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Umbilical Artery Lactate Correlates with Brain Lactate in Term Infants

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Abstract

Objective—The objective of this study was to determine the correlation between umbilical artery lactate with brain lactate in nonanomalous term infants.

Study Design—We performed a nested case–control study within an on-going prospective cohort of more than 8,000 consecutive singleton term (> 37 weeks) nonanomalous infants. Neonates underwent cerebral magnetic resonance imaging (MRI) within the first 72 hours of life. Cases (umbilical artery pH < 7.10) were gender and race matched 1:3 to controls (umbilical artery pH > 7.20). Single voxel magnetic resonance spectroscopy (MRS), lactate, and N-acetyl aspartate (NAA) for normalization were calculated using Siemens software (Plano, TX). Linear regression estimated the association between incremental change in umbilical artery lactate and brain lactate, both directly and as a ratio with NAA.

Results—Of 175 infants who underwent MRI with spectral sequencing, 52 infants had detectable brain lactate. The 52 infants with brain lactate peaks had umbilical artery lactate values of 1.6 to 11.4 mmol/L. For every 1.0 mmol/L increase in umbilical artery lactate, there was an increase in brain lactate of 0.02, which remained significant even when corrected for NAA.

Conclusion—MRS measured brain lactate is significantly correlated with umbilical artery lactate in nonanomalous term infants, which may help explain the observed association between umbilical artery lactate and neurologic morbidity.

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Note

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Keywords

cerebral lactate; umbilical artery lactate; brain injury; magnetic resonance spectroscopy

Fetal lactate in labor measured by scalp sampling has been associated with low 5-minute Apgar scores,¹ admission to the neonatal intensive care unit, and hypoxic-ischemic encephalopathy (HIE).^{2,3} Recent studies have suggested that umbilical artery lactate is superior to pH or base excess in predicting adverse outcomes,^{4,5} likely because lactate is a direct product of anaerobic metabolism and the source of umbilical artery lactate has been shown to be fetal (as opposed to maternal or placental).⁶ Thus, umbilical artery lactate is a direct measure of fetal hypoxia, and it is known that the fetal brain is exquisitely sensitive to hypoxic injury.⁷

Cerebral magnetic resonance imaging (MRI) techniques exist which allow noninvasive detection and quantification of brain lactate. Specifically, magnetic resonance spectroscopy (MRS) can detect different metabolites with characteristic resonant frequencies that can be encoded and identified.⁸ It offers insight into the biochemical and metabolic status in the tissue, and often precedes anatomic changes seen on conventional T1- or T2-weighted images. In a normal full-term neonate without brain injury, there are robust N-acetyl aspartate (NAA), choline, and creatine peaks visible on MRS but no evidence of a lactate peak. NAA is present in high concentrations in the central nervous system (CNS) and is a marker of the functional integrity of neuronal mitochondrial metabolism.⁹ It is reduced in most neurodegenerative processes and neuronal and axonal injury. Choline is a precursor for membrane synthesis in the CNS and reflects the structural components of the membrane myelin sheaths.¹⁰ Choline peaks increase with increased cellular and myelin sheath injury. The creatine peak consists of the creatine and phosphocreatine protons and remains relatively stable, making it a useful standard for comparison with other metabolic peaks. In contrast, in HIE, brain lactate measured in the deep gray matter, specifically in the thalamus, is elevated, reflecting anaerobic glycolysis.^{11,12} Brain lactate measured by MRS is an established biomarker of long-term neurologic morbidity in infants born preterm and those with HIE.^{13,14} However, no data exist regarding the relationship between brain lactate and cord blood lactate in infants in term-born infants not selected by HIE.

We aimed to use MRS techniques to detect and quantify cerebral lactate shortly after birth and to correlate brain lactate with umbilical artery lactate in anatomically normal term infants.

Materials and Methods

We performed a nested case-control study within a prospective cohort study of more than 8,000 consecutive term (> 37 weeks) births. Women with singleton, nonanomalous pregnancies admitted for delivery were included in the parent cohort, which is aimed at identifying patterns of electronic fetal monitoring (EFM) and intrapartum factors predictive of term birth morbidity. Additional inclusion criteria were the continuous use of EFM in labor and umbilical artery lactate obtained at birth, both of which are universal at our institution. Lactate is part of the routine analysis performed on all umbilical artery pH

samples. For umbilical artery cord samples, a clamped segment of cord immediately after delivery was obtained. To measure umbilical artery pH and umbilical artery lactate, whole blood was placed in automated bench-top analyzers. Specifically, the GEM Premier 4000 analyzer (Bedford, MA) was used to measure umbilical artery pH and the DXC-800 automated chemistry analyzer (Brea, CA) was used for the umbilical artery lactate assays. Informed consent was obtained from all participants.

Cases were identified as the first 55 infants born with an umbilical artery pH ≤ 7.10 . Three controls (with an umbilical artery pH > 7.20) were chosen for every case using a random number generator based on study identification number in the parent cohort, then matched by gender and race to be representative of the cohort population. The neonatal participants underwent nonsedated cerebral MRI in the first 72 hours of life on a Siemens 3T Tim Trio scanner. After T1 and T2 sequences were acquired, research sequences including MRS were obtained, allowing for the detection and quantification of brain lactate. Participants underwent a single slice chemical shifting imaging slash study. Scan parameters were field of view (140 mm) 2, thickness 12 mm, repetition time 1,650 ms, echo time (TE) 144 ms, Hz/Px (bandwidth) 1,200, and voxel size $8.8 \times 8.8 \times 12 \text{ mm}^3$. Spectroscopy data were analyzed using algorithms provide by the Siemen's spectroscopy tab at the scanner console, as previously used in prior studies in humans and animals.¹⁵ Blind to umbilical artery lactate and clinical data, a single technician placed a region of interest (ROI) over the left thalamus where MRS data were obtained to measure brain lactate. The thalamus is the accepted neuroimaging standard ROI when evaluating MRS in the setting of HIE.¹¹ The basal ganglia are affected more severely in HIE because they have higher energy demands and more developed neurotransmission compared with the cortical gray matter. Quantitation of metabolites was done by measuring the integral values of each metabolite. The integral value of the metabolite is proportional to the tissue concentrations; therefore, the ratios of the integral values are proportional to the ratios of the concentrations.¹⁶ The lactate peak, completely inverted at a TE of 144 ms, was identified as a doublet at 1.33 ppm resonance frequency. As is standard, NAA and choline were measured and used for normalization (Fig. 1).¹⁷

Descriptive analyses were used to describe the participants overall and by presence or absence of brain lactate with the use of Fisher exact test, two-sample Student *t*-test, or Wilcoxon rank-sum test. Stratified analyses identified potentially confounding factors, and linear regressions were used to estimate the relationship between umbilical artery lactate and brain lactate. The final models adjusted for the remaining significant variables, day of life at delivery was not retained, but mode of delivery, nulliparity, and fever remained and the models were tested with the Hosmer–Lemeshow goodness- of-fit test. All analyses were performed using STATA Version 12 (College Station, TX).

Results

In this study, 220 infants underwent MRI. Of those, 20 underwent MRI before the lactate sequencing was added to the protocol, an additional 22 had no spectral sequence performed due to intolerance of length of exam and three more had MRI studies with quality insufficient for MRS interpretation, leaving 175 infants available for analysis. Fifty-two

infants had an inverted lactate doublet peak qualitatively identified on the single voxel in the left thalamus. Selected clinical characteristics assessed based on the presence or absence of brain lactate peak demonstrated no significant difference in average maternal age, parity, or body mass index, although the majority of the women were obese (Table 1). Infants with a visible brain lactate peak on the MRI studies were more likely to deliver vaginally, either spontaneously or by operative vaginal delivery. Importantly for this analysis, case or control status did not differ between the groups ($p = 0.93$).

Of the infants with a brain lactate peak, umbilical artery lactate values ranged from 1.6 to 11.4 mmol/L, and correlated with a rise in brain lactate (Fig. 2). After adjusting for mode of delivery, fever, and nulliparity, increasing umbilical artery lactate was significantly associated with an increase in quantitative brain lactate. These results were replicated with a significant association between umbilical artery gas and the lactate to NAA ratios. For every 1 mmol/L increase in umbilical artery lactate, we found an increase in quantitative brain lactate of 0.02 (Table 2). We also found that often proposed surrogate markers for morbidity in term-born infants, such as Apgar scores,¹ umbilical artery pH, and level of nursery admission did not distinguish infants with brain lactate peaks from those without. More than 95% of the infants with a brain lactate peak on MRS were admitted to the normal nursery without encephalopathy, and none was admitted to the NICU (Table 3).

Discussion

We found that MRS measured brain lactate is significantly correlated with umbilical artery lactate in nonanomalous term infants, which may help explain the observed association between umbilical artery lactate and neurologic morbidity. Other previously described markers of morbidity such as Apgar scores,¹ level of nursery admission, and umbilical artery pH did not identify infants with increased brain lactate. However, increased brain lactate alone is not sufficient to identify infants with injury, as most went to the normal nursery with no evidence of abnormality.

MRS has been found useful in the evaluation and management of other neonatal conditions. Miller et al¹⁸ combined MRS with diffusion-weighted imaging to demonstrate that neonates with congenital heart disease had brain abnormalities prior to open heart surgery, including higher lactate/choline ratios correlated with adverse short-term outcomes. Holshouser et al¹⁹ evaluated MRS in neonates and children with acute accidental and nonaccidental brain injury and demonstrated that elevated lactate/NAA ratios were associated with adverse outcome including death or neurologic deficits. In another study of infants with shaken baby syndrome, Haseler et al²⁰ demonstrated that biochemical changes detected on MRS precede any anatomic changes detectable on MRI.

The ability to correlate brain lactate to umbilical artery lactate is meaningful. In a large prospective cohort study by Tuuli et al,²¹ the measurement of umbilical artery lactate was found to be a superior predictor of neonatal morbidity in comparison to umbilical artery pH or base excess in term infants. The authors performed detailed analyses that suggested umbilical artery lactate provided greater sensitivity and specificity compared with pH (83.9 and 74.1% compared with 75.0 and 70.6%).²¹ The use of umbilical artery lactate is a

significant surrogate marker because of its ability to directly measure anaerobic metabolism, which has a stronger biological basis than either umbilical artery pH or base excess level due to the varying methods by which pH and base excess are calculated and estimated.^{4,21}

There are potential limitations of our study to consider. Due to its observational nature, the potential for confounding is present. However, multivariable analyses allowed us to adjust for potential confounders in our estimates of the relationship between lactate in the umbilical artery and the brain. There is also an inherent component of subjectivity in certain components of advanced MRI techniques, such as MRS. We attempted to minimize these by having a single, experienced MR analyst conduct the MRS analysis in standard fashion blind to all clinical data including umbilical cord blood parameters. Finally, while umbilical artery lactate and brain lactate were significantly associated, correlation was weak in our study.

We would like to offer some strengths to consider as well. First, this is a large study that included not just acidotic infants undergoing cerebral MRI shortly after birth, but nonacidotic, otherwise normal, full-term neonates as well. The random sampling of the controls and nesting of this study within an unselected larger cohort allows generalizability and reduces selection bias. Robust clinical data allowed us to plan for and measure relevant potentially confounding factors.

In conclusion, we found that in nonanomalous term infants, umbilical artery lactate is significantly correlated with the amount of brain lactate detected by MRS. We also noted that the majority of infants in our cohort with elevated cord and brain lactate were clinically normal and that, contrary to reports in the literature, these metabolic abnormalities are transiently present in a subset of transitioning normal newborns. Thus, the presence of elevated brain lactate may be necessary but not sufficient to detect brain injury in neonatal HIE. This finding may begin to explain why recent observational data have demonstrated an association between umbilical artery lactate and morbidities in term-born infants, and described it to be a superior marker compared with others.²¹ These findings represent one step within the overarching aims of this study to explore the use of neonatal MRI to identify term-born infants at risk to allow intervention. Additional advanced analyses will allow us to explore the use of MRS lactate in combination with other MRI findings both in correlation to risk of injury as well as to potentially explain, in part, the relationship between umbilical artery lactate and term infant morbidity. However, we believe this was an important first step in pursuit of biomarkers for the majority of neurologic injuries at term.

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References

1. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anest Anal.* 1953; 32(4):260–267.

2. Kruger K, Hallberg B, Blennow M, Kublickas M, Westgren M. Predictive value of fetal scalp blood lactate concentration and pH as markers of neurologic disability. *Am J Obstet Gynecol.* 1999; 181(5 Pt 1):1072–1078. [PubMed: 10561620]
3. Allen RM, Bowling FG, Oats JJ. Determining the fetal scalp lactate level that indicates the need for intervention in labour. *Aust N Z J Obstet Gynaecol.* 2004; 44(6):549–552. [PubMed: 15598295]
4. Wiberg N, Källén K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. *Acta Obstet Gynecol Scand.* 2010; 89(10):1263–1269. [PubMed: 20846059]
5. Gjerris AC, Staer-Jensen J, Jørgensen JS, Bergholt T, Nickelsen C. Umbilical cord blood lactate: a valuable tool in the assessment of fetal metabolic acidosis. *Eur J Obstet Gynecol Reprod Biol.* 2008; 139(1):16–20. [PubMed: 18063469]
6. Nordström L, Malcus P, Chua S, Shimojo N, Arulkumaran S. Lactate and acid-base balance at delivery in relation to cardiotocography and T/QRS ratios in the second stage of labour. *Eur J Obstet Gynecol Reprod Biol.* 1998; 76(2):157–160. [PubMed: 9481566]
7. Gunn AJ, Bennet L. Fetal hypoxia insults and patterns of brain injury: insights from animal models. *Clin Perinatol.* 2009; 36(3):579–593. [PubMed: 19732615]
8. Xu D, Vigneron D. Magnetic resonance spectroscopy imaging of the newborn brain—a technical review. *Semin Perinatol.* 2010; 34(1):20–27. [PubMed: 20109969]
9. 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. [PubMed: 17275978]
10. Zeisel SH. Nutritional importance of choline for brain development. *J Am Coll Nutr.* 2004; 23(6, Suppl):621S–626S. [PubMed: 15640516]
11. Barkovich AJ, Miller SP, Barth A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *Am J Neuroradiol.* 2006; 27(3):533–547. [PubMed: 16551990]
12. Wolf RL, Zimmerman RA, Clancy R, Haselgrove JH. Quantitative apparent diffusion coefficient measurements in term neonates for early detection of hypoxic-ischemic brain injury: initial experience. *Radiology.* 2001; 218(3):825–833. [PubMed: 11230663]
13. Leth H, Toft PB, Peitersen B, Lou HC, Henriksen O. Use of brain lactate levels to predict outcome after perinatal asphyxia. *Acta Paediatr.* 1996; 85(7):859–864. [PubMed: 8819555]
14. Cowan FM, Pennock JM, Hanrahan JD, Manji KP, Edwards AD. Early detection of cerebral infarction and hypoxic ischemic encephalopathy in neonates using diffusion-weighted magnetic resonance imaging. *Neuropediatrics.* 1994; 25(4):172–175. [PubMed: 7824088]
15. Munkeby BH, De Lange C, Emblem KE, et al. A piglet model for detection of hypoxic-ischemic brain injury with magnetic resonance imaging. *Acta Radiol.* 2008; 49(9):1049–1057. [PubMed: 18720081]
16. Nelson SJ. Analysis of volume MRI and MR spectroscopic imaging data for the evaluation of patients with brain tumors. *Magn Reson Med.* 2001; 46(2):228–239. [PubMed: 11477625]
17. Thayyil S, Chandrasekaran M, Taylor A, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics.* 2010; 125(2):e382–e395. [PubMed: 20083516]
18. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med.* 2007; 357(19):1928–1938. [PubMed: 17989385]
19. Holshouser BA, Ashwal S, Shu S, Hinshaw DB Jr. Proton MR spectroscopy in children with acute brain injury: comparison of short and long echo time acquisitions. *J Magn Reson Imaging.* 2000; 11(1):9–19. [PubMed: 10676615]
20. Haseler LJ, Arcinue E, Danielsen ER, Bluml S, Ross BD. Evidence from proton magnetic resonance spectroscopy for a metabolic cascade of neuronal damage in shaken baby syndrome. *Pediatrics.* 1997; 99(1):4–14. [PubMed: 8989330]
21. Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA, Cahill AG. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. *Obstet Gynecol.* 2014; 124(4):756–761. [PubMed: 25198278]

Fig. 1.

A MR spectral map from a voxel placed in the left thalamus demonstrating metabolite peaks and integral values. Note the inverted lactate peak at 1.33 ppm in this sequence run at a TE of 144 ms. MR, magnetic resonance; TE, echo time.

Fig. 2.

A correlation graph demonstrating the distribution of MRI and umbilical artery lactate in infants with a qualitative lactate peak. MRI, magnetic resonance imaging.

Table 1

Clinical characteristics among those with a brain lactate peak and those without

	Brain lactate > 0 (N = 52)	Brain lactate = 0 (N = 123)	p-Value ^a
Maternal age, y	24.6 ± 4.8	24.6 ± 6.2	0.98
Maternal age ≥ 35 y	1 (1.9)	11 (8.8)	0.19
Gestational age at delivery, wk	38.8 ± 1.3	39.1 ± 1.2	0.15
Body mass index	32.3 ± 7.1	34.4 ± 8.0	0.11
African American race	43 (82.7)	106 (84.8)	0.82
Any gestational hypertension or preeclampsia	5 (9.6)	21 (16.8)	0.25
Gestational diabetes mellitus	0 (0.0)	3 (2.4)	0.56
Pregestational diabetes mellitus	0 (0.0)	2 (1.6)	1.00
Nulliparous	13 (25.0)	41 (32.8)	0.37
Prior cesarean	5 (9.6)	14 (11.2)	1.00
Labor type			
Spontaneous	20 (38.5)	34 (27.2)	0.32
Augmented	11 (21.2)	28 (22.4)	
Induction	21 (40.4)	63 (50.4)	
Prostaglandin	7 (13.5)	23 (18.4)	0.51
Foley bulb	7 (13.5)	20 (16.0)	0.82
Oxytocin	31 (59.6)	86 (68.8)	0.30
Birth weight, g	3,183 ± 421	3,280 ± 494	0.22
Birth weight > 4,000 g	2 (3.9)	12 (9.6)	0.24
Birth weight < 1,800 g	0 (0.0)	0 (0.0)	N/A
Mode of delivery			
Vaginal	37 (71.2)	81 (64.8)	0.05
Operative vaginal	6 (11.5)	5 (4.0)	
Cesarean	9 (17.3)	39 (31.2)	
Maternal fever			
At delivery	1 (1.9)	4 (3.2)	1.00
Postpartum	0 (0.0)	7 (5.6)	0.11
Umbilical artery lactate	3.8 ± 2.4	3.9 ± 2.7	0.67
Umbilical artery pH	7.24 ± 0.11	7.23 ± 0.11	0.38
Apgar			
1 min	8 (8, 8)	8 (7, 8)	0.30
5 min	9 (9, 9)	9 (9, 9)	0.32
Admitting nursery			
Newborn	50 (96.2)	105 (85.4)	0.13
Special care	2 (3.9)	13 (10.6)	
NICU	0 (0.0)	5 (4.1)	

Abbreviation: NICU, neonatal intensive care unit.

Note: $N(\%)$ or mean (standard deviation).

^a p -Values based on Fisher exact test, two sample Student t -test, or Wilcoxon rank-sum test.

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Table 2

Association between brain and umbilical artery lactate

Dependent variable	N	Unadjusted		Adjusted ^a	
		b	p-Value	b	p-Value
Brain lactate	175	-0.001	0.94	0.006	0.52
Brain lactate > 0	52	0.010	0.11	0.021	0.02
Brain lactate to NAA ratio	52	0.005	0.11	0.008	0.05

Abbreviation: NAA, N-acetyl aspartate.

Note: b represents the change in dependent variable per unit change in umbilical artery lactate.

^a Adjusted for nulliparity, fever, and mode of delivery.

Table 3

Clinical characteristics by presence of brain lactate

	Brain lactate > 0 (N = 52)	Brain lactate= 0 (N = 123)	p-Value^a
1-min Apgar	8 (8, 8)	8 (7, 8)	0.30
5-min Apgar	9 (9, 9)	9 (9, 9)	0.32
Umbilical artery pH	7.24 ± 0.11	7.23 ± 0.10	0.38
Nursery level			
I	50 (96.2)	105 (85.4)	0.13
II	2 (3.9)	13 (10.6)	
IV	0 (0.0)	5 (4.1)	

Note: N(%), mean (standard deviation), median (p25, p75).

^a p-Values based on Fisher exact test, two sample Student *t*-test, or Wilcoxon rank-sum test.