at risk for neurodevelopmental disorders, as well as document the presence of preexisting conditions that account for their occurrence.

Conclusion

¹H-MRS may be of prognostic value for children with serious CNS injury associated with cardiac disease or operation. The presence of lactate and reduced NA/Cr ratio are suggestive of poor neurologic outcome. Additional studies are needed to define criteria for performing these studies, including the age of the patients, optimal timing and number of studies to obtain valid and reliable data, and quantitation of metabolites.

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Appendix

This appendix includes the case histories of the nine patients, divided into three groups according to timing of insult (preoperative, perioperative, and postoperative).

Preoperative insults

CASE 1. A 1-week-old female infant had a prolonged out-of-hospital cardiac arrest 2 days after birth (pH 6.93, carbon dioxide tension 87 mm Hg, oxygen tension 23 mm Hg, and base excess -14.7). Seizures developed, and the patient was treated with phenobarbital and intubated. Neurologic examination could not be performed because the patient was receiving a fentanyl drip. Her electroencephalogram appeared mildly abnormal. MRI scan 5 days after insult showed diffuse edema. Her ^1H -MRS scan, which showed no reduction in NA, a normal NA/Cr ratio, and no lactate, was interpreted as normal for age and suggestive of a good outcome. Ultrasonographic diagnosis was a dilated cardiomyopathy of undetermined origin, and a transplant was performed when the patient was 2 months old. Follow-up examination 6 months after operation noted mild spasticity and delay. Examination at 10 months of age was normal.

CASE 2. A 1-week-old female infant had a prolonged cardiorespiratory arrest 4 days after birth (pH 6.80, carbon dioxide tension 18 mm Hg, oxygen tension 220 mm Hg, and base excess -28) and was found to have interrupted aortic arch type A, patent ductus arteriosus, and ventricular septal defect. She had generalized sepsis with multiorgan failure, required sedation and ventilator support, had small reactive pupils and normal tone, withdrew to painful stimuli, and showed no focal findings. Her electroencephalogram showed left hemispheric slowing. MRI scan 3 days after insult showed diffuse edema. Parietal ^1H -MRS scan showed a normal NA/Cr ratio and an unusual doublet at 1.10 ppm that was not lactate (Fig. 3) and suggested potential for recovery. Aortic arch repair, pulmonary artery banding, and ligation and division of the patent ductus arteriosus were performed (day 22 after birth). The patient required gavage feeding because of impaired sucking and swallowing. At 6 months of age, she was readmitted for ventricular septal defect repair, pulmonary artery debanding and reconstruction, subaortic resection, and additional aortic arch repair. An MRI scan revealed mild cortical atrophy. Although her development was normal, she had mild increased tone and slightly decreased movements in the left arm and leg (mild disability).

CASE 3. A 10-day-old girl with an interrupted aortic arch and ventricular septal defect had progressive cyanosis (pH 6.98, carbon dioxide tension 23 mm Hg, oxygen tension 86 mm Hg, and base excess -24). She began having generalized seizures, was intubated, and was treated with phenobarbital, alprostadil (Prostin), and sodium bicarbonate. Her initial ionized calcium level was decreased, and she required repeated intravenous calcium infusions. Her electroencephalogram showed multifocal seizure activity. Neurologic examination on day 11 after birth was normal except for the effects of sedation but she had several focal seizures and was started on a regimen of phenytoin. The next day, the patient underwent a complete repair of her interrupted aortic arch and ligation of her patent ductus arteriosus. Absence of a thymus was

noted, and the patient was considered to have DiGeorge syndrome. On day 17 after birth, an MRI scan revealed cerebral edema. ^1H -MRS scan showed a mild decrease in the NA peak, no evidence of lactate, and a normal NA/Cr ratio, suggestive of good outcome. She had mild impairment at discharge; follow-up examination at 6 months after discharge yielded normal results.

Preoperative and perioperative insult

CASE 4. A male neonate of 38 weeks' gestation was in hemodynamically unstable condition and was anuric (pH 7.24, carbon dioxide tension 44 mm Hg, oxygen tension 22 mm Hg, and base excess -8). One day after birth, he had undergone a modified arterial switch operation for correction of a transposition of the great arteries, patch closure of his ventricular septal defect and interrupted aortic arch, transatrial suture closure of an atrial septal defect, and ligation of a patent ductus arteriosus. The patient began having seizures 2 days later and was treated with phenobarbital. Electroencephalography showed generalized slowing and spike discharges, and head ultrasonography showed a left occipital hemorrhagic infarction. He was extubated (day 12 after birth), required gavage feeding, and was discharged after 21 days. He was readmitted at 5 weeks after birth for fever and vomiting. MRI scan showed a large resolving left temporooccipital hematoma, bifrontal subdural hematomas, and mild atrophy. ^1H -MRS scan showed a normal NA peak and NA/Cr ratio with no lactate and was suggestive of potential for recovery. He was treated for suspected meningitis, had a pyloromyotomy, and was discharged on a regimen of phenobarbital, furosemide (Lasix), and spironolactone (Aldactone). Follow-up at 6 months after initial scans noted extremely mild abnormalities on neurologic examination, no further seizure activity, and normal development.

Perioperative insults

CASE 5. A 5-week-old boy with hypoplastic left heart syndrome underwent cardiac transplantation. During operation, before arrival of the donor heart, he had ventricular fibrillation and cardiac arrest for 12 minutes before CPB and was treated with open cardiac massage. The transplantation was subsequently completed without complications. The next day, generalized seizures developed, the patient's electroencephalogram showed a burst-suppression pattern, and he was treated with phenobarbital, midazolam, and diazepam. Initial neurologic examination was deferred because the patient was receiving paralytic agents. MRI scan (day 9 after transplantation) showed bilateral petechial hemorrhages in the occipital lobes. ^1H -MRS scan showed significant decreases in the NA and Cr peaks, which accounted for the normal NA/Cr ratio. The Ch/Cr ratio was elevated, and lactate was present in the parietal white matter. The study suggested that this patient was at risk for long-term neurologic problems. Examination at discharge showed minimal spontaneous movement, no response to visual stimuli, facial muscle weakness, poor and uncoordinated sucking and swallowing, and an impaired gag reflex. Follow-up at the age of 6 months noted blindness, generalized spasticity, and functioning at a 2- to 3-month level.

CASE 6. A 10-month-old girl underwent correction of a partial atrioventricular canal defect and ligation of a

patent ductus arteriosus. She was treated for seizures the next day with phenobarbital and diazepam. Examination 2 days later showed that she was in a vegetative state. Her electroencephalogram was mildly abnormal, with diffuse slowing, and results of visual evoked-response studies were abnormal. MRI scan revealed bilateral T2 hyperintensities within the lentiform and caudate nucleus and parietooccipital watershed infarction. Another MRI done 12 days after operation demonstrated central and peripheral atrophy. ^1H -MRS scan showed a normal spectrum without a lactate peak and suggested potential for improvement. The patient was discharged after 42 days in a vegetative state. Within 3 months, she had recovered to a level of mild disability. She was alert with normal visual function, had mild spasticity and disequilibrium, and was able to reach for and transfer objects.

CASE 7. A 14-month-old girl with tetralogy of Fallot underwent total correction and patch pulmonary arterioplasty. Four days later, seizures developed and were treated with phenobarbital. She had general irritability and cortical blindness. Her electroencephalogram showed generalized slowing. Visual evoked responses were normal. MRI scan 16 days after operation revealed mild central and peripheral atrophy. Results of MRI angiography were normal. Parietal white matter ^1H -MRS spectrum showed a reduced NA peak with a preserved Cr peak. Lactate was not present. The study was interpreted as abnormal, putting her at risk for future developmental problems, but also suggested potential for recovery. At discharge (29 days after operation), she had recovered most of her visual function and could feed herself but required assistance with sitting, mobility, and position changes. At 6-month follow-up, her seizures had resolved and she had normal vision, strength, and cranial nerve function. She remained unsteady with delayed language function and was considered to have mild disability.

CASE 8. A 42-month-old boy with Williams syndrome, mild developmental delay, supraaortic stenosis, and right ventricular outflow tract obstruction underwent Doty patch repair of his aortic stenosis. After operation, he was poorly responsive. Electroencephalography suggested a diffuse encephalopathy. MRI scan (day 6 after operation) disclosed bilateral patchy caudate, lentiform, globus pallidus, thalamic, and bilateral cerebellar foci of

infarction with diffuse edema and herniation. Results of MRI angiography were normal. Examination 7 days after operation noted a vegetative state. Parietal white matter ^1H -MRS (day 9 after operation) showed a moderate reduction in NA and mildly reduced Cr without lactate (Fig. 2, A); the reductions suggested risk for long-term problems, but the absence of lactate suggested potential for recovery. The patient was discharged (36 days after operation) in a vegetative state. He regained consciousness within 2 months and a follow-up ^1H -MRS scan 9 months after the first study showed an increase in the NA/Cr and NA/Ch ratios, corresponding with the return of developmental function (Fig. 2, B). By 12 months after operation, he had recovered to a level of mild disability. He was able to speak in four-word sentences and walk independently.

Postoperative insult

CASE 9. A 20-month-old girl had undergone ligation of her patent ductus arteriosus, pulmonary artery banding, and coarctation repair at the age of 1 month. She was readmitted at the age of 20 months for transatrial patch closure of her ventricular septal defect, pulmonary artery debanding, and right ventricular outflow tract reconstruction. Two days later, cardiac tamponade developed; the patient had an arrest, was resuscitated, and underwent an exploratory sternotomy with tamponade release (pH 7.18, carbon dioxide tension 67 mm Hg, oxygen tension 53 mm Hg, and base excess -2). After operation, the patient was comatose. Three days later, generalized seizures developed and were treated with phenobarbital and diazepam. Electroencephalography revealed generalized spike discharges. Neurologic examination showed little spontaneous movement or purposeful activity. An MRI scan 13 days after her arrest showed diffuse ischemic injury. ^1H -MRS scan showed significantly reduced NA and Cr peaks and a prominent lactate peak (Fig. 1); this spectrum was considered abnormal and highly suggestive of a poor prognosis. At discharge 13 weeks after the operation, the patient had cortical blindness and severe developmental delay with a left hemiparesis; she required nasogastric tube feedings. Follow-up 1 year later noted cortical blindness with spastic quadriplegia and severe developmental delay.