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

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Abstract

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.

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Portions of the study was presented at the meeting of the American Heart Association, <city, state>, <dates>.

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. Interventions in the perioperative period might have the potential to improve neurodevelopmental outcomes in term CHD.

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 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 cm³) 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

MRS Data Processing

Examples of 1H-MRS spectra are provided in Figure 2. Me-tabolite concentrations were quantified with fully automated LCModel software (Stephen Provencher, Inc, Ontario, Canada, version V6.13-1C). This software automatically applies zero-order and first-order corrections for phase, estimates a baseline, and corrects for ppm shift and eddy currents as needed. Data fitting was determined from the linear combination of model spectra of known concentration, which included metabolites indicative of (1) brain maturation (NAA, total choline, myo-inositol, creatine); NAA is stored within neurons and axons and thought to be an measure of neuronal-axonal integrity; myo-inositol is thought to be a marker of immature myelination and an indicator of glial cells as part of signaling pathways a precursor for the phosphoinositide second messenger system; (2) neurotransmitters (glutamate and GABA);

GABA is considered the principal inhibitory neurotransmitter; (3) energy metabolism (glutamine, citrate, glucose, and phosphocreatine); phosphocreatine is critical for cellular energy homeostasis and in the setting of increased energy demand, phosphocreatine functions as a cellular energy reserve; and (4) injury/repair/apoptosis (lipids and lactate).^{15,16} For quantification, the unsuppressed water signal was used as a concentration reference with tissue water content estimated at a standardized value (86%) based on published reference data as previously described by our group.^{15,16}

Statistical Analyses

Multivariable regression with false discovery rate (FDR) correction was used, with covariates including postmenstrual age at time of scan. The FDR is one way of conceptualizing the rate of type I errors in null hypothesis testing when conducting multiple comparisons. We defined our “exposure” as the patient and clinical factors and the “neuroimaging outcome measure” as the MRS metabolites. We separated the preoperative and postoperative MRI/MRS data to analyze what specific exposure could be associated with which neuroimaging outcome. We defined “concurrent” to correspond to neuroimaging outcomes, which include both pre- and postoperative MRI in a mixed effect model to leverage both time points of the scan; the model corrects for some subjects having 2 scans, some only preoperative, and some only postoperative. We also tested clinical variable exposures against individual preoperative and postoperative imaging outcomes separately to clarify further the relative contribution of scan time. As such, patient specific/prenatal/preoperative time variables were compared with both only the preoperative time point and the “concurrent” time period, which includes all MRIs. In contrast, for the intraoperative and postoperative exposures, we logically compared these time points with only the postoperative MRI.

Results

Ninety subjects were enrolled from June 2009 to January 2016, of whom 64 (71%) were enrolled prenatally. Subsequently, 35 were excluded because of no MRI was able to be performed (18), death pre-MRI (8), absence of neonatal surgery (5), post-natal major genetic diagnoses (2), or prematurity (2). Among the deaths, 1 was a fetal demise; 5 were not offered surgery due to extracardiac organ failure (2), severity of cardiac disease (2), or poor neurologic/genetic prognosis (1); and 2 had surgery and died pre-MRI (2). Therefore, 55 term infants with CHD with analyzable brain MRI/MRS comprised the study group (Figure 1).

Table I lists patient demographic as well as clinical factor data; 58% of the clinical cohort of term CHD neonates were male, had single ventricle, and underwent surgery involving cardiopulmonary bypass, and 96% of subjects had cyanotic forms of CHD. The rates of preoperative brain injuries were 12% punctate white matter lesions, 6% focal infarcts, and 6% hemorrhage. The rate of postoperative brain injuries was 15% punctate white matter lesions, 9% focal infarcts, and 16% hemorrhage. There was no statistical difference in the rate of injury between pre- and postoperative imaging time point and no association between injury and metabolic measurements. The mortality rate for the study population prior to

discharge was 7%. Multiple significant associations between postmenstrual age and metabolites were found in the parietal white matter voxel (Tables II and III; available at www.jpeds.com). In contrast, there were fewer associations between postmenstrual age and metabolites detected in the parieto-occipital gray matter (myo-inositol and NAA; $P < .0004$, $P < .0002$, respectively) and no significant associations between postmenstrual age and metabolites detected in the thalamus voxel.

No significant associations were detected between patient/prenatal factors (Table I) and any brain maturation metabolites (NAA, choline, myo-inositol) or lactate in the concurrent parietal white matter voxel. The presence of 22q11 microdeletion was associated with reduced concurrent white matter phosphocreatine (mixed effect model; $P < .0055$, FDR-corrected, Table IV). Post hoc analyses showed that the relationship between 22q11 microdeletion and reduced phosphocreatine was seen in the preoperative scans only.

No significant associations were detected between preoperative clinical factors (Table I) and any brain maturation metabolites (NAA, choline, myo-inositol) or lactate in the concurrent parietal white matter voxels. Age at surgery less than or equal to 7 days was associated with increased concurrent white matter phosphocreatine (mixed effect model; $P < .0004$; FDR-corrected, Table IV).

No significant associations were detected between most of intraoperative clinical factors (Table I) and any brain maturation postoperative metabolites (NAA, choline, myo-inositol) or lactate. The only significant association was that increased duration of deep hypothermic circulatory arrest (DHCA) was associated with reduced postoperative white matter GABA ($P < .0072$; FDR-corrected, Table IV).

Increased number of extracorporeal membrane oxygenation (ECMO) days ($P < .0067$; FDR-corrected), increased number of days in the intensive care unit ($P < .0047$; FDR-corrected), presence of seizures in the intensive care unit ($P < .0009$; FDR-corrected) and being sent home on antiepileptic drugs ($P < .0002$; FDR-corrected) were all associated with reduced white matter NAA on the postoperative scan (Table IV). Need for cardiopulmonary resuscitation in the postoperative period was associated with reduced white matter phosphocreatine ($P < .0017$; FDR-corrected). No association between total hospital days, gastrostomy tube placement, or tracheostomy was noted for any metabolites. No predictors of elevated lactate were identified.

None of the associations between patient/clinical factors and metabolic alterations seen for the parietal white matter were found for the parietal gray matter. There were, however, some unique findings specific to gray matter. The presence of 22q11 microdeletion was associated with reduced concurrent gray matter glucose ($P < .006$, FDR-corrected) (Table V). For preoperative variables, reduced postnatal and postmenstrual age at surgery was associated with increased concurrent gray matter myo-inositol ($P < .007$, FDR-corrected). Increased cardiopulmonary bypass time was associated with reduced postoperative gray matter myo-inositol ($P < .003$, FDR-corrected). Lastly, the postoperative factors showed that an increased number of unplanned interventions were associated with decreased gray matter choline in

the postoperative scan ($P < .0015$) (Table V). There were no patient or clinical factors that were found to be associated with elevated lactate in the parietal gray matter.

Discussion

Understanding the relative importance of risk factors of neurodevelopmental disability in CHD is an important priority toward understanding the pathogenesis of brain dysmaturation and brain injury in patients with CHD. As such, the ability to identify modifiable risk factors could be an important step towards enhancing long-term neurodevelopmental outcomes via future interventional clinical trials.^{3,4} Quantitative MRS can measure multiple brain metabolites that are biomarkers not only for brain dysmaturation but also potentially for brain function, such as energy processes and neurotransmitters. Although most previous studies of MRS in patients with CHD have measured major brain metabolites (eg, NAA, choline, and lactate) via the long-echo magnetic resonance technique,^{6–8,18,24–26} few studies have measured other metabolites more readily detectable with short-echo MRS, such as myo-inositol, phosphocreatine, glutamate, and GABA. We identified in our study multiple postoperative factors associated with altered brain metabolism (reduced postoperative white matter NAA). In contrast, we could not establish patient/ prenatal, preoperative, or intraoperative factors to be associated with metabolic brain dysmaturation or elevated lactate.

One of the most significant findings in our study was the strong association between multiple important postoperative clinical variables and decreased NAA in postoperative parietal white matter. The association between postoperative variables and poor neurodevelopmental outcomes has been well described in the literature on CHD,²⁷ but the exact timing and etiology is poorly understood. Our study suggests that there is vulnerability of the white matter in the immediate postoperative period in term infants with CHD. We also found an association between postoperative ECMO days and decreased white matter NAA, which supports other published studies that have associated ECMO with poor neurodevelopmental outcomes in both children with and without CHD.^{28–30} Furthermore, we found a strong association between postoperative seizures and decreased NAA. Seizures also may portend poor neurodevelopmental outcomes.³¹ Importantly, reduced NAA on the postoperative scan may represent an early surrogate marker of poor neurodevelopmental outcome; studies of subsequent neurodevelopment in our cohort are underway for confirmation of this.

Notably, we were unable to identify patient or prenatal, pre-operative, or intraoperative factors associated with white matter metabolites that are known important surrogates of early brain maturation¹⁴; however, our analyses were limited by small samples of subjects undergoing preoperative, postoperative, or concurrent MRI. Our lack of association between intraoperative factors and brain maturation metabolites also could be concordant with recent studies showing that intraoperative factors seem to account for less variance in neurodevelopment outcomes.³² Furthermore, a recent meta-analysis of fetal/ neonatal neuroimaging findings did suggest that abnormal post-natal brain development is likely due to prenatal factors, some of which were not evaluated in this study (ie, absence of antegrade aortic blood flow).³³ Of note, we did find a novel association between length of DHCA and

lower levels of GABA, an inhibitory neurotransmitter implicated in a variety of neuropsychiatric conditions including epilepsy, anxiety disorders, and schizophrenia.³⁴ Given that length of DHCA has been correlated with postoperative seizure activity by Gaynor et al,³⁵ our results suggest a potential relationship between a modifiable intraoperative factor and seizure activity.

We could not establish any of the patient and clinical factors that we examined predicted lactate elevation, which has been described in previous studies.^{6–8,18} This could be related to our small samples and a low incidence of brain injury in this cohort relative to other published cohorts.^{8,10,13,19,36} We did, however, delineate novel findings regarding alterations in phosphocreatine—an important energy metabolite not previously described in infants with CHD. In normal brain metabolism, phosphocreatine stores energy and maintains levels of adenosine triphosphate and, thus, is an important indicator of energy reserves as well as a potential marker of mitochondrial dysfunction.³⁷ Subjects with chromosome 22q11 microdeletion had a reduction in concurrent white matter phosphocreatine, and subjects who required cardiopulmonary resuscitation in the postoperative period displayed reduced postoperative phosphocreatine. In contrast, we saw increases in concurrent white matter phosphocreatine in patients who underwent surgery within a week of birth, suggesting a possible protective mechanism related to earlier cardiac surgical correction or palliation, as postulated by others.¹⁰ As such, there may be a fundamental dysregulation of energy metabolism related to genetic and subtle hypoxic-ischemic risk factors in CHD. In addition, the connection between risk factors and both NAA and/or phosphocreatine raises the novel possibility of primary mitochondrial brain dysfunction in patients with CHD, which would need future studies to elucidate.

There were some limitations to our study. Although our cohort had severe forms of CHD, requiring surgery within the first month of life, there was heterogeneity of cardiac lesions. The timing of our pre- and postoperative brain imaging was not standardized, because it varied with clinical stability for transport and MRI scanner availability. We did not present data from healthy neonates controls for comparison in this study. Finally, our sample of 55 subjects had overall low rates of brain injury compared with other studies. This low incidence of injury may affect the generalizability of our results, and in the setting of a small sample and subsamples could lead to false-negative findings.

In conclusion, we did find multiple postoperative factors associated with altered brain metabolism in term infants with CHD, suggesting that interventions in the perioperative period might have the potential to improve neurodevelopmental outcomes in term CHD. We noted novel selective associations with phosphocreatine which suggest vulnerability of white matter energy reserves to both genetic and hypoxic/ischemic risk factors.

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Glossary

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

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Figure 1.

Enrollment during the study period. A majority of cases were enrolled prenatally. The number of cases excluded and reasons are depicted. Approximately one-half of the cases had both preoperative (Pre-op) and postoperative (Post-op) brain imaging time points obtained.

Figure 2.

Quantitative MRS via the short-echo technique in a term neonate with CHD. Short-echo technique allows quantitation of additional metabolites (phosphocreatine [PCr], myo-inositol [mI], glutamine [Gln], and glutamate [Glu] and lipids/ macromolecules [Lip/MM], above and beyond long echo technique, which can measures NAA, choline [Cho], and creatine [Cr]). Three voxel locations were obtained in the order of frequency: *top row*, parietal white matter; *middle row*, parietal-occipital gray matter; and *bottom row*, thalamus.

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

Characteristics	Number of patients (N = 55, %)
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.

Postconceptual age as it affects metabolite changes in 3 regions of the brain, as well as in comparison of the 3 regions

Table II

Metabolites	WM P value	GM P value	THAL P value	WM vs GM P value	WM vs THAL P value	GM vs THAL P value
Creatine	.0007 [*]	.0548 [†]	.72	.21	.016 [‡]	.20
Phosphocreatine	.0036 [*]	.13	.96	.43	.023 [‡]	.21
GABA	.87	.82	.0722 [†]	.95	.14	.18
Glucose	.08 [†]	.12	.12	.95	.74	.72
Glutamine	.15	.90	.11	.24	.53	.10
Glutamate	<.0001 [*]	.14	.10	.001 [‡]	.002 [‡]	.82
Glycerophosphocholine	.0053 [*]	.52	.58	.012 [‡]	.08	.33
Myo-inositol	.001 [*]	.0004 [*]	.31	.38	.03 [‡]	.003 [‡]
Lactate	.89	.32	.41	.65	.44	.10
NAA	.0006 [*]	.0002	.0488 [‡]	.23	.48	.06
Glx; glutamine and glutamate	<.0001 [*]	.33	.0239 [‡]	.004 [‡]	.08	.19
Lipid 13ab	.50	.56	.34	.45	.99	.21
Citrate	<.0001 [*]	.93	.18	<.0001 [‡]	<.0001 [‡]	.37

GM, gray matter; THAL, thalamus; WM, white matter.

^{*} $P < .05$ AND FDR corrected ($q < 0.05$).

[†] $P < .1$; no FDR.

[‡] $P < .05$; no FDR.

Changes from preoperative to postoperative as it affects metabolite changes in 3 regions of the brain as well as comparison of the 3 regions

Table III

Metabolites	WM P value	GM P value	THAL P value	WM vs GM P value	WM vs THAL P value	GM vs THAL P value
Creatine	.0192 [*]	.13	.37	.54	.32	.70
Phosphocreatine	.0003 [*]	.0764 [†]	.94	.21	.005 [‡]	.17
GABA	.25	.88	.0674 [†]	.46	.01 [‡]	.06
Glucose	.0958 [†]	.31	.76	.71	.30	.55
Glutamine	.32	.26	.91	.10	.39	.44
Glutamate	.0009 [*]	.80	.23	.016 [‡]	.12	.34
Glycerophosphocholine	.0006 [*]	.47	.0429 [‡]	.002 [‡]	0 [‡]	.10
Myo-inositol	.01 [*]	.0395 [‡]	.67	.69	.029 [‡]	.10
Lactate	.92	.81	.29	.95	.28	.12
NAA	.46	.02 [‡]	.36	.15	.61	.34
Glx; glutamine and glutamate	.0042 [*]	.52	.47	.009 [‡]	.11	.26
Lipid 13ab	.0294 [*]	.23	.48	.27	.22	.82
Citrate	<.0001 [*]	.52	.39	<.0001 [‡]	<.0001 [‡]	.84

^{*} $P < .05$ AND FDR corrected ($q < 0.05$).

[†] $P < .1$; no FDR.

[‡] $P < .05$; no FDR.

Table IV

Patient and clinical factors association with MRS metabolites for parietal white matter

Patient and clinical factors	Metabolite	Direction	Primary analysis P value*	Post hoc P value
Patient-specific/prenatal				
Genetic abnormality (FISH)	Phosphocreatine	Decreased	<.0055	<.0086 [†]
Preoperative variable				
Surgery =7d of age	Phosphocreatine	Increased	<.0004	NS
Intraoperative variable				
DHCA	GABA	Decreased	<.0072	NA
Postoperative variables				
CPR	Phosphocreatine	Decreased	<.0017	NA
ECMO days	NAA	Decreased	<.0067	NA
ICU days	NAA	Decreased	<.0047	NA
Seizures in ICU	NAA	Decreased	<.0009	NA
Antiepileptic drugs at discharge	NAA	Decreased	<.002	NA

CPR, cardiopulmonary resuscitation; FISH, fluorescence in situ hybridization; NA, for intraoperative and postoperative clinical variables, no post-hoc analysis was performed as only the postoperative scan data points were used in the primary analysis; NS, neither preoperative nor postoperative scan data point was significant.

* $P < .05$ and meets family wise error correction for multiple comparison using FDR; for patient-specific/prenatal variables, both preoperative and postoperative scan data points were used in a mixed-effect model; for intraoperative and postoperative variables, only postoperative scan data point used with a general linear model.

[†] Preoperative scan only was significant, postoperative scan data point was not significant.

Table V

Patient and clinical factors association with MRS metabolites for parieto-occipital gray matter

Patient and clinical factors	Metabolite	Direction	Primary analysis <i>P</i> value*	Post hoc <i>P</i> value
Patient-specific/prenatal				
Genetic abnormality (FISH)	Glucose	Decreased	<.006	<.002 [†]
Preoperative variable				
Postnatal age at surgery	Myo-inositol	Increased	<.0004	<.0002 [‡]
Postconceptional age at surgery	Myo-inositol	Increased	<.0007	<.0048 [‡]
Intraoperative variable				
Cardiopulmonary bypass time (dichotomized)	Myo-inositol	Decreased	<.003	NA
Postoperative variables				
Number of unplanned interventions	Choline	Decreased	<.0015	NA

* $P < .05$ and meets family wise error correction for multiple comparison using FDR; for patient-specific/prenatal variables, both preoperative and postoperative scan data points were used in a mixed-effect model; for intraoperative and postoperative variables, only postoperative scan data point used with a general linear model.

[†] Postoperative scan only was significant, preoperative scan data point was not significant.

[‡] Preoperative scan only was significant, postoperative scan data point was not significant.