Clinical Factors Associated with Cerebral Metabolism in Term Neonates with Congenital Heart Disease

Anna Lonyai Harbison, MD[1], Jodie K. Votava-Smith, MD[1], Sylvia del Castillo, MD[2], S. Ram Kumar, MD, PhD[3], Vince Lee, BS[4], Vincent Schmithorst, PhD[4], Hollie A. Lai, MD[5], Sharon O'Neil, PhD[6], Stefan Bluml, PhD[5], Lisa Paquette, MD[7], and Ashok Panigrahy, MD[4]

Objective To determine associations between patient and clinical factors with postnatal brain metabolism in term neonates with congenital heart disease (CHD) via the use of quantitative magnetic resonance spectroscopy.

Study design Neonates with CHD were enrolled prospectively to undergo pre- and postoperative 3T brain magnetic resonance imaging. Short-echo single-voxel magnetic resonance spectroscopy of parietal white matter was used to quantify metabolites related to brain maturation (n-acetyl aspartate, choline, myo- inositol), neurotransmitters (glutamate and gamma-aminobutyric acid), energy metabolism (glutamine, citrate, glucose, and phosphocreatine), and injury/apoptosis (lactate and lipids). Multivariable regression was performed to search for associations between (1) patient-specific/prenatal/preoperative factors with concurrent brain metabolism and (2) intraoperative and postoperative factors with postoperative brain metabolism.

Results A total of 83 magnetic resonance images were obtained on 55 subjects. No patient-specific, prenatal, or preoperative factors associated with concurrent metabolic brain dysmaturation or elevated lactate could be identified. Chromosome 22q11 microdeletion and age at surgery were predictive of altered concurrent white matter phosphocreatine ($P < .0055$). The only significant intraoperative association found was increased deep hypothermic circulatory arrest time with reduced postoperative white matter glutamate and gamma-aminobutyric acid ($P < .0072$). Multiple postoperative factors, including increased number of extracorporeal membrane oxygenation days ($P < .0067$), intensive care unit, length of stay ($P < .0047$), seizures in the intensive care unit ($P < .0009$), and home antiepileptic use ($P < .0002$), were associated with reduced postoperative white matter n-acetyl aspartate.

Conclusion Multiple postoperative factors were found to be associated with altered brain metabolism in term infants with CHD, but not patient-specific, preoperative, or intraoperative factors. *(J Pediatr 2017;183:67-73).*

Neonates with complex congenital heart disease (CHD) are at risk for poor neurodevelopmental outcomes, which likely are related to an interplay of cerebral dysmaturation and acquired brain injury.[1,2] The relationship between cerebral immaturity and risk factors of adverse neurodevelopmental outcome in patients with CHD is poorly defined. In addition, identifying modifiable risk factors that could help enhance long-term neurodevelopmental outcomes via future interventional clinical trials is a priority.[3,4] Abnormalities of cerebral maturation have been delineated in CHD by the use of a variety of structural and metabolic neuroimaging techniques such as brain magnetic resonance spectroscopy (MRS).[5-13] MRS measures metabolites that are not only relevant to understanding structural brain maturation but also important for delineating physiological processes such as energy metabolism.[14]

Here, we used quantitative MRS in term newborns with CHD to test the hypothesis that specific epochs of patient and clinical factors (ie, preoperative, intraoperative, and postoperative) are associated with metabolic brain dysmaturation and elevated lactate. We compared multiple patient and preoperative factors with concurrent (pre- and postoperative) brain metabolite measurements. We also compared intraoperative and postoperative factors with postoperative brain metabolite measurements. We used quantitative short-echo 3T MRS, which allows for measurement of metabolites beyond that of long echo MRS technique (limited

CHD	Congenital heart disease	GABA	Gamma-aminobutyric acid
CTICU	Cardiothoracic intensive care unit	MRI	Magnetic resonance imaging
DHCA	Deep hypothermic circulatory arrest	MRS	Magnetic resonance spectroscopy
ECMO	Extracorporeal membrane oxygenation	NAA	N-acetyl aspartate
FDR	False discovery rate		

From the [1]Division of Cardiology, Department of Pediatrics; [2]Department of Anesthesiology, Critical Care Medicine, Children's Hospital of Los Angeles, Los Angeles, CA; [3]Division of Cardiac Surgery, Department of Surgery, Children's Hospital of Los Angeles/University of Southern California, Los Angeles, CA; [4]Department of Pediatric Radiology, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center and University of Pittsburgh School of Medicine, Pittsburgh, PA; [5]Division of Radiology; [6]Division of Neurology; and [7]Division of Neonatology, Department of Pediatrics, Children's Hospital of Los Angeles, Los Angeles, CA

Supported by National Institute of Neurological Disorders and Stroke (K23-063371), the Children's Heart Foundation, the Twenty-Five Club Fund of Magee Women's Hospital, the Mario Lemieux Foundation, University of Southern California Clinical and Translational Science Institute, which is part of the Clinical and Translational Science Awards, a national network funded through the National Center for Advancing Translational Sciences at the National Institutes of Health (UL1TR000130), and Rudi Schulte Foundation. The authors declare no conflicts of interest.

Portions of the study was presented at the meeting of the American Heart Association, Orlando, Florida, November 7-11, 2015.

http://dx.doi.org10.1016/j.jpeds.2016.12.061

to n-acetyl aspartate [NAA], creatine, choline, and lactate) to include additional metabolites related to brain maturation (myo-inositol), neurotransmitters (glutamate and gamma-aminobutyric acid [GABA]), energy metabolism (glutamine, citrate, glucose, creatine, and phosphocreatine), and injury/repair/apoptosis (lipids and lactate).[15,16]

Methods

Patients with critical CHD were recruited prospectively both pre- and postnatally for enrollment in this prospective, observational neuroimaging study at a single center (Children's Hospital Los Angeles, Los Angeles, California). Parental consent was obtained, and the study was approved by the institutional review boards of Children's Hospital Los Angeles (CCI-10-00235 and CCI-09-00055). Critical CHD was defined as a heart defect expected to require corrective or palliative cardiac surgery within the first month of life (exclusion criteria are in **Figure 1**; available at www.jpeds.com). The data collection sources included the electronic medical record as well as intraoperative records. A comprehensive set of patient and clinical factors were selected based on previous studies on neurodevelopment in CHD as well as criteria included in the RACHS-1 scoring system. These are listed in **Table I**.[17-20]

Neonatal Brain Magnetic Resonance Imaging (MRI) and MRS Protocol

Preoperative research brain imaging was conducted when the cardiothoracic intensive care unit (CTICU)/cardiology team determined the patient was stable for transport to the MRI scanner. A postoperative research scan was performed when the patient was younger than 3 months of postnatal age either as an inpatient or outpatient. Most of our scans were research indicated and, as such, no additional sedation/anesthesia was given for purpose of the scan. Most of the preoperative scans were performed on nonintubated, nonsedated patients; however, if a patient was intubated and sedated for clinical reasons at the time of the scan (38% of subjects were intubated preoperatively, **Table I**), their clinically indicated sedation continued under care of the primary CTICU team. Most of the postoperative scans were performed after the infant had stepped down from the CTICU and were done as "feed and bundle" scans without sedation.

MR data were acquired on a Philips 3T Achieva MR System (Ver. 3.2.1.1; Philips Healthcare, Foster City, California) with the use of either a neonatal SENSE coil or a standard 8-channel SENSE head coil. To minimize movement during imaging, infants were secured in Med-Vac Immobilization Bag (CFI Medical, Fenton, Michigan) with multiple levels of ear protection, including ear plugs, MiniMuffs (Natus Medical Inc, Pleasanton, California), and standard headphones. 1H-MRS data were acquired via single-voxel, point-resolved spectroscopy sequence (repetition time = 2 seconds; echo time = 35 milliseconds; 128 signal averages; voxel size: ~3 cm^3) localized to the left parietal white matter, parietal medial cortical gray matter, and left thalamus on axial T2-weighted images (**Figure 2**).[21,22] The scan time for each single-voxel point-resolved spectroscopy acquisition was approximately 5 minutes. In addition, conventional T1-weighted, T2-weighted, and diffusion-weighted images were acquired and reviewed by 2 pediatric neuroradiologists for evidence of punctate white matter lesion, acute focal infarction, and hemorrhage as described previously.[23]

Table I. Patient characteristics for study participants

Characteristics	Number of patients (N = 55, %)
Patient factors	
Male	32 (58%)
Gestational age, wk	38.8 ± 0.91
Birth weight, g	3153 ± 445
Birth weight percentile	31.1 ± 27
Head circumference, cm	33.8 ± 1.6
Head circumference percentile	33.7 ± 1.6
Length, cm	48.3 ± 4
Length percentile	31.8 ± 29
Apgar scores at 1 and 5 min	7.6 ± 1.9, 8.2 ± 1.7
22q11 microdeletion	4 (7%)
Cardiac lesions	
Single ventricle	32 (58%)
Without arch obstruction	10 (18%)
With arch obstruction	23 (40%)
Transposition of great arteries	6 (11%)
Heterotaxy	4 (7%)
Other	12 (22%)
Preoperative factors	
Preoperative ABG pH	7.36 ± 0.07
Preoperative ABG pO_2	51 ± 19
Preoperative ABG lactate	15 ± 6.8
Preoperative renal dysfunction, sepsis, or NEC	0
Preoperative hepatic dysfunction	1 (2%)
Preoperative inotrope use	18 (3%)
Preoperative ventilator use	21 (38%)
Age at surgery, d	6.8 ± 5.4
Intraoperative factors	
Bypass	48 (87%)
Bypass time, min	56.6 ± 31
Aortic cross-clamp	21 (38%)
Aortic cross-clamp, min	48.0 ± 33
Circulatory arrest/DHCA	32 (58%)
Circulatory arrest/DHCA, min	30.2 ± 16
Postoperative factors	
ECMO	6 (11%)
Punctate white matter injury postoperatively	21.2
Unplanned interventions first hospitalization (patients)	24 (44%)
Total ICU days	30.5 ± 33
Total hospital days	44 ± 41
Expired first hospitalization	4 (7%)
Expired total	10 (18%)
Cardiopulmonary resuscitation	2 (4%)
Seizures in ICU	9 (16%)
Home antiepileptics	2 (3.5%)
Home with G-tube	11 (20%)
Home with tracheostomy	3 (5%)
Home on ventilator	1 (2%)

ABG, arterial blood gas; *g-tube*, gastrostomy tube; *hepatic dysfunction*, hepatic dysfunction international normalized ratio > 2; *ICU*, intensive care unit; *NEC*, necrotizing enterocolitis; *renal dysfunction*, renal dysfunction creatinine > 1.

MRS Data Processing

Examples of 1H-MRS spectra are provided in **Figure 2**. Metabolite concentrations were quantified with fully automated