Risk factors for preoperative periventricular leukomalacia in term neonates with hypoplastic left heart syndrome are patient related

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Background: Preoperative brain injury is common in neonates with complex congenital heart disease. Increasing evidence suggests a complex interaction of prenatal and postnatal risk factors for development of brain white matter injury, called periventricular leukomalacia (PVL), in neonates with complex congenital heart disease. To date, there remains a limited understanding of the risk factors contributing to preoperative PVL in hypoplastic left heart syndrome (HLHS).

Methods: Neonates with HLHS or HLHS variants from 3 prospective magnetic resonance imaging studies (2003-2010) were selected for this cohort. Preoperative brain magnetic resonance imaging was performed the morning of the surgery. Stepwise multilogistic regression of patient characteristics, mode of delivery (cesarean section vs vaginal), time of diagnosis (prenatal vs postnatal), HLHS subtypes, brain total maturation score, time to surgery, individual averaged daily preoperative blood gases, and complete blood cell count values was used to determine significant associations.

Results: A total of 57 neonates with HLHS were born at 38.7 ± 2.3 weeks; 86% (49/57) had a prenatal diagnosis, with 31% (18/57) delivered by cesarean section. HLHS with aortic atresia (AA) was common in this cohort, 71% (41/57). Preoperative PVL was identified in 19% (11/57). Male patients with AA ($P = .004$) were at higher risk for PVL. Lower total brain maturation score was also identified as a strong predictor for preoperative PVL ($P = .005$).

Conclusions: In neonates with HLHS, nonmodifiable patient-related factors, including male sex with AA (lack of antegrade blood flow) and lower total brain maturation score, placed neonates at the greatest risk for preoperative white matter injury. (J Thorac Cardiovasc Surg 2014;147:1312-8)

CHD

Advances in the medical and surgical management for children with complex congenital heart disease (CHD) has led to increased survival, along with an increased recognition of the associated morbidity. Learning disabilities, attention-deficit disorder, and speech and motor problems are increasingly recognized among the spectrum of developmental problems in school-aged survivors of heart surgery in infancy.[1-4] It is estimated that 50% of these patients are affected by neurodevelopmental issues that have a significant impact on their academic achievement and quality of life.[5]

Neonates with hypoplastic left heart syndrome (HLHS) and d-transposition of the great arteries (d-TGA) have been the most widely studied. Brain white matter injury in the form of periventricular leukomalacia (PVL) has been recognized as the most prevalent brain injury in neonates after surgery for these complex defects.[6] Several studies have demonstrated that, in neonatal cohorts with various types of complex CHD, 17% to 40% had evidence of PVL on preoperative magnetic resonance imaging (MRI),[7,8] whereas almost 50% had evidence of PVL on postoperative MRI.[9] White matter injury or PVL has been associated with neurodevelopmental problems and impaired functional outcomes in very-low-birth-weight and preterm neonates.[10] In neonates with various types of complex CHD lesions, lower basal cerebral blood flow,[8] brain immaturity,[9] and preoperative instrumentation[11] have been identified as risk factors for PVL. It is possible, however, that each heart lesion

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Abbreviations and Acronyms
AA = aortic atresia
AIS = arterial ischemic stroke
AS = aortic stenosis
CHD = congenital heart disease
d-TGA = d-transposition of the great arteries
HLHS = hypoplastic left heart syndrome
MRI = magnetic resonance imaging
PVL = periventricular leukomalacia
TMS = total maturation score

carries its own risk for preoperative PVL based on differences in genetics and underlying cardiac physiology. We have recently published findings suggesting that neonates with d-TGA were at increased risk for preoperative PVL compared with other heart lesions, with a prevalence of PVL of 38% (10/26 patients studied).[12] In that study, analysis of risks for PVL demonstrated that increased time to surgery and lower average daily Pao_2 were specific risks for preoperative PVL in neonates with d-TGA. This study also suggested that further investigations should be directed at evaluating CHD lesion-specific risk factors for preoperative PVL, rather than looking for factors in a heterogeneous congenital heart disease group. By using retrospective review of a prospectively acquired database on brain injury in CHD, this study investigates the risk factors that contribute to preoperative periventricular leukomalacia (PVL) in neonates with HLHS.

METHODS

Patient Population

Patients with HLHS or HLHS variant (double-outlet right ventricle with mitral atresia), born between January 1, 2003, and December 31, 2009, were considered for inclusion in this study. Patients were included from 3 prospective research protocols studying the incidence of preoperative brain injury using MRI in neonates with complex congenital heart disease.[8,13] Neonates with multiple forms of complex congenital heart disease were recruited from 2003-2005, whereas neonates with only d-TGA or HLHS were recruited from 2006-2009. Other than type of CHD, inclusion criteria were identical and included term gestational age (40 ± 4 weeks), an intention to undergo surgical intervention with cardiopulmonary bypass (CPB) with or without deep hypothermic circulatory arrest, and medical stability for 24 hours before surgery. Infants were excluded if there was a history of birth asphyxia (5-minute Apgar score of ≤ 5 or a cord pH of <7.0), preoperative seizures, signs of end-organ damage, preoperative cardiac arrest, or need for extracorporeal membrane oxygenation either preoperatively or postoperatively. Only patients with HLHS ($n = 57$) from the larger cohort of 124 were included in the current study. The Investigational Review Board of The Children's Hospital of Philadelphia (Philadelphia, Pa) approved the study protocol. Informed consent was obtained from the parent or guardian.

Study Protocol

All patients were prepared for surgery following our previously published standard clinical protocols.[8,13] Briefly, on the morning of surgery, neonates were brought to the operating room by the cardiac anesthesia team to induce anesthesia, perform endotracheal intubation, and secure vascular access. Patients were then transported to the MRI suite. Heart rate, blood pressure, electrocardiographic, peripheral oxygen saturations, and end-tidal CO_2 measurements were monitored throughout transport and during the performance of the MRI.

Brain MRI

All MRI scans were performed on Siemen's Avanto, Sonata, or Trio scanners (Siemens, Erlangen, Germany). Preoperative brain MRI scans performed before January 1, 2005 ($n = 20$), were performed on a 1.5-T Sonata. MRI scans performed between 2005 and October 2008 ($n = 29$) were completed on a 3T Trio scanner, whereas MRIs acquired after this date were performed on a 1.5-T Avanto ($n = 8$). The variation in MR scanners that occurred during the study period was due, in part, to changes in imaging technology that became available. The most recent switch back to a 1.5-T scanner was due to the recent placement of the 1.5-T Avanto on the same floor as the cardiac intensive care unit and operating rooms, thus substantially reducing patient transport risk. PVL was diagnosed based on its appearance as hyperintense lesions on T1 sequences. Slice thickness on T1 ranged from 3 mm (1.5-T Sonata) to 0.9 mm (3-T Trio), with no gaps between slices, regardless of scanner. All neonates underwent preoperative brain MRI scanning immediately before surgery for the stage I palliation procedure. MRI study protocols were described in detail previously.[8,12,13]

A neuroradiologist (A.V.), blinded to the patients' clinical history and gestational age, reviewed all brain MRI images for congenital and acquired abnormalities. Focal acquired abnormalities included subdural hemorrhage, choroid plexus hemorrhage, arterial ischemic stroke (AIS), and/or PVL. *AIS* was defined as a focal area of diffusion restriction in an arterial territory involving cortex. *PVL* was defined as punctate periventricular white matter lesions associated with T1 hyperintensity, with or without restriction of water diffusion on diffusion-weighted imaging. PVL was graded with a published 4-point scale ranging from none to severe.[11] Furthermore, PVL lesions were manually segmented using ITK-SNAP (http://www.itksnap.org), which has excellent intraoperator and interoperator reliability for measuring regional brain volumes. User-guided 3-dimensional active contour segmentation of anatomic structures significantly improved efficiency and reliability.[14] PVL volumes were expressed in mm^3.

Total maturation score (TMS) was available in 37 (65%) of 57 neonates. TMS is an observational scale developed and validated by Childs and colleagues.[15] TMS uses standard T1 and T2 MR imaging to grade 4 aspects of brain development: (1) cortical folding complexity, (2) myelination progress, (3) presence and number of migrating glial bands in the frontal white matter, and (4) presence and location of germinal matrix. For this study, TMS was determined by 2 investigators (A.V. and D.J.L.), according to methods published previously.[13] Image quality for earlier MRI scans (2003-January 2005) made TMS evaluations unreliable, and they were not included for this study.

Data Preparation and Analysis

Data preparation. For each subject, summary measures were computed for all preoperative arterial and venous blood gases and combined readings. For example, a mean daily preoperative blood gas oxygen saturation was computed for each subject using arterial blood gas samples only, whereas mean daily Pco_2 values were based on both venous and arterial blood gases.

Exploratory analysis. The analysis plan called for using multiple logistic regression models to predict presence of PVL based on combinations of a list of selected variables, including sex, gestational age, birth weight, head circumference, prenatal versus postnatal diagnosis, subtype of HLHS (aortic atresia [AA] vs aortic stenosis [AS]), mode of delivery (cesarean section vs vaginal delivery), time to surgery, hemoglobin levels,