

Magnetic Resonance Spectroscopy Predicts Outcomes for Children With Nonaccidental Trauma

AUTHORS: Gregory S. Aaen, MD,^a Barbara A. Holshouser, PhD,^b Clare Sheridan, MD,^c Cherie Colbert, MD,^b Melinda McKenney, BS,^b Daniel Kido, MD,^b and Stephen Ashwal, MD^a

Divisions of ^aChild Neurology and ^cForensic Medicine, Department of Pediatrics, and ^bDepartment of Radiology, School of Medicine, Loma Linda University, Loma Linda, California

KEY WORDS

children, infants, nonaccidental trauma, MRI, magnetic resonance spectroscopy, traumatic brain injury

ABBREVIATIONS

CC—corpus callosum

FWM—frontal white matter

GCS—Glasgow Coma Scale

MRSI—magnetic resonance spectroscopic imaging

NAT—nonaccidental trauma

PCPCS—Pediatric Cerebral Performance Category Score

TR—repetition time

TE—echo time

TBI—traumatic brain injury

HII—hypoxic-ischemic injury

www.pediatrics.org/cgi/doi/10.1542/peds.2008-3312

doi:10.1542/peds.2008-3312

Accepted for publication Aug 12, 2009

Address correspondence to Stephen Ashwal, MD, Loma Linda University School of Medicine, Department of Pediatrics, 11175 Campus St, Room A1120, Loma Linda, CA 92354. E-mail: sashwal@llu.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2010 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.



WHAT'S KNOWN ON THIS SUBJECT: There are very limited data on the role of MRSI in outcome prediction for NAT.



WHAT THIS STUDY ADDS: This study provides new data demonstrating that MRSI is very useful for outcome prediction for children with NAT.

abstract



OBJECTIVE: We evaluated proton magnetic resonance spectroscopic imaging (MRSI) findings for children with traumatic brain injury attributable to nonaccidental trauma (NAT) early after injury, to determine whether brain metabolite changes predicted outcomes.

METHODS: Proton MRSI (1.5 T) was performed (mean: 5 days after injury [range: 1–30 days]) through the level of the corpus callosum for 90 children with confirmed NAT. Regional *N*-acetylaspartate/total creatine, *N*-acetylaspartate/total choline, and choline/creatine ratios and the presence of lactate were measured. Data on long-term outcomes defined at ≥ 6 months were collected for 44 of 90 infants. We grouped patients into good (normal, mild disability, or moderate disability; $n = 32$) and poor (severe disability, vegetative state, or dead; $n = 12$) outcome groups.

RESULTS: We found that *N*-acetylaspartate/creatine and *N*-acetylaspartate/choline ratios (mean total, corpus callosum, and frontal white matter) were significantly decreased in patients with poor outcomes ($P < .001$). A logistic regression model using age, initial Glasgow Coma Scale score, presence of retinal hemorrhage, lactate on MRSI scans, and mean total *N*-acetylaspartate/creatine ratio predicted outcomes accurately in 100% of cases.

CONCLUSIONS: Reduced *N*-acetylaspartate levels (ie, neuronal loss/dysfunction) and elevated lactate levels (altered energy metabolism) correlated with poor neurologic outcomes for infants with NAT. Elevated lactate levels may reflect primary or secondary hypoxic-ischemic injury, which may occur with NAT. Our data suggest that MRSI performed early after injury can be used for long-term prognosis. *Pediatrics* 2010;125:295–303

Traumatic brain injury (TBI) is a major cause of death and disability in children, with an annual incidence of 63 hospitalizations per 100 000 children <14 years of age.¹ Efforts have been made to develop tools that aid in detecting injury severity and subsequent outcomes. The more-commonly used indicators of TBI severity include Glasgow Coma Scale (GCS) scores,² duration of impaired consciousness and posttraumatic amnesia,³ presence of nonreactive pupils,⁴ and brain imaging techniques.⁵ Unfortunately, these indicators of severity have not proved sufficiently accurate in predicting long-term outcomes.

TBI in children <2 years of age is attributed to nonaccidental trauma (NAT) in ~24% to 32% of cases.^{6,7} In 2006, state and local child protective services in the United States investigated 3.6 million reports of children being abused or neglected and classified >900 000 of those children (12.1 children per 1000) as victims, with ~144 000 cases being attributable to physical abuse.⁸ Outcomes after NAT are recognized to be worse than those after accidental TBI.⁹

Even when there is apparent early recovery from inflicted head trauma, long-term developmental follow-up monitoring frequently reveals neurocognitive deficits.¹⁰ Magnetic resonance spectroscopic imaging (MRSI) offers a unique noninvasive method to quantify the magnitude and regional distribution of injury, because it is capable of measuring levels of *N*-acetylaspartate, a marker of neuronal function and integrity.¹¹ Reduced *N*-acetylaspartate levels commonly are used as a marker for neuronal loss after traumatic or hypoxic-ischemic injury (HII). However, because *N*-acetylaspartate is produced in neuronal mitochondria and adenosine triphosphate is required for synthesis, mitochondrial dysfunction may con-

tribute to the temporary reduction in *N*-acetylaspartate levels seen after TBI.^{12–14} It has been postulated that a temporary decrease in *N*-acetylaspartate levels after brain injury may be caused by accelerated lipid synthesis involved in myelin repair or may be attributable to *N*-acetylaspartate providing a temporary source of cellular energy locally at the site of axonal injury, which would produce a transient decrease that might precede any loss of *N*-acetylaspartate as a result of axonal death.¹⁵ Therefore, *N*-acetylaspartate measurements may serve as a sensitive specific biomarker of neuronal injury, dysfunction, loss, or repair.

There has been speculation that HII is more common with NAT and may be an additional major factor causing poor outcomes.¹⁶ Some studies have shown that infants with NAT are more likely to have HII, as determined on the basis of metabolic acidosis¹⁷ and reduced cerebral perfusion pressure.¹⁸ A study of 30 children with NAT found that 37% had HII on diffusion-weighted MRI scans, compared with only 9% of children with accidental trauma.¹⁹ Production of lactate through impaired aerobic glycolysis is a specific marker for HII that can be detected along with *N*-acetylaspartate changes. In a study of 11 victims of NAT, 45% had cerebral lactate and all had worse discharge outcomes, compared with those without lactate.²⁰

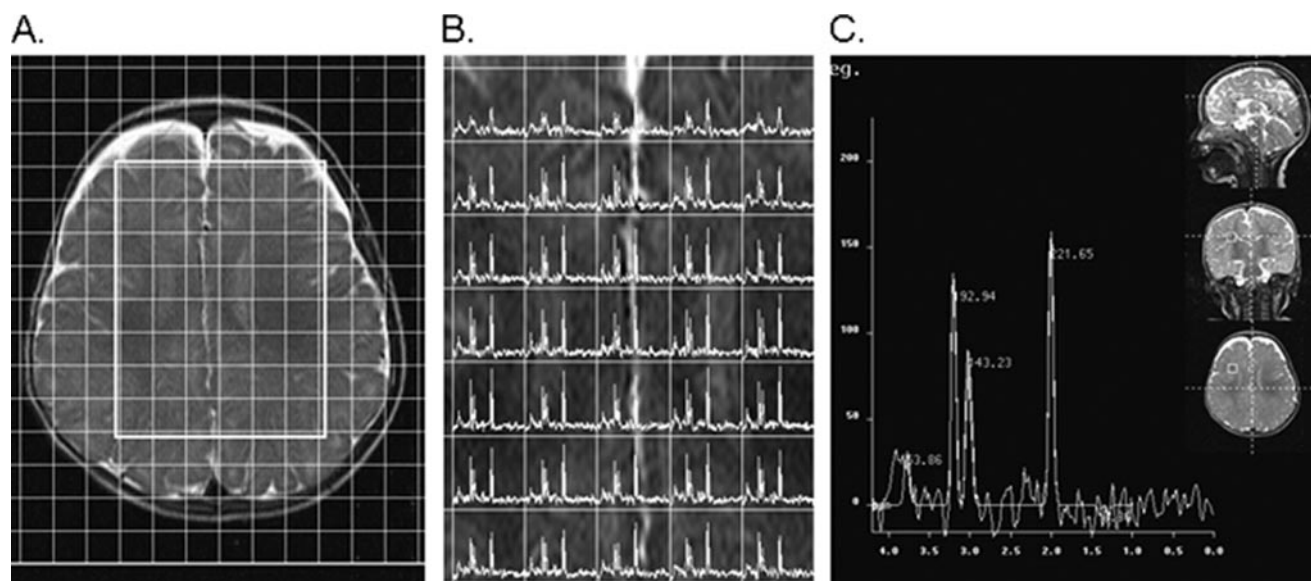
As discussed above, MRSI has been used to evaluate the extent of TBI in children and has shown utility in predicting outcomes of pediatric TBI.^{21–25} The current study extends the use of MRSI to predict outcomes for children after NAT. It was hypothesized that lower *N*-acetylaspartate ratios and the presence of lactate detected by MRSI would better reflect the extent of injury and would provide valuable data, in combination with clinical indicators, about long-term neurologic prognoses

that would be more accurate than clinical indicators alone.

METHODS

Data Source and Study Group

This study was approved by the Loma Linda University Medical Center institutional review board. We reviewed the charts of 244 children who underwent MRI studies as part of an evaluation for suspected NAT while they were hospitalized at Loma Linda University Children's Hospital between 1998 and 2007. A forensic pediatric specialist (Dr Sheridan) subsequently reviewed the charts of those patients, applied published criteria,²⁶ and determined that 114 patients were injured as a result of NAT. We excluded patients with preexisting cognitive delays, known central nervous system malformations, previous brain injuries, or birth before gestational age of 30 weeks, as well as patients who did not undergo MRSI as part of their MRI study ($n = 19$). As a result, 90 patients were included in this study. Other prognostic data, including initial GCS scores, hemoglobin and sodium levels, presence of retinal hemorrhage, hypotension, need for intubation, cardiopulmonary arrest, and need for craniotomy, were noted. The occurrence of seizures, time when seizures first occurred (ie, <24 hours versus >24 hours), and duration of seizures (ie, <15 minutes versus >15 minutes) were determined and analyzed to assess whether they were correlated with outcomes. We were not able to compare the seizure type or frequency of seizures because there was insufficient consistent documentation of these variables. Electroencephalograms were obtained for 25 of the 44 patients and were graded by using a standardized, 4-tiered scoring system (ie, normal or mildly, moderately, or severely abnormal).²⁷ Electroencephalographic scores were examined to deter-

**FIGURE 1**

A, T2-weighted image of a 7-month-old child with a normal outcome, shown with MRSI grid overlay. B, Spectral map showing proton spectra for acceptable voxels. C, Individual spectrum from a voxel taken from the right FWM. Spectra were acquired 2 days after injury.

mine whether they were correlated with outcomes.

Long-term outcomes at >6 months after injury were determined by using the Pediatric Cerebral Performance Category Score (PCPCS)²⁸ in review of the charts of patients who returned to Loma Linda University Children's Hospital for follow-up evaluations. The PCPCS is a 6-point Likert scale that includes the following outcomes: (1) normal (can perform all age-appropriate activities), (2) mild disability (conscious, alert, and able to interact in most age-appropriate activities but may have mild neurologic deficits), (3) moderate disability (conscious, with sufficient cerebral function for age-appropriate activities of daily living, but has significant cognitive impairment), (4) severe disability (conscious but dependent on others for daily support because of impaired brain function), (5) persistent vegetative state, and (6) death. Patients were dichotomized into groups with good outcomes (normal, mild disability, or moderate disability) or poor outcomes (severe disability, vegetative state, or dead).

MRI and MRSI

MRI and MRSI were performed by using a circularly polarized head coil in a conventional, 1.5-T, whole-body imaging system (VISION; Siemens Medical Systems, Erlangen, Germany), as described previously. MRI sequences included axial and coronal, fast spin-echo, T2-weighted acquisition (repetition time [TR] of 4200 milliseconds, echo time [TE] of 96 milliseconds, 2 acquisitions, and 4-mm slices), sagittal, spin-echo, T1-weighted acquisition (TR of 550 milliseconds, TE of 22 milliseconds, 2 acquisitions, and 5-mm slices), axial fluid attenuated inversion recovery acquisition (TR of 9000 milliseconds, TE of 110 milliseconds, inversion time of 2200 milliseconds, 1 acquisition, and 4-mm slices), axial diffusion-weighted imaging (echo planar single shot, with TR of 4000 milliseconds, TE of 110 milliseconds, and 5-mm slices), and 3-dimensional, susceptibility-weighted imaging (TR of 57 milliseconds, TE of 18 milliseconds, flip angle of 15°, and 2-mm partitions). MRI scans and reports were reviewed by a neuroradiologist (Dr Kido), and the presence or

absence of each of the following findings was recorded: skull fracture (confirmed on radiographs), extraaxial hemorrhage (including subdural, epidural, and subarachnoid hemorrhage), intraaxial hemorrhage (including intraparenchymal and intraventricular hemorrhage), contusion, and ischemia (focal infarctions or global ischemia). Patients were considered to have evidence of focal infarctions on the basis of diffusion-weighted imaging abnormalities confined to a focal area, as opposed to global ischemia, which was determined on the basis of diffuse diffusion-weighted imaging and T2-weighted signal abnormalities, as established by neuroradiologists.

Immediately after MRI, 2-dimensional MRSI was performed by using a water-suppressed, point-resolved MRSI sequence with a TR of 3000 milliseconds, TE of 144 milliseconds, number of images averaged of 1, and 1024 data points sampled, with a dwell time of 1 milliseconds. As shown in Fig 1A, images from 3 orthogonal planes acquired during the MRI portion of the study were used for slab placement

for MRSI. A multivoxel, single-slice acquisition was performed with a 10-mm slab (maximum of 160-mm field of view, 16×16 phase encodings, up to 64 voxels (8×8) per volume of interest, and nominal voxel volume of 1 mL) through the level of the corpus callosum (CC). The voxels included areas of obvious injury, if present, as well as normal-appearing brain. MRSI spectra were postprocessed by using an MRSI analysis software package available for the scanner (Luise; Siemens Medical Systems). Integral peak values for *N*-acetylaspartate (2.02 ppm), total creatine (3.02 ppm; includes phosphocreatine), total choline (3.20 ppm; includes other choline moieties such as phosphocholine and glycerophosphocholine), and lactate, if present (identified as an inverted doublet at 1.33 ppm, with 7-Hz splitting), were measured for each voxel with an acceptable spectrum and were transferred to a spreadsheet for further analysis and calculation of metabolite ratios (*N*-acetylaspartate/creatine, *N*-acetylaspartate/choline, and choline/creatine). The MRSI grid was overlaid on T2-weighted images, and each voxel was assigned to one of the following regions: frontal white matter (FWM), frontal gray matter, CC, parietooccipital white matter, or parietooccipital gray matter. Metabolite ratios for each region were averaged. Ratios for all voxels were averaged to obtain mean total ratios.

Statistical Analyses

To determine whether there were differences between good and poor outcome groups with respect to continuous variables (demographic, clinical, and metabolite data), *t* tests were used; χ^2 tests were used to determine differences between groups with respect to nominal variables. Differences between groups were considered statistically significant at $P \leq .05$.

TABLE 1 Patient Characteristics

	Good Outcome (<i>N</i> = 32)	Poor Outcome (<i>N</i> = 12)	<i>P</i>
Age, mean \pm SD, mo	7.2 \pm 5.4	4.3 \pm 5.1	.13
Intubated, %	9	50	.003 ^a
Retinal hemorrhage, %	59	92	.04 ^a
Initial GCS score, mean \pm SD	11.8 \pm 3.8	6 \pm 2.9	<.001 ^b
Seizures, %	53	75	.19
Nonreactive pupils, %	6	33	.02 ^a
Cardiopulmonary arrest, %	3	25	.025 ^a
External ventricular drain, %	3	42	.001 ^a
Initial serum sodium level, mean \pm SD, mEq/dL	138.2 \pm 2.3	138.3 \pm 8.3	.97
Initial blood glucose level, mean \pm SD, mg/dL	145.1 \pm 77.4	206.3 \pm 89.5	.03 ^b
Initial hemoglobin level, mean \pm SD, g/dL	9.5 \pm 2.0	9.0 \pm 2.3	.51
Time to MRSI, mean \pm SD, d	4.3 \pm 3.8	7.3 \pm 12.1	.42
Time to follow-up evaluation, mean \pm SD, mo	24.2 \pm 16.4	43.6 \pm 27.6	.04 ^b

^a Pearson's χ^2 analysis, significant at $P \leq .05$.

^b Student's *t* test, significant at $P \leq .05$.

Logistic regression models were built to assess the predictive accuracy for dichotomized outcomes of various combinations of clinical and spectroscopic variables. Variables were included in the model on the basis of clinical and statistical significance. Age was included in all models because spectral data for normal infants vary with age, because of brain maturation.

RESULTS

Study Group

A total of 44 patients (28 boys and 16 girls) of the 90 reviewed underwent MRI studies and follow-up medical visits ≥ 6 months after injury (mean \pm SD: 29.5 \pm 21.6 months [range: 6–84 months]), to determine outcomes. A comparison of demographic and clinical variables between patients with and without follow-up data was performed (Table 1, which is published as supplemental information at www.pediatrics.org/content/full/125/2/295). Patients who returned for follow-up evaluations were more likely to have had lower GCS scores, higher rates of seizures and retinal hemorrhage, and initial lower hemoglobin and higher blood glucose levels and to have required intubation. They also were more likely to have had imaging findings of intraaxial and extraaxial hem-

orrhage and ischemia or infarction. The total *N*-acetylaspartate/creatine and *N*-acetylaspartate/choline ratios were significantly lower for patients who returned for follow-up evaluations, and such patients were much more likely to have had lactate present in their spectra.

Patient Characteristics

Clinical data for the 44 patients (good outcome, *n* = 32; poor outcome, *n* = 12) are summarized in Table 1. The ages of children at the time of MRI/MRSI were not significantly different between the 2 outcome groups. The initial GCS score was 6 in the poor outcome group, compared with 12 in the good outcome group ($P < .001$). Infants with poor outcomes were more likely to have suffered cardiopulmonary arrest ($P = .025$), to have been intubated ($P = .003$), to have had nonreactive pupils ($P = .02$) or retinal hemorrhage ($P = .04$), and to have required placement of an external ventricular drain ($P = .001$).

Patients with seizures were not more likely to have poor outcomes. We found no significant difference between the proportions of patients with seizures (ie, 17 of 26 patients [65.3%]) and without seizures (15 of 18 patients [83.3%]; $\chi^2 = 0.19$) and the likelihood of having a poor outcome. Conversely, there was

no difference in the proportion of patients with good outcomes who had seizures (53%), compared with those with poor outcomes (75%; $\chi^2 = 0.19$). For the 26 patients with seizures, we found that neither the time when seizures occurred (ie, <24 hours versus >24 hours; $\chi^2 = 0.18$) nor the duration of seizures (ie, <15 minutes versus >15 minutes; $\chi^2 = 0.19$) differed significantly for good versus poor outcome groups. We also found that the severity of electroencephalographic abnormalities did not differ significantly between outcome groups ($\chi^2 = 0.84$).

MRI and MRSI Data

MRI and MRSI data were obtained a mean of 5 days after admission (range: 1–30 days). The time to MRSI was longer in the poor outcome group (7 days) than in the good outcome group (4 days), which likely was attributable to the children with poor outcomes being in less-stable medical condition early in the hospital course (Table 1).

Table 2 compares the frequency of commonly detected MRI abnormalities in the 44 patients with good versus poor outcomes. Patients with poor outcomes were more likely to have intraaxial hemorrhage (67% vs 19%; $P < .003$), global ischemia (58% vs 9%; $P = .001$), and extraaxial hemorrhage (100% vs 72%; $P < .04$), compared with patients with good outcomes. Global ischemic injury was significantly associated with poor outcomes ($P = .001$), whereas focal ischemic injury was not. Outcomes of focal infarctions were more dependent on the size and location of the infarctions.

As shown in Table 3, we found that *N*-acetylaspartate/creatine and/or *N*-acetylaspartate/choline ratios were decreased significantly in 4 of the 5 regions analyzed (CC, FWM, parietooccipital white matter, and parietooccipital gray matter) in children with poor

TABLE 2 MRI Findings for Good Versus Poor Outcome Groups

	Proportion, %		<i>P</i>
	Good Outcome (<i>N</i> = 32)	Poor Outcome (<i>N</i> = 12)	
Skull fracture	38	25	.44
Extraaxial hemorrhage	72	100	.04 ^a
Intraaxial hemorrhage	19	67	.003 ^a
Infarction	34	33	.95
Global ischemia	9	58	.001 ^a
Contusions	9	17	.50

Data represent the proportions of patients in the good and poor outcome groups who had the specific imaging finding.

^a Pearson's χ^2 analysis, significant at $P \leq .05$.

outcomes. Although regional choline/creatine ratios were higher in children with poor outcomes, the differences were not significant. The mean total *N*-acetylaspartate/creatine and *N*-acetylaspartate/choline ratios were significantly lower in children with poor outcomes ($P = .001$). The mean total choline/creatine ratio tended to be higher in children with poor outcomes, but the result did not reach significance. Figure 1 shows MRI and

MRSI data for a patient with a good outcome, which can be compared with MRSI data for a patient with a poor outcome (Fig 2), showing decreased *N*-acetylaspartate levels in all spectra. Lactate was present for 10 (83%) of 12 of children with poor outcomes, compared with 12 (38%) of 32 children with good outcomes ($P \leq .007$), and was present in spectra for all children with global injury and children with infarcted areas included within the MRSI sampling volume.

Decreased metabolite ratios from areas susceptible to shaking or impact, such as the CC, FWM, and occipital gray matter, were significantly correlated with the presence of retinal hemorrhage. Spearman correlation coefficients for correlations between regional *N*-acetylaspartate/creatine ratios and retinal hemorrhage were as follows: mean total, correlation coefficient = -0.379 ($P = .01$); CC, correlation coefficient = -0.400 ($P = .008$); FWM, correlation coefficient = -0.404 ($P = .007$); parietal occipital

TABLE 3 MRSI Ratios for Good Versus Poor Outcome Groups

	Good Outcome (<i>N</i> = 32)	Poor Outcome (<i>N</i> = 12)	<i>P</i> ^a
MRSI ratio, mean \pm SD			
Total NAA/creatine	1.30 \pm 0.28	0.92 \pm 0.31	<.001 ^a
Total NAA/choline	1.00 \pm 0.26	0.68 \pm 0.27	.001 ^a
Total choline/creatine	1.36 \pm 0.20	1.5 \pm 0.29	.09
CC NAA/creatine	1.37 \pm 0.41	0.89 \pm 0.32	.001 ^a
CC NAA/choline	0.94 \pm 0.32	0.55 \pm 0.24	<.001 ^a
CC choline/creatine	1.42 \pm 0.25	1.75 \pm 0.57	.08
FWM NAA/creatine	1.29 \pm 0.26	0.94 \pm 0.34	.001 ^a
FWM NAA/choline	0.99 \pm 0.22	0.70 \pm 0.30	.001 ^a
FWM choline/creatine	1.35 \pm 0.21	1.43 \pm 0.26	.28
FGM NAA/creatine	0.89 \pm 0.54	0.75 \pm 0.65	.49
FGM NAA/choline	0.75 \pm 0.47	0.53 \pm 0.44	.16
FGM choline/creatine	0.95 \pm 0.56	1.23 \pm 0.62	.17
POWM NAA/creatine	1.36 \pm 0.51	0.90 \pm 0.41	.008 ^a
POWM NAA/choline	1.01 \pm 0.45	0.77 \pm 0.43	.13
POWM choline/creatine	1.44 \pm 0.57	1.39 \pm 0.34	.78
POGM NAA/creatine	1.19 \pm 0.42	0.88 \pm 0.63	.06
POGM NAA/choline	1.01 \pm 0.48	0.63 \pm 0.52	.03 ^a
POGM choline/creatine	1.25 \pm 0.47	1.42 \pm 0.88	.41
Lactate presence, %	38	83	.007 ^b

FGM indicates frontal gray matter; POWM, parietooccipital white matter; POGM, parietooccipital gray matter; NAA, *N*-acetylaspartate.

^a Student's *t* test, significant at $P \leq .05$.

^b Pearson's χ^2 analysis, significant at $P \leq .05$.

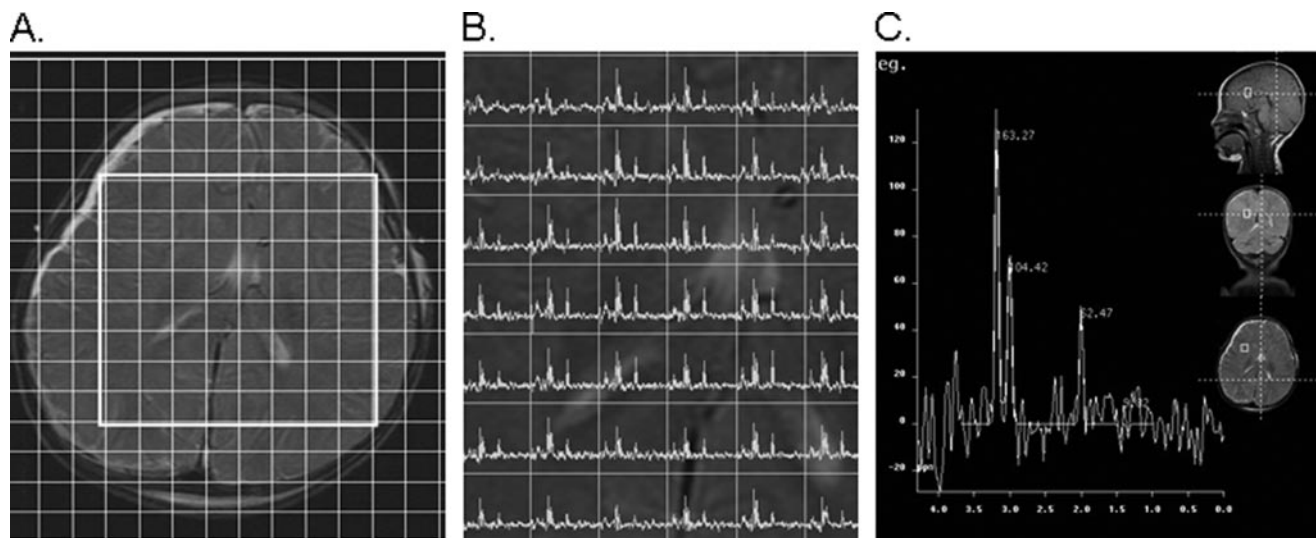


FIGURE 2

A, T2-weighted image of a 7-month-old child with an outcome of severe disability, shown with MRSI grid overlay. B, Spectral map showing diffusely decreased *N*-acetylaspartate levels. C, Individual spectrum from a voxel taken from the right FWM, showing markedly decreased *N*-acetylaspartate levels. Spectra were acquired 5 days after injury.

gray matter (POGM) correlation coefficient = -0.386 ($P = .01$). Similar correlation coefficients for correlations between *N*-acetylaspartate/choline ratios and retinal hemorrhage were as follows: CC, correlation coefficient = -0.436 ($P = .003$); FWM, correlation coefficient = -0.309 ($P = .04$); POGM, correlation coefficient = -0.352 ($P = .02$). Decreased mean total metabolite *N*-acetylaspartate/creatinine and *N*-acetylaspartate/choline ratios were significantly correlated with the presence of extraaxial hemorrhage (*N*-acetylaspartate/creatinine, correlation coefficient = -0.482 ; $P = .001$; *N*-acetylaspartate/choline, correlation coefficient = -0.453 ; $P = .002$) and ischemic injury (*N*-acetylaspartate/creatinine, correlation coefficient = -0.549 ; $P < .001$; *N*-acetylaspartate/choline, correlation coefficient = -0.522 ; $P < .001$) but not intraaxial hemorrhage, skull fractures, or contusions. Lactate presence was strongly and significantly correlated with ischemic injury (correlation coefficient = 0.872 ; $P < .001$). Analysis of variance with Bonferroni corrections showed that patients with global injury also had

significantly lower *N*-acetylaspartate/creatinine and *N*-acetylaspartate/choline ratios and higher choline/creatinine ratios than did patients with focal injury or those with no evidence of any type of ischemic injury (Table 4).

Logistic Regression Analysis

A base model using logistic regression was constructed to assess predictive accuracy, using patient age (in months) and initial GCS scores, because scores were significantly different between outcome groups. Different variables were then tested with the base model, separately and in combination, to develop a model with the highest predictive accuracy. Table 5 reports the results of this development for significant variables, as ev-

idenced statistically by decreasing values of the -2 log-likelihood factor. Further discussion of model development is included in the Data Supplement.

DISCUSSION

Overall Findings

Accurately predicting long-term outcomes after NAT remains difficult.²⁹ Our data show that MRSI can add prognostic information for children with NAT; children who had poorer outcomes 6 months after injury had reduced *N*-acetylaspartate ratios and increased presence of lactate, compared with children with good outcomes. These findings also were seen for children who had more-

TABLE 4 Metabolite Ratios Versus Ischemia

	Ratio, Mean \pm SD			P^a
	No Ischemia	Infarction	Global Ischemia	
Total NAA/creatinine	1.40 ± 0.30	1.07 ± 0.30	0.99 ± 0.20	$<.001$
Total NAA/choline	1.09 ± 0.26	0.83 ± 0.28	0.69 ± 0.19	$<.001$
Total choline/creatinine	1.32 ± 0.19	1.39 ± 0.20	1.58 ± 0.28	.012

NAA indicates *N*-acetylaspartate.

^a Analysis of variance.

TABLE 5 Prediction Models

Model	Variables Included	Correct Prediction of Good Outcome, %	Correct Prediction of Poor Outcome, %	Overall Outcome Prediction, %	−2 Log Likelihood
Base	Age	94	67	86	26.64
1	Initial GCS score				
1	Age	94	75	89	26.4
	Initial GCS score				
2	Retinal hemorrhage				
2	Age	94	92	94	24.52
	Initial GCS score				
	Retinal hemorrhage				
	Lactate present				
3	Age	97	92	96	10.72
	Initial GCS score				
	Lactate present				
	Mean total NAA/creatinine ratio				
4	Age	97	92	96	7.47
	Initial GCS score				
	Retinal hemorrhage				
	Mean total NAA/creatinine ratio				
5	Age	100	100	100	0.000
	Initial GCS score				
	Retinal hemorrhage				
	Lactate present				
	Mean total NAA/creatinine ratio				

NAA indicates *N*-acetylaspartate.

complicated hospital courses, as reflected by increased intracranial pressure and the need for assisted ventilation.

Several clinical variables (Table 1), including the presence of retinal hemorrhage, were significantly different for children with poor outcomes, as expected and as reported previously.^{18–20,29} We found strong correlations between the presence of retinal hemorrhage and reduced *N*-acetylaspartate ratios, taken as possible evidence of traumatic axonal injury in areas susceptible to impact or shaking such as the CC.

MRI findings of subdural or subarachnoid hemorrhage, skull fractures, and ischemia are seen for large proportions of children after NAT, regardless of outcomes. Although these findings are useful for determining that traumatic abuse has occurred, we did not find them as useful for outcome prediction as metabolite data.

Outcome Prediction

Our logistic regression analysis found that a combination of age, clinical variables, and metabolite data was most accurate in predicting outcomes. The clinical variables of age and initial GCS score alone were quite good at predicting which children would have good outcomes; however, they identified only two thirds of the patients with poor outcomes. The addition of brain metabolite data, particularly the mean total *N*-acetylaspartate/creatinine ratio and the presence of lactate, improved our ability to predict poor outcomes.

It is not surprising that decreases in *N*-acetylaspartate levels in children with brain injury would improve prediction of poor outcomes. Previous studies using MRSI in a pediatric cohort with accidental TBI (GCS scores of 3–15) found that MRSI detected significantly decreased *N*-acetylaspartate/creatinine ratios in brain tissue that appeared normal on MRI scans and MRSI

was a sensitive technique for detecting diffuse axonal injury even in mild TBI.²² A follow-up study with that cohort showed that *N*-acetylaspartate measurements and derived ratios were positively and moderately to strongly correlated with cognitive scores and with memory and visual perceptual functioning and that total mean *N*-acetylaspartate/creatinine ratios from MRSI alone explained >40% of the variance in intellectual and neuropsychological scores.²⁵ As pointed out by others, diffuse axonal injury is a general term, because the pathogenesis of axonal injury includes traumatic, vascular, and metabolic factors.^{30,31} In the setting of NAT, both traumatic (acceleration-deceleration forces) and vascular (axonal HII) factors are likely to produce associated metabolic changes, as evidenced in our data.

Decreased *N*-acetylaspartate levels attributable to neuronal injury, as well as the presence of lactate on MRSI scans, seem to be especially useful in predicting outcomes after HII.^{32–34} It has been suggested that HII is more likely to occur after NAT.^{17,19} Victims of abuse usually are younger, compared with children with TBI resulting from accidental causes. Infants and young children have less-mature airway-protective reflexes, which places them at higher risk of respiratory failure, as reflected in the higher rates of intubation with NAT, compared with accidental TBI.¹⁹ Animal models have shown that TBI can produce hyperacute central apnea and respiratory dysfunction.³⁵ Autopsy studies with victims of NAT have shown that injuries to the lower brainstem and spinal cord are associated with apnea and microscopic evidence of HII.^{36,37}

Lactate is thought to be a marker for HII and has been reported in victims of NAT. Several studies have associated the presence of lactate on MRSI scans with poor outcomes.^{21,23,25} Lactate

presence has been related to multiple factors, including excessive release of glutamate, disordered mitochondrial and oxidative metabolism, and systemic responses to trauma.^{38–41} The presence of lactate in 83% of NAT victims with poor outcomes in our study is in line with the work of other investigators who found evidence of HII in patients with inflicted trauma,^{17,19} and this suggests that the presence of HII (ie, lactate) and *N*-acetylaspartate changes are integral in determining prognosis.

In this study, metabolite changes on MRSI scans were shown to be more predictive of outcomes than were other clinical and MRI findings commonly seen in patients after NAT, which

demonstrates that metabolic information from MRSI adds value to the study of NAT. It was interesting that *N*-acetylaspartate/creatine ratios were more predictive than lactate presence. Perhaps this is because decreased *N*-acetylaspartate/creatine ratios reflect neuronal injury or dysfunction resulting from both traumatic and ischemic injury, whereas lactate reflects primarily HII.

Study Limitations

There are a number of limitations to our study. Our retrospective chart review included only patients who returned to a clinic at our hospital ≥ 6 months after injury. Therefore, a large proportion of subjects with greater initial injury and with poorer outcomes

than normally expected was included in our study, because children with good outcomes might not have needed or sought follow-up medical care. In addition, metabolite levels change rapidly in young children during brain maturation and, although the age groups compared in this study were not significantly different, it is possible that metabolite ratios were somewhat affected by maturational changes. Another limitation of our study is the use of the PCPCS, which provides only overall neurologic outcomes. Additional studies with comprehensive neuropsychological batteries are needed to determine whether MRSI metabolite data correlate with specific areas of cognitive and motor impairment in children with NAT.

REFERENCES

- Langlois JA, Rutland-Brown W, Thomas KE. The incidence of traumatic brain injury among children in the United States: differences by race. *J Head Trauma Rehabil*. 2005;20(3):229–238
- Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975; 1(7905):480–484
- Broman SH, Michel ME. *Traumatic Head Injury in Children*. New York, NY: Oxford University Press; 1995
- Levin HS, Aldrich EF, Saydjari C, et al. Severe head injury in children: experience of the Traumatic Coma Data Bank. *Neurosurgery*. 1992;31(3):435–443
- van der Naalt J, Hew JM, van Zomeren AH, Sluiter WJ, Minderhoud JM. Computed tomography and magnetic resonance imaging in mild to moderate head injury: early and late imaging related to outcome. *Ann Neurol*. 1999;46(1):70–78
- Dashti SR, Decker DD, Razzaq A, Cohen AR. Current patterns of inflicted head injury in children. *Pediatr Neurosurg*. 1999;31(6): 302–306
- Duhaime AC, Alario AJ, Lewander WJ, et al. Head injury in very young children: mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. *Pediatrics*. 1992;90(2):179–185
- US Department of Health and Human Services, Administration on Children, Youth, and Families. *Child Maltreatment 2006*. Washington, DC: US Government Printing Office; 2008
- Duhaime AC, Christian C, Moss E, Seidl T. Long-term outcome in infants with the shaking-impact syndrome. *Pediatr Neurosurg*. 1996;24(6):292–298
- Makaroff KL, Putnam FW. Outcomes of infants and children with inflicted traumatic brain injury. *Dev Med Child Neurol*. 2003; 45(7):497–502
- Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. *N*-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. *Prog Neurobiol*. 2007;81(2):89–131
- Demougeot C, Garnier P, Mossiat C, et al. *N*-Acetylaspartate, a marker of both cellular dysfunction and neuronal loss: its relevance to studies of acute brain injury. *J Neurochem*. 2001;77(2):408–415
- Clark JB. *N*-Acetyl aspartate: a marker for neuronal loss or mitochondrial dysfunction. *Dev Neurosci*. 1998;20(4–5):271–276
- Signoretti S, Marmarou A, Fatouros P, et al. Application of chemical shift imaging for measurement of NAA in head injured patients. *Acta Neurochir Suppl*. 2002;81: 373–375
- Cecil KM, Hills EC, Sandel ME, et al. Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. *J Neurosurg*. 1998;88(5):795–801
- Gilles EE, Nelson MD Jr. Cerebral complications of nonaccidental head injury in childhood. *Pediatr Neurol*. 1998;19(2):119–128
- Johnson DL, Boal D, Baule R. Role of apnea in nonaccidental head injury. *Pediatr Neurosurg*. 1995;23(6):305–310
- Barlow KM, Minns RA. The relation between intracranial pressure and outcome in nonaccidental head injury. *Dev Med Child Neurol*. 1999;41(4):220–225
- Ichord RN, Naim M, Pollock AN, Nance ML, Margulies SS, Christian CW. Hypoxic-ischemic injury complicates inflicted and accidental traumatic brain injury in young children: the role of diffusion-weighted imaging. *J Neurotrauma*. 2007;24(1):106–118
- Makaroff KL, Cecil KM, Care M, Ball WS Jr. Elevated lactate as an early marker of brain injury in inflicted traumatic brain injury. *Pediatr Radiol*. 2005;35(7):668–676
- Ashwal S, Holshouser BA, Shu SK, et al. Predictive value of proton magnetic resonance spectroscopy in pediatric closed head injury. *Pediatr Neurol*. 2000;23(2):114–125
- Holshouser BA, Tong KA, Ashwal S. Proton MR spectroscopic imaging depicts diffuse axonal injury in children with traumatic brain injury. *AJNR Am J Neuroradiol*. 2005; 26(5):1276–1285
- Brenner T, Freier MC, Holshouser BA, Burley T, Ashwal S. Predicting neuropsychologic outcome after traumatic brain injury in children. *Pediatr Neurol*. 2003; 28(2):104–114
- Yeo RA, Phillips JP, Jung RE, Brown AJ,

- Campbell RC, Brooks WM. Magnetic resonance spectroscopy detects brain injury and predicts cognitive functioning in children with brain injuries. *J Neurotrauma*. 2006;23(10):1427–1435
25. Babikian T, Freier MC, Ashwal S, Riggs ML, Burley T, Holshouser BA. MR spectroscopy: predicting long-term neuropsychological outcome following pediatric TBI. *J Magn Reson Imaging*. 2006;24(4):801–811
 26. Hymel KP, Makoroff KL, Laskey AL, Conaway MR, Blackman JA. Mechanisms, clinical presentations, injuries, and outcomes from inflicted versus noninflicted head trauma during infancy: results of a prospective, multicentered, comparative study. *Pediatrics*. 2007;119(5):922–929
 27. Holmes G, Rowe J, Hafford J, Schmidt R, Testa M, Zimmerman A. Prognostic value of the electroencephalogram in neonatal asphyxia. *Electroencephalogr Clin Neurophysiol*. 1982;53(1):60–72
 28. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr*. 1992;121(1):68–74
 29. Adelson PD. Prognosis and recovery. In: Marion DW, ed. *Traumatic Brain Injury*. New York, NY: Thieme Medical; 1999: 283–290
 30. Dolinak D, Reichard R. An overview of inflicted head injury in infants and young children, with a review of β -amyloid precursor protein immunohistochemistry. *Arch Pathol Lab Med*. 2006;130(5):712–717
 31. Gill JR, Goldfeder LB, Armbrustmacher V, Coleman A, Mena H, Hirsch CS. Fatal head injury in children younger than 2 years in New York City and an overview of the shaken baby syndrome. *Arch Pathol Lab Med*. 2009;133(4):619–627
 32. Dubowitz DJ, Bluml S, Arcinue E, Dietrich RB. MR of hypoxic encephalopathy in children after near drowning: correlation with quantitative proton MR spectroscopy and clinical outcome. *AJNR Am J Neuroradiol*. 1998;19(9):1617–1627
 33. Kreis R, Arcinue E, Ernst T, Shonk TK, Flores R, Ross BD. Hypoxic encephalopathy after near-drowning studied by quantitative ^1H -magnetic resonance spectroscopy. *J Clin Invest*. 1996;97(5):1142–1154
 34. Holshouser BA, Ashwal S, Luh GY, et al. Proton MR spectroscopy after acute central nervous system injury: outcome prediction in neonates, infants, and children. *Radiology*. 1997;202(2):487–496
 35. Atkinson JL, Anderson RE, Murray MJ. The early critical phase of severe head injury: importance of apnea and dysfunctional respiration. *J Trauma*. 1998;45(5):941–945
 36. Geddes JF, Vowles GH, Hackshaw AK, Nickols CD, Scott IS, Whitwell HL. Neuropathology of inflicted head injury in children, part II: microscopic brain injury in infants. *Brain*. 2001;124(7):1299–1306
 37. Geddes JF, Hackshaw AK, Vowles GH, Nickols CD, Whitwell HL. Neuropathology of inflicted head injury in children, part I: patterns of brain damage. *Brain*. 2001;124(7):1290–1298
 38. Krishnappa IK, Contant CF, Robertson CS. Regional changes in cerebral extracellular glucose and lactate concentrations following severe cortical impact injury and secondary ischemia in rats. *J Neurotrauma*. 1999;16(3):213–224
 39. Hovda DA, Becker DP, Katayama Y. Secondary injury and acidosis. *J Neurotrauma*. 1992;9(suppl 1):S47–S60
 40. Prasad MR, Ramaiah C, McIntosh TK, Dempsey RJ, Hipkens S, Yurek D. Regional levels of lactate and norepinephrine after experimental brain injury. *J Neurochem*. 1994;63(3):1086–1094
 41. Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Lactate accumulation following concussive brain injury: the role of ionic fluxes induced by excitatory amino acids. *Brain Res*. 1995;674(2):196–204

Overturning the Best Evidence: An article in The Wall Street Journal (Groopman J and Hartzband P, The Wall Street Journal, August 31, 2009) on myths versus realities of health care today noted a study from the Ottawa Health Research Institute regarding how quickly results of best evidence clinical studies are overturned by subsequent studies. The study reveals that within one year, 15 of 100 recommendations for care based on best evidence were reversed, 23 within 2 years, and 50 by 5½ years. Examples cited included reversing recommendations regarding the benefits of estrogen for postmenopausal women, low fat diets for obese individuals, and the need for tight control of blood sugar.

Noted by JFL, MD

Magnetic Resonance Spectroscopy Predicts Outcomes for Children With Nonaccidental Trauma

Gregory S. Aaen, Barbara A. Holshouser, Clare Sheridan, Cherie Colbert, Melinda McKenney, Daniel Kido and Stephen Ashwal

Pediatrics 2010;125:295

DOI: 10.1542/peds.2008-3312

Updated Information & Services	including high resolution figures, can be found at: /content/125/2/295.full.html
Supplementary Material	Supplementary material can be found at: /content/suppl/2010/02/18/125.2.295.DC1.html
References	This article cites 38 articles, 6 of which can be accessed free at: /content/125/2/295.full.html#ref-list-1
Citations	This article has been cited by 3 HighWire-hosted articles: /content/125/2/295.full.html#related-urls
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Endocrinology /cgi/collection/endocrinology_sub Metabolic Disorders /cgi/collection/metabolic_disorders_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2010 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Magnetic Resonance Spectroscopy Predicts Outcomes for Children With Nonaccidental Trauma

Gregory S. Aaen, Barbara A. Holshouser, Clare Sheridan, Cherie Colbert, Melinda McKenney, Daniel Kido and Stephen Ashwal

Pediatrics 2010;125;295

DOI: 10.1542/peds.2008-3312

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[/content/125/2/295.full.html](http://content/125/2/295.full.html)

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2010 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

