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ORIGINAL RESEARCH

Cerebral Microhemorrhages in Children With Congenital Heart Disease: Prevalence, Risk Factors, and Association With Neurodevelopmental Outcomes

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BACKGROUND: Infants with congenital heart disease require early lifesaving heart surgery, which increases risk for brain injury and neurodevelopmental delay. Cerebral microhemorrhages (CMH) are frequently seen after surgery, but whether they are benign or constitute injury is unknown.

METHODS AND RESULTS: One hundred ninety-two infants with congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass were evaluated with pre- (n=183) and/or postoperative (n=162) magnetic resonance imaging. Perioperative risk factors for CMH and neurodevelopmental outcomes were analyzed using linear regression. Eighteen-month neurodevelopmental outcomes were assessed in a subset of patients (n=82). The most common congenital heart disease subtypes were hypoplastic left heart syndrome (37%) and transposition of the great arteries (33%). Forty-two infants (23%) had CMH present on magnetic resonance imaging presurgery and 137 infants (85%) postsurgery. We found no significant risk factors for preoperative CMH. In multivariable analysis, neurodevelopmental duration (P<0.0001), use of extracorporeal membrane oxygenation support (P<0.0005), postoperative seizure(s) (P=0.02), and lower birth weight (P=0.03) were associated with new or worsened CMH postoperatively. A higher CMH number was associated with lower motor scores (P=0.01) at 18 months.

CONCLUSIONS: CMH are common imaging findings in infants with congenital heart disease, particularly after cardiopulmonary bypass conferring adverse impact on neurodevelopmental outcomes at 18 months. Longer duration of cardiopulmonary bypass and extracorporeal membrane oxygenation use demonstrated greatest risk for developing CMH. However, the presence of CMH on preoperative scans indicates yet unidentified nonperioperative risk factors. Neuroprotective strategies to mitigate CMH risk may improve neurodevelopmental outcomes in this vulnerable population.

Key Words: cardiopulmonary bypass ■ cerebral microhemorrhage ■ congenital heart disease ■ neurodevelopmental outcomes

Infants with complex congenital heart disease (CHD) often undergo corrective surgery with cardiopulmonary bypass (CPB) within the first weeks of life. These infants are at increased risk for brain immaturity at birth, disordered brain development, acquired brain injury, and neurodevelopmental impairments spanning early development to adolescence and into adulthood.[1–6] However, the underlying causes of this

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CLINICAL PERSPECTIVE

What Is New?

- We present the pre- and postoperative prevalence of cerebral microhemorrhages (CMH) in the largest published cohort to date of infants with congenital heart disease (37% hypoplastic left heart syndrome, 33% transposition of the great arteries) who underwent corrective cardiac surgery with cardiopulmonary bypass within the first weeks of life.
- We found that longer duration of cardiopulmonary bypass was most strongly associated with the development of new or worsened CMH, and further found that 23% of infants had CMH present preoperatively, which has not been previously described.
- In a subset of patients with CMH present on postoperative magnetic resonace imaging, we investigated the association between CMH and neurodevelopmental outcomes at 18 months, and found that a higher CMH number is associated with worse motor development scores.

What Are the Clinical Implications?

- Our data show that higher CMH burden is linked with poorer neurodevelopmental outcomes in infants with severe congenital heart disease, indicating these are not benign imaging findings.
- Given the substantial preoperative CMH prevalence observed, there may be perinatal risk factors yet to be identified that contribute to CMH development in this population.
- Further research is needed to better understand the mechanism of injury and to elucidate strategies to mitigate preoperative and postoperative CMH risk to improve neurodevelopmental outcomes in this population.

Nonstandard Abbreviations and Acronyms

CMH	cerebral microhemorrhage
CPB	cardiopulmonary bypass
DHCA	deep hypothermic circulatory arrest
WMI	white matter injury

brain injury are not fully understood, and the impact on prognosis in the individual patient is variable. White matter injury (WMI) is the best characterized and most extensively studied type of injury in this patient population.[7–9] Risk factors for WMI have been well-characterized.[7,10,11] In contrast, although cerebral microhemorrhages (CMH) are the most common finding on perioperative brain magnetic resonance imaging (MRI), there are limited available data on risk factors for and clinical significance of CMH. In this study, we aimed to identify the prevalence of CMH, risk factors for CMH development, and association of CMH with neurodevelopmental outcomes in a cohort of infants with CHD who underwent surgery with CPB within the first 2 weeks of life.

CMH are rounded hypointense foci of <5 mm best visualized on susceptibility weighted imaging sequences on MRI but can also sometimes be seen on gradient-echo sequences.[12] In other contexts, these foci are most common in perivascular locations throughout the parenchyma and are thought to represent deposits of hemosiderin that are associated with previous hemorrhagic events.[12–14] Acute microhemorrhages, as seen postoperatively in our cohort, may represent other blood degradation products (eg, extracellular deoxyhemoglobin, methemoglobin), all of which demonstrate susceptibility. Although CMH have been attributed to microscopic embolic material from the bypass pump, this would not account for their presence before surgery. CMH have been well-studied in adult populations and are frequently observed in healthy older individuals, as well as patients with traumatic brain injury, dementia, cerebral amyloid angiopathy, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[12] In traumatic brain injury, CMH are thought to arise from forces causing axonal sheer and compromise of the vasa nervorum with resulting microhemorrhage. Age has been shown to be an independent risk factor for developing CMH, with a 20% to 40% higher incidence of CMH in those >65 years of age.[15] When located in the lobar regions of the brain, CMH are part of the diagnostic criteria for cerebral amyloid angiopathy.[16] Hypertension is another independent risk factor for CMH, most commonly resulting in lesions that are distributed in deep and infratentorial brain regions.[15] Importantly, the presence of CMH in these populations is a clinically significant finding that is linked with cognitive impairment, gait disturbances, and risk of intraventricular hemorrhage.[12,17,18]

In children, there are significantly fewer studies examining the prevalence and impact of CMH. Two prior studies have investigated CMH in children with CHD; however, these were limited by MRIs performed at 1 year of age (thus remote from the surgical insult) and small sample size. In this study, we address this gap in knowledge by analyzing a large single-center cohort of infants with CHD who underwent corrective surgery with CPB within the first weeks of life. Our prospective study benefited from the collection of both pre- and postoperative imaging as well as the collection of long-term neurodevelopmental outcomes. Our goals were to: (1) determine the prevalence of CMH in both the preoperative and postoperative time periods, (2) elucidate antenatal preoperative and operative risk factors associated with CMH, and (3) investigate

the association of CMH with neurodevelopmental outcomes in this population.

METHODS

Study Design and Population

We performed a post hoc analysis of data prospectively collected from 2008 to 2019 as part of a longitudinal cohort study of term infants with CHD who underwent neonatal cardiac surgery with CPB at the Children's Hospital of Philadelphia. This study was approved by the institutional review board (IRB 11-008191), and all participating families provided informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request. Full-term neonates (born at ≥36 weeks estimated gestational age) who required cardiac surgery with CPB within the first 2 weeks of life were eligible for inclusion. Infants who were small for gestational age (<2 kg) or who experienced neonatal depression (5-minute APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score <5, or cord pH <7), failed to undergo surgery, experienced preoperative cardiac arrest requiring chest compressions, significant intracerebral hemorrhage, or showed evidence of end-organ injury (as indicated by an aspartate aminotransferase (AST) to alanine transaminase (ALT) ratio above twice the normal value, creatinine >2 mg/dL, or heart failure) were excluded. Patients underwent at least 1 prospective brain MRI (pre- or postoperatively).

Patient characteristics, surgical, and medical history from the neonatal hospitalization were prospectively collected in a REDCap (Research Electronic Data Capture, Nashville, TN) research database hosted at the Children's Hospital of Philadelphia. Captured variables included patient demographics (sex, race, ethnicity, gestational age), birth information (type of delivery, birth weight, head circumference, maternal pregnancy complications), cardiac diagnoses, genetic syndromes, surgical management, and details of pre-, intra-, and postoperative clinical care. For analysis purposes, cardiac diagnosis was divided into 3 subgroups: hypoplastic left heart syndrome, transposition of the great arteries, or other, due to the small numbers of patients with diagnoses other than hypoplastic left heart syndrome and transposition of the great arteries. Note was made of patients who received preoperative cardiac catheter interventions, which included balloon atrial septostomy, atrial septal stent placement, and diagnostic catheter angiograms. Subgroups for race included Black, Asian, White, Native American/Pacific Islander, Mixed, other, or unknown. Ethnicity was collected as either Hispanic and Latino or other.

Cardiac Surgery

All infants underwent corrective or palliative surgery with CPB within the first 2 weeks of life. Surgery was performed with deep hypothermic circulatory arrest (DHCA) for all subjects requiring aortic arch repair. Normothermic continuous bypass strategies were used for all biventricular repairs. All patients received modified ultrafiltration on termination of CPB as standard of care. The total duration of CPB, DHCA, and cross-clamp was calculated from anesthesia and operative records. For patients receiving DHCA, the total CPB time was defined as the time from initiation of bypass until the start of DHCA plus the time from the end of DHCA to removal from CPB.

Neuroimaging

Brain MRIs were performed under general endotracheal anesthesia immediately before the neonatal cardiac surgery and approximately 1 week postsurgery. MRIs were performed on a single 1.5T Avanto MRI system (Siemens Medical Systems, Malvern, PA) with a 12-channel head coil. Brain MRI sequences included T1-weighted magnetization-prepared rapid acquisition gradient echo (repetition time/echo time/inversion time=1980/2.65/1100 milliseconds, flip angle=15°, voxel size=0.4×0.4×1.5 mm, matrix=256×256), T2-weighted sampling perfection with application-optimized contrasts using different flip angle evolution (repetition time/echo time=3200/453 milliseconds, voxel size=0.9×0.9×2 mm, matrix=256×254), diffusion-weighted imaging (repetition time/echo time=2903/86 milliseconds; slice thickness=4 mm; *b* values=0, 1000 mm/s2; 20 directions; matrix 128×128), and susceptibility-weighted imaging (repetition time/echo time=49/40 milliseconds, slice thikness=2 mm, matrix=256×177). T1- and T2-weighted sequences were acquired in the axial plane and reformatted in the sagittal and coronal planes.

MRIs were reviewed by a pediatric neurologist (D.J.L.) with expertise in brain image interpretation. WMI was identified by T1 hyperintensity and was rated using the validated quartered point system with increasing scale indicating increasing severity in WMI: 0 signifies no WMI, 1 signifies mild WMI, 2 to 3 signifies moderate WMI, and 4 signifies severe WMI.[19] Volumetric measurements of WMI were performed by manual segmentation using ITK/SNAP (a medical image segmentation and registration software).[20] Presence of WMI was assessed as a binary variable, defined as any non-0 WMI volume value.[7] CMH severity was determined by the number of lesions counted on susceptibility-weighted imaging. We considered CMH as both a dichotomous variable (either present or absent) and as a continuous variable (number of lesions). Worsening was defined as a change in number of CMH from preoperative to postoperative MRI. Enlargement of individual CMH lesions was not measured given the small size of a microhemorrhage and limitations of MRI in detecting millimeter-level

changes. Preoperative MRIs were additionally evaluated for total maturation score, a previously validated semiquantitative scoring system used to assess whole-brain maturity across 4 parameters: myelination, cortical infolding, involution of glial cell migration bands, and presence of germinal matrix tissue.[7]

Neurodevelopmental Assessment

A subgroup of 82 patients with postoperative MRI returned for detailed neurodevelopmental assessment at 18 months of age, as part of their standard clinical care. Motor, language, and cognitive functions were evaluated using the Bayley-III Scales of Infants and Toddler Development, which were performed by a certified child psychologist. Weight, length, and head circumference were also measured on the day of testing. The composite scores for each domain of this test are calculated based on comparison with normative age-matched samples. The standardized Bayley-III Scales of Infants and Toddler Development mean score of 100±15 indicates midaverage function, <85±1 (below mean) indicates mild impairment and risk of developmental delay, and <70±2 (below the mean) indicates moderate to severe impairment.[21]

Statistical Analysis

Summary statistics are reported as mean±SD or median and interquartile range (IQR) for continuous variables, as appropriate, and count and percentage for categorical variables. For each outcome, we first performed univariable analysis on each risk factor, and then considered the variables with a *P* value <0.2 for subsequent multivariable modeling using the stepwise selection approach to determine the final models. Two-sided *P* values of <0.05 were considered statistically significant. We performed all statistical analyses using R (R Core Team, Vienna, Austria).

Our first analysis was to assess for preoperative risk factors that predicted the presence of CMH on preoperative MRI. Due to the low incidence of preoperative CMH, associations with lesion number were not examined. The association for each risk factor with presence of preoperative CMH was assessed using the Fisher exact test for categorical variables or Wilcoxon rank sum test for continuous variables. We did not pursue multivariable modeling for preoperative CMH, because none of the risk factors reached a *P* value of 0.2 in the univariable analysis.

Next, we performed linear regression to identify risk factors that predicted the change in number of CMH from pre- to postoperative MRI with univariable and subsequent multivariable analyses. In the multivariable analysis, we included risk factors that reached a *P* value of 0.2 in the univariable analysis, and also forced birth weight into the model, because we thought it was an important clinical parameter due to prior evidence of predictive usefulness.[1]

Finally, we assessed the association of postoperative CMH with neurodevelopmental outcomes measured at 18 months. We calculated the Spearman correlation coefficient between each neurodevelopmental outcome (composite scores on the cognition, language, and motor tests of the Bayley-III Scales of Infant and Toddler Development; weight, length, and head circumference) with postoperative CMH, and additionally performed linear regression to adjust for covariates of interest including sex, gestational age, duration of bypass, use of postoperative extracorporeal membrane oxygenation (ECMO), and seizure. The association of WMI (total WMI volume, quartered point system score, total maturation score) with neurodevelopment was assessed using simple linear regression.

RESULTS

Patient Characteristics

Of a total of 192 consented patients enrolled in the study; 183 (95.3%) received a preoperative brain MRI. Reasons for not receiving an MRI included: parents rescinded consent (n=2), medical instability (n=1), and unavailability of the MRI on the morning of surgery (n=6). One hundred sixty-two patients had both a pre- and postoperative MRI, 21 had only a preoperative MRI, and 4 had only a postoperative MRI (Table 1, Figure 1). The median time from surgery to postoperative MRI was 7 days (IQR, 5–8). A subset of patients with postoperative imaging (n=82) returned for neurodevelopmental assessment at 18 months of age and were evaluated using the Bayley-III Scales of Infants and Toddler Development.

The median age of patients at the time of cardiac surgery was 4 days (IQR, 3–5 days). The majority of patients were White (n=142; 76%), and a minority identified as Hispanic and Latino (n=13; 7%). Sixty-nine infants (37%) had a diagnosis of hypoplastic left heart syndrome, and 62 (33%) had transposition of the great arteries. The remaining 56 (30%) had structural heart defects that included aortic arch anomalies (total n=25, interrupted aortic arch n=8, aortic arch hypoplasia/coarctation n=8, aortic arch hypoplasia/coarctation with ventricular septal defect n=9), unbalanced common atrioventricular canal (n=7), tetralogy of Fallot (n=9), Ebstein anomaly (n=1), tricuspid atresia (n=1), right ventricular aorta with pulmonary atresia (n=1), truncus arteriosus (n=2), double inlet left ventricle (n=3), and double outlet right ventricle (n=7).

CMH Prevalence and Distribution

Of 183 infants analyzed, 42 (23%) had ≥1 CMH present on preoperative MRI. The number of CMH in the

Table 1. Baseline Characteristics of Infants With Congenital Heart Disease Who Underwent Surgery With CPB, According to Analysis Group

Patient characteristics, median [IQR] or n (%)	Preoperative MRI	Preoperative to postoperative MRI comparison	Neurodevelopmental outcomes
Demographics	n=183	n=162	n=82
Sex			
Girls	77 (42)	69 (43)	48 (59)
Boys	106 (58)	93 (57)	34 (41)
Race			
White	138 (75)	121 (75)	70 (85)
Black	21 (12)	19 (12)	7 (9)
Asian	4 (2)	4 (2)	1 (1)
Other	20 (11)	18 (11)	4 (5)
Ethnicity			
Latino	13 (7)	10 (6)	3 (4)
Birth history			
Gestational age, wk	39 [38–40]	39 [38–39]	39 [38–39]
Birth weight, kg	3 [3–4]	3 [3–4]	3 [3–4]
Head circumference, cm	34 [33–35]	34 [33–35]	34 [33–35]
Vaginal delivery	106 (58)	95 (59)	54 (66)
Cardiac diagnosis			
HLHS	68 (37)	58 (36)	27 (33)
TGA	59 (32)	53 (32)	28 (34)
Other	56 (31)	51 (31)	27 (33)
Preoperative factors			
Cardiac catheter intervention	39 (21)	35 (22)	15 (18)
Arrhythmia	12 (6.6)	9 (5.6)	6 (7)
Hemoglobin*, g/dL	15 [13–16]	15 [13–16]	14 [13–16]
Platelets†, $10^3/\mu L$	268 [222–315]	274 [226–318]	280 [231–331]
Presence of WMI	97 (53)	…	…
WMI volume	0 [0–0]	…	…
QPS score	0 [0–0]	…	…
TMS score	10 [9–11]	…	…
Surgical factors			
Age at surgery, d	4 [3–5]	4 [3–5]	4 [3–6]
CPB duration, min	49 [39–76]	49 [39–74]	51 [39–79]
Cross clamp duration, min	45 [38–60]	44 [37–59]	44 [37–57]
DHCA duration, min	33 [0–44]	32 [0–43]	24 [0–41]
Maximum ACT, s	861 [662–1500]	887 [661–1500]	737 [620–1039]
Intraoperative arrhythmia	27 (15)	20 (12)	9 (11)
Postoperative factors			
ECMO support	7 (3.8)	4 (2.5)	3 (4)
Seizure	17 (9.3)	16 (9.9)	10 (12)
Cardiac arrest	13 (7.1)	10 (6.2)	5 (6)
Hemoglobin*, g/dL	13 [11–15]	13 [11–15]	13 [11–14]
Platelets†, $10^3/\mu L$	102 [75–163]	102 [75–163]	108 [85–153]
Presence of WMI	…	96 (59)	51 (62)
WMI volume	…	19 [0–89]	21 [0–124]
QPS score	…	1 [0–2]	1 [0–2]

ACT indicates activated clotting time; CHD, congenital heart disease; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; IQR, interquartile range; MRI, magnetic resonance imaging; QPS, quartered point system; TGA, transposition of the great arteries; TMS, total maturation score; and WMI, white matter injury.

*Hemoglobin values were collected from blood gas records within 72 h of surgery.

†Platelet values were collected from blood gas records within 72 h of surgery.

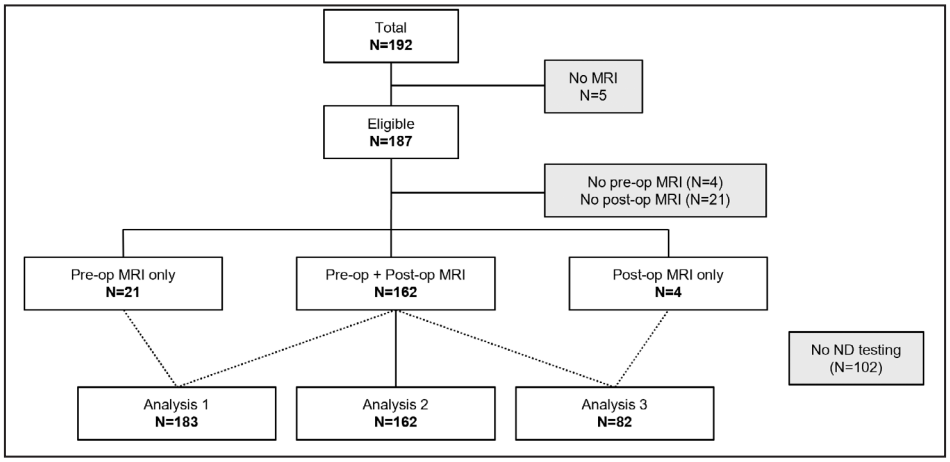

Figure 1. Flowchart of included patients in the study analysis.
Analysis 1 includes patients with preoperative MRI. Analysis 2 includes patients with pre- and postoperative MRI. Analysis 3 includes patients with postoperative MRI and ND outcomes. MRI indicates magnetic resonance imaging; ND, neurodevelopmental outcomes; post-op, postoperative; and pre-op, preoperative.

preoperative subgroup ranged from 0 to 9, with a median of 0 (Figure 2A). CMH were distributed throughout the brain in the posterior fossa (midbrain, cerebellum, and brainstem; 52%) and cerebral cortex/subcortical white matter junction (48%) (Figure 2B). Additionally, 97 patients (53%) had WMI, with a median total maturation score of 10 (9–11).

Of 162 infants with both pre- and postoperative scans, 137 (85%) had ≥1 CMH on postoperative MRI (Figure 2A). Of the patients in this group, the median number of CMH on postoperative MRI was 3 (IQR, 1–5), and the mean change in CMH number between pre- and postoperative MRI was 2 (IQR, 0–4) (representative MRIs shown in Figure 3). Postoperative CMH were located in the cerebral cortex/subcortical white matter junction (40%), posterior fossa (midbrain, cerebellum, and brainstem, 45%), and deep gray matter structures (15%) (Figure 2B). Of this group, 96 patients had WMI, with a median WMI volume of 19 (0–89) and a median quartered point system score of 1 (0–2).

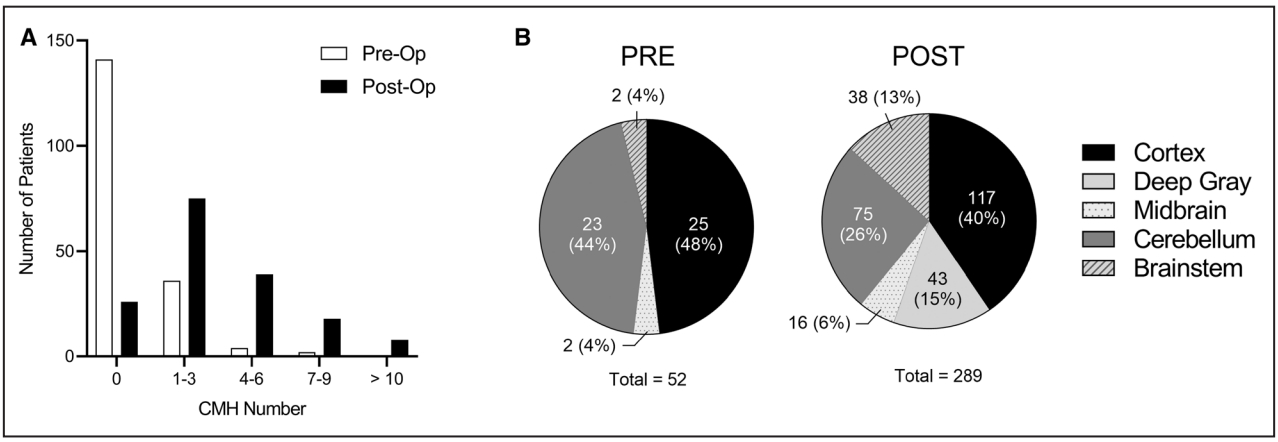

Figure 2. Prevalence and location of pre- and postoperative CMH in infants with CHD.
A, Increased prevalence of CMH on postoperative scans compared with preoperative imaging. White bars indicate patients with preoperative imaging. Black bars indicate patients with postoperative imaging. **B**, Location of CMH on preoperative vs postoperative brain MRI. Total denotes the total number of microhemorrhages. Cortex refers to CMH in both the cortex proper and subcortical white matter junction. Posterior fossa structures include the midbrain, cerebellum, and brainstem. CMH indicates cerebral microhemorrhage; MRI, magnetic resonance imaging; Post and POST, postoperative; and Pre and PRE, preoperative.

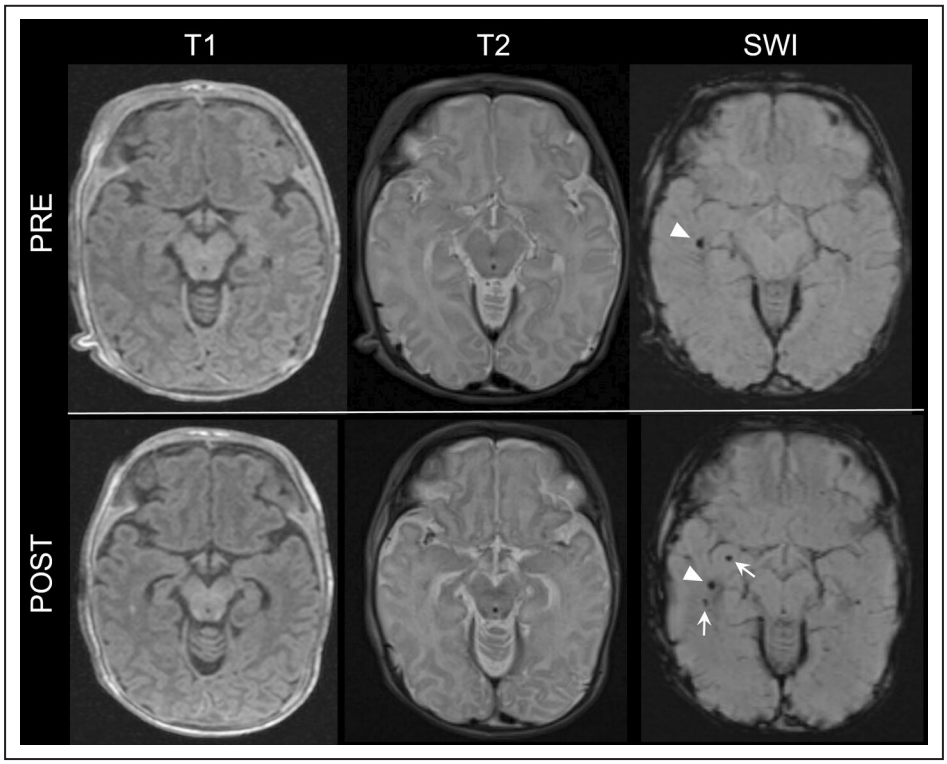

Figure 3. Representative MRI of a single patient with pre- and postoperative CMH.
CMH are often not visible on T1-weighted or T2-weighted MRI but are visible on SWI. Arrowheads demarcate CMH present on both preoperative and postoperative SWI. Arrows highlight the accrual of additional CMH on postoperative SWI. CMH indicates cerebral microhemorrhage; MRI, magnetic resonance imaging; POST, postoperative; PRE, preoperative; SWI, susceptibility weighted imaging; T1, T1-weighted MRI; and T2, T2-weighted MRI.

Risk Factors for Preoperative Microhemorrhages

The prevalence and severity of preoperative CMH was not affected by sex, gestational age, delivery type (vaginal versus cesarean section), or cardiac diagnosis (Table 2). Additionally, there was no significant association with race, ethnicity, gestational factors (ie, maternal hypertension, diabetes, preeclampsia), total maturation score, or preoperative arrhythmia. However, the small number of patients within each of these subgroups limited the ability to detect any potentially significant effects. Of 40 patients who had catheter interventions before surgery, 12 (30%) had CMH present, which was not statistically different from patients without such interventions (30/143 or 21% with CMH, P=0.29). Stroke as a consequence of balloon atrial septostomy was not seen in this cohort.

Risk Factors for Postoperative Microhemorrhages

The median duration of CPB was 49 minutes (IQR, 39–74 minutes). Longer duration of CPB was the risk factor most strongly associated with new or increased number of postoperative CMH (P<0.0001) (Figure 4A). Specifically, patients with postoperative CMH experienced a median CPB duration of 51 minutes (IQR, 40–84 minutes), compared with patientswithout CMH, who had a median CPB duration of 40 minutes (IQR, 30–44 minutes). Additionally, need for postoperative ECMO support (P=0.0004), presence of postoperative seizure(s) (P=0.02), and low birth weight (defined as <2500 g) (P=0.03) were associated with worsened severity of postoperative CMH (Table 3). Age at surgery (P=0.3), duration of DHCA (P=0.3), lowest brain temperature (P=0.98), maximum activated clotting time (P=0.2), intraoperative arrhythmia (P=0.3), and postoperative cardiac arrest (P=0.7) were not associated with change in number of CMH (Table S1).

Neurodevelopmental Outcomes

A subset of 82 patients with postoperative MRI underwent neurodevelopmental assessment using the Bayley-III Scales of Infants and Toddler Development at 18 months of age (Table 4). Neurodevelopmental testing revealed a wide range of composite scores for cognitive (53–125), motor (61–120), and language (47–129) function. The mean composite scores for cognitive, motor, and language function were 94±12, 92±12, and

Table 2. Association Between Candidate Risk Factors and CMH on Preoperative Magnetic Resonance Imaging

Risk factor	CMH+, n (%) n=42	CMH−, n (%) n=141	Overall, n (%) n=183	*P* value
Demographics				
Sex				>0.99
Girls	18 (43)	59 (42)	77 (42)	
Boys	24 (57)	82 (58)	106 (58)	
Race				0.55
White	34 (25)	104 (74)	138 (75)	
Black	3 (14)	18 (13)	21 (11)	
Asian	1 (2)	3 (2)	4 (2)	
Ethnicity				0.72
Hispanic and Latino	4 (31)	9 (6)	13 (7)	
Birth history				
Gestational age				0.85
37–38 wk	7 (23)	23 (16)	30 (16)	
39–40 wk	26 (26)	75 (53)	101 (55)	
Birthweight				0.55
<2.5 kg	0 (0)	4 (3)	4 (2)	
Head circumference				0.63
<34 cm	21 (27)	58 (41)	79 (43)	
Preoperative				
Cardiac diagnosis				0.82
HLHS	17 (25)	51 (36)	68 (37)	
TGA	12 (20)	47 (33)	59 (32)	
Other	13 (23)	43 (30)	56 (31)	
Cardiac catheter intervention	12 (31)	27 (19)	39 (21)	0.27
Type of birth				0.68
Vaginal	26 (25)	80 (57)	106 (58)	
Cesearean section	16 (21)	61 (43)	77 (42)	
Gestational diabetes	3 (23)	10 (7)	13 (7)	>0.99
Gestational hypertension	3 (25)	9 (6)	12 (7)	>0.99
Gestational preeclampsia	0 (0)	2 (1)	2 (1)	>0.99
Hemoglobin*				0.51
<14 g/dL	15 (22)	52 (37)	67 (37)	
Platelets†				0.59
<150×10^3/μL	1 (14)	6 (4)	7 (4)	
Arrhythmia	3 (25)	9 (6)	12 (7)	>0.99
TMS				0.29
<12	41 (24)	132 (94)	173 (95)	

Fisher exact test was performed for categorical risk factors, whereas Wilcoxon rank sum test was performed for continuous risk factors. Cardiac catheter interventions included balloon atrial septostomy and atrial stents. CMH indicates cerebral microhemorrhage; HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; and TMS, total maturation score.

*Hemoglobin values were collected from blood gas records within 72 h of surgery.

†Platelet values were collected from blood gas records within 72 h of surgery.

89±16, respectively. Although these scores indicate midaverage function for the cohort as a whole, 48% (n=39) of children in our cohort demonstrated below average neurodevelopmental function in at least 1 domain, defined as a Bayley-III Scales of Infants and Toddler Development score falling <1 SD of the mean. Additionally, 17% (n=14) showed pronounced impairment, falling <2 SD of the mean in at least 1 domain. Specifically, 5% (n=4) had moderate to severe cognitive impairment, 13% (n=11) had moderate to severe language impairment, and 5% (n=4) had moderate to severe motor impairment. Four patients had severe impairment in >1 domain, and 1 patient fell <2 SD of the mean in all 3 domains. Severity of CMH on postoperative MRI was associated with lower composite scores on the motor Bayley-III Scales of Infants and Toddler

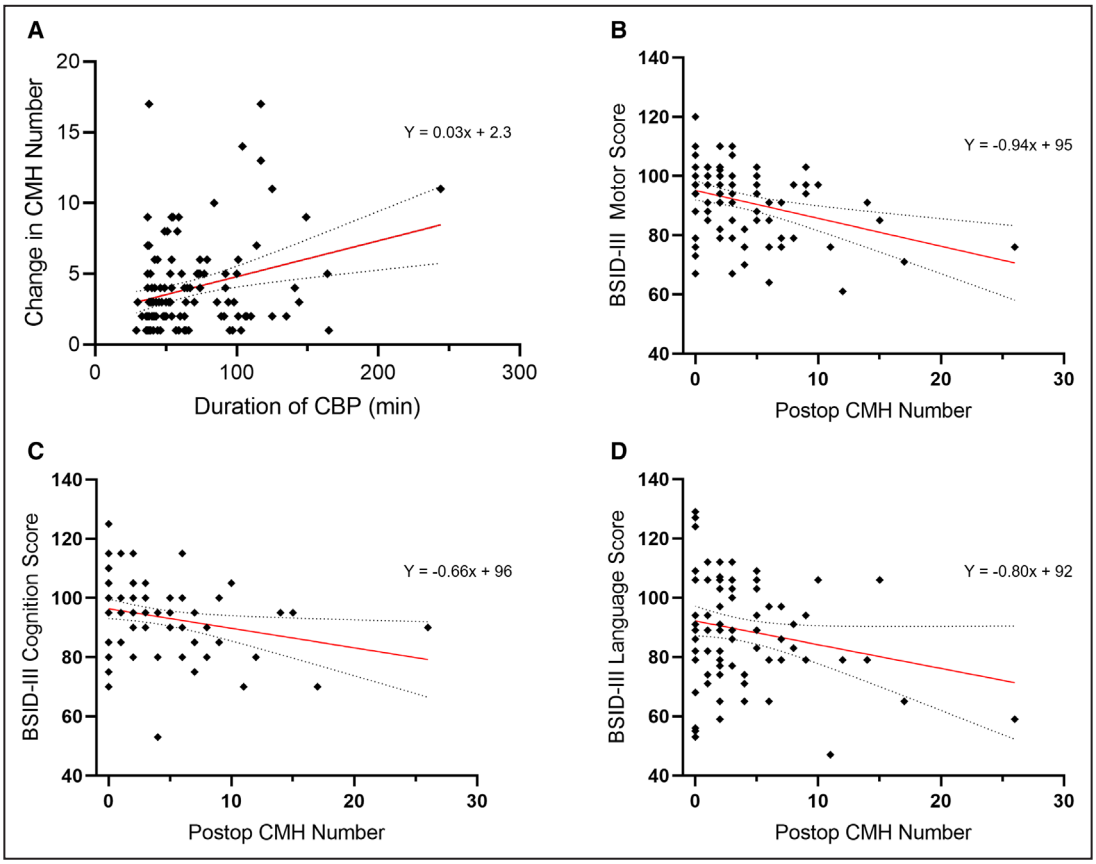

Figure 4. Relationship among CMH, CPB, and neurodevelopmental outcomes at 18 months.
A, Increased duration of CPB is a significant risk factor for worsened CMH severity (P<0.0001). CMH severity is defined as an increased number of CMH. **B**, The higher total number of CMH on postoperative scans is associated with lower composite motor scores at 18 months of age (P=0.001). **C** and **D**, Higher total number of CMH on postoperative scans is not associated with lower composite cognition (P=0.12) or language scores (P=0.06). BSID-III indicates neurodevelopmental testing using Bayley-III Scales of Infant and Toddler Development at 18 months; CMH, cerebral microhemorrhage; CPB, cardiopulmonary bypass; and Postop, postoperative.

Development scales in both univariable (P=0.001) and multivariable (P=0.012) analysis (Table 4, Figure 4B). The simple linear regression analysis suggested that with every 1-point increase in CMH number, the Bayley-III Scales of Infants and Toddler Development motor score was predicted to decrease on average by 0.94 point (95% CI, 0.39–1.50). Lower composite cognitive scales were associated with CMH number on univariable (P=0.023) but not multivariable analysis (P=0.118). The use of postoperative ECMO was associated with lower composite cognitive (P=0.007) and language (P=0.02) scores in multivariable analysis. The simple linear regression analysis suggested a 0.66- point decrease (95% CI, 0.09–1.22) in average Bayley-III Scales of Infants and Toddler Development cognitive score for every 1-point increase in CMH number (Figure 4C). Moreover, male sex was associated with a lower motor composite score on multivariable analysis (P=0.027).

Table 3. Risk Factors Significantly Associated With New or Worsened Cerebral Microhemorrhage on Postoperative Magnetic Resonance Imaging Using Multivariable Linear Regression

Risk factor	Regression coefficient [95% CI]	*P* value
Birthweight	–1.04 [–1.979 to –0.101]	0.03
Duration of bypass	0.03 [0.016 to 0.044]	<0.0001
ECMO support	5.23 [2.408 to 8.052]	0.0004
Seizure	1.94 [0.339 to 3.541]	0.02

ECMO indicates extracorporeal membrane oxygenation.

CMH was not associated with language function scores (P=0.064), weight (P=0.352), length (P=0.712), or head circumference (P=0.185) in univariable analysis; these variables were not included in multivariable analyses. The slope was not significant in simple linear regression, where the regression equation was y=−0.80×+92. In this cohort using simple linear regression analysis, WMI (total WMI volume and quartered point systemscore, respectively) was not associated with lower composite scores on cognition (P=0.680,

Table 4. Association Between Candidate Risk Factors in Patients Who Received Postoperative Magnetic Resonance Imaging and Composite Cognition, Language, and Motor Neurodevelopmental Outcomes Scores on Bayley-III Scales of Infant and Toddler Development at 18 Months

Risk factor	Neurodevelopmental outcome					
	Cognition		Language		Motor	
	Univariable [95% CI]	Multivariable [95% CI]	Univariable [95% CI]	Multivariable [95% CI]	Univariable [95% CI]	Multivariable [95% CI]
Postoperative CMH	0.02 to [−1.214 to −0.103]	0.12 [−1.004 to 0.106]	0.06 [−1.635 to 0.034]		0.001 [−1.489 to −0.394]	0.012 [−1.286 to −0.175]
Sex	0.07 [−9.846 to 0.2774]		0.01 [−16.891 to −2.111]		0.01 [−11.695 to −1.570]	0.03 [−10.378 to −0.710]
GA	0.46 [−4.206 to 1.882]		0.45 [−2.771 to 6.271]		0.81 [−3.502 to 2.721]	
CPB duration	0.49 [−0.113 to 0.054]		0.20 [−0.203 to 0.042]		0.59 [−0.108 to 0.061]	
Postoperative ECMO	0.002 [−34.001 to −8.522]	0.007 [−31.508 to −5.298]	0.007 [−46.330 to −7.822]	0.02 [−42.70 to −4.537]	0.07 [−26.169 to 0.912]	
Seizure	0.42 [−10.959 to 4.542]		0.28 [−17.836 to 5.114]		0.03 [−16.355 to −0.957]	0.1 [−13.470 to 1.392]
WMI volume	0.68 [−0.024 to 0.037]		0.83 [−0.039 to 0.049]		0.91 [−0.033 to 0.029]	
QPS score	0.35 [−1.536 to 4.340]		0.86 [−3.908 to 4.701]		0.50 [−1.965 to 4.061]	
TMS	0.99 [−2.527 to 2.561]		0.42 [−2.211 to 5.315]		0.59 [−3.292 to 1.882]	

Linear regression was performed for both univariable and then multivariable analyses. CMH indicates cerebral microhemorrhage; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; GA, gestational age; QPS, quartered point score; TMS, total maturation score; and WMI, white matter injury.

P=0.352), motor (*P*=0.906, *P*=0.497), or language (*P*=0.827, *P*=0.857). Similarly, total maturation score was not associated with lower composite scores on cognition (*P*=0.989), motor (*P*=0.595), or language (*P*=0.421) in simple linear regression.

DISCUSSION

A major finding of our study was that CMH are not merely incidental findings but have clinical relevance as a prognostic imaging biomarker. The presence and severity of postoperative CMH are associated with impaired neurodevelopmental outcomes on the motor tests of the Bayley-III Scales of Infant and Toddler Development at 18 months of age. Specifically, for every 1-point increase in CMH number, the Bayley-III Scales of Infants and Toddler Development motor score was predicted to decrease on average by 0.94 points (95% CI, 0.39–1.50), whereas the average Bayley-III Scales of Infants and Toddler Development cognitive score was predicted to decrease by 0.66 points (95% CI, 0.09–1.22). This finding is consistent with a prior study in this patient population that found that patients with CMH on MRI at 1 year of age had a 10-point lower score on the psychomotor development index when compared with those without CMH.[22] Our findings underscore the importance of reducing CMH burden.

Risk Factors for Preoperative CMH

The high prevalence of preoperative CMH in our cohort indicates that antenatal and/or preoperative factors contribute to a risk of CMH. Although none of the antenatal and preoperative risk factors analyzed in this study was associated with the presence of preoperative CMH, we note that many of these analyses were underpowered to detect potentially meaningful differences. Although previous studies have reported focal brain injury on preoperative MRI in infants with CHD who underwent the balloon atrial septostomy procedure,[8,23] catheter interventions on the atrial septum were not a predictor for CMH in our cohort. Stroke as a consequence of balloon atrial septostomy was not seen in this cohort.

Risk Factors for Postoperative CMH

We found longer duration of CPB to be the strongest predictor of an increased number of CMH on postoperative MRI. With CPB duration >70 minutes, the median number of CMH was >2-fold higher compared with duration <70 minutes. This finding is consistent with prior studies and may be the result of prolonged blood exposure to synthetic surfaces resulting in inflammation or embolic debris from the bypass machine.[24,25] Moreover, the gross movement of brain tissue caused either by cerebral edema resulting from CPB or cerebral

dehydration resulting from diuretic use, such as furosemide, may contribute to axonal stretching and the rupture of local vascular supply to affected brain tissue. This mechanism of injury is similar to that inflicted by trauma in diffuse axonal injury.[17,26] Our analysis also showed that intraoperative factors including nadir temperature, duration of DHCA, and maximum activated clotting time were not risk factors for CMH. We had hypothesized that deep hypothermia, which can lead to brain shrinkage or water crystallization, would be a risk factor, but our results did not support this.

In addition to the duration of CPB, the use of postoperative ECMO was also associated with increased postoperative CMH burden. Both CPB and ECMO are forms of extracorporeal support that likely share similar mechanisms of cerebral injury. As previously mentioned, systemic inflammation is triggered by prolonged patient contact with nonphysiologic circuit components (ie, pump and oxygenator) causing disruption to blood–brain barrier integrity, contributing to microvascular fragility.[27,28] Infants with CHD have known structural brain immaturity,[7,15] and therefore may be more vulnerable to developing CMH with the use of extracorporeal support, because such interventions commonly impair cerebral autoregulation and cause hemodynamic instability that may further precipitate small vessel rupture.[27,29] The use of anticoagulants with extracorporeal support may further contribute to CMH risk, although we did not detect an association between intraoperative activated clotting time and postoperative microhemorrhages in our cohort.[28] Importantly, although these phenomena may explain the observed increase in postoperative microhemorrhages, they do not explain their presence preoperatively.

We report postoperative seizure and low birth weight as additional risk factors for postoperative CMH, which have not been previously reported to the best of our knowledge. Although the high prevalence of CMH (85%) and the much lower prevalence of seizures (9%) in this study suggest that seizures may be a consequence of CMH and cortical irritation from hemorrhage rather than the reverse, it is not possible to determine whether seizure is a consequence or cause of CMH burden. In line with this, prior research has shown that longer duration of CPB in infants undergoing CHD repair is a risk factor for postoperative seizure.[30,31] Thus, both CMH and seizures may be sequelae due to a common underlying risk factor, although the presence of seizures may amplify the severity of the CMH. Seizures after neonatal cardiac surgery have been associated with worse long-term neurodevelopmental outcomes.[30,31] Lower birth weight has previously been associated with higher mortality rates, poorer growth trajectories, and greater neurodevelopmental impairment.[19] Future research investigating CMH in this population should evaluate the relationship between CMH, seizure, and lower birth weight.

CMH Distribution

Although preoperative CMH were infrequently distributed in the deep gray structures (0%) and brainstem (4%), these regions showed the highest relative increase of CMH postoperatively (28%, 7-fold increase). Although the reason(s) for this are as yet unknown, this discrepancy may be explained by differing mechanisms of CMH development based on the timing of injury. CMH detected on preoperative scans may have arisen at any time point before the first MRI. Currently, we have not identified a specific risk factor(s) for these preoperative CMH, and given our study's results (with the caveat of overall small numbers of CMH on preoperative MRIs), these risk factors are likely to be ones that are less obvious, thereby suggesting heretofore unknown mechanisms for why and how CMH develop in the fetal or immediately postnatal brain in this patient population.

Additional factors that may contribute to the differences in distribution of pre- and postoperative CMH within the brain include changes in cerebral oxygenation and cerebral blood flow in the pre- to postnatal brains of infants with CHD. During in utero development, there is decreased cerebral oxygenation, and therefore the brains of infants with CHD are in an ongoing steady state of relative hypoxia.[7] Because the cerebellum is vulnerable to hypoxic–ischemic injury, this may account for nearly half of the preoperative CMH being located within this brain region. Once born, the systemic and cerebral oxygenation levels may be more prone to fluctuations dependent on ex utero cardiac and respiratory demands. Because the deep gray and brainstem structures are more vulnerable to hypoxic–ischemic injury, this may account, in part, for the higher postoperative prevalence of CMH in these brain regions compared with the relatively unchanged cortical/subcortical areas, suggesting potential shared risk factors for CMH and hypoxic–ischemic brain injury.[32] The distribution of cerebral blood flow also shifts pre- to postnatally with increasing flow to cortical structures, which may also contribute to the absolutely highest number of CMH seen in the cerebral cortex on postoperative MRIs.

Pathophysiology

CMH have most commonly been reported in adult and older populations with several proposed underlying pathophysiologies. Diffuse axonal injury caused by rapid acceleration and deceleration of the brain in traumatic brain injury leads to mechanical stretching of axons.[26] This stretching can trigger mitochondrial dysfunction, oxidative stress, and increased activity of

metalloproteinases contributing to damage and dysfunction of the local microvasculature, possibly giving rise to CMH.[26] In contrast, CMH have also been widely detected in Alzheimer disease, where they are thought to arise from inflammatory processes triggered by the accumulation of amyloid β, τ, and cellular debris that characterize this disease.[33] This proposed mechanism is supported by a previous study in patients with Alzheimer disease that found an association between CMH and amyloid β and τ load.[34] Although CMH are defined radiologically, a few studies have investigated their histopathological correlates, finding a heterogenous pattern of diseased microvessels.[14,35] These studies have been limited by access to postmortem brains and the biases inherent in ex vivo analysis.[35] Developing a suitable animal model to further elucidate the mechanism underlying CMH injury has remained a challenge, because it is difficult to disentangle the role of vascular risk factors and the underlying primary brain disease in existing models.[35] Given this gap in the literature, we have drawn on what is known in adult populations to speculate on what may underlie CMH in our population.

An interesting potential link between the mechanisms that give rise to CMH in adult and infant populations may be disruption to neurofluid balance via the glymphatic circulation. The glymphatic system is a waste clearance pathway within the brain that involves the exchange of cerebral spinal fluid and interstitial fluid to facilitate the removal of metabolic waste that accumulates in the brain during awake periods.[36] Proteins and other metabolic waste products accumulate in the brain during waking hours due to the blood–brain barrier, which prevents their movement into systemic circulation and subsequent elimination from the body. Therefore, sleep is critical as a temporal regulator of the glymphatic system, facilitating fluid transport and promoting waste clearance.[36] Disruption to metabolic waste removal via the glymphatic system has been implicated in Alzheimer disease and other neurodegenerative processes, where impaired glymphatic flow is thought to exacerbate the protein aggregation that is characteristic of these pathologies.[36,37] Both CPB and DHCA may act to impede or disrupt normal neurofluid flow and metabolic waste clearance.

Although CMH in the context of CHD is thought to be the result of debris and/or inflammation from the CPB/ECMO circuit, this does not explain our observations of preoperative CMH. We hypothesize that disruption to the glymphatic system and neurofluid clearance may contribute to CMH generation in this period. Glymphatic flow is driven by arterial pulsations generated by cardiac activity,[36] and therefore low cardiac ejection fraction, as seen in infants with CHD, contributes to poor glymphatic flow and compromised metabolic waste clearance. Such disruptions to neurofluid circulation may leave the vasculature susceptible to oxidative stress and inflammatory processes that give rise to CMH via an Alzheimer disease-like mechanism. Alternatively, impaired neurofluid circulation may contribute to local swelling and dehydration of the brain that may give rise to CMH via a traumatic brain injury-like mechanism.

Cardiovascular impairment for infants with CHD begins in utero and contributes to brain immaturity at birth with a delay of approximately 1 month of development.[7] Such immaturity may be the result of placental insufficiency and a mismatch in oxygenation due to placental thrombosis or insufficient villous tree branching.[38,39] This is supported by the recent finding that increased placental weight is protective against WMI.[11] The glymphatic system may provide a link connecting cardiovascular risk factors to cerebrovascular health in this critical time period when there is enhanced fragility of small cerebral vessels that make them more vulnerable to developing preoperative CMH. Understanding the role of the glymphatic system in CMH may provide insights into its underlying pathophysiology and provide potential therapeutic strategies to mitigate the clinical burden of these lesions. However, further research is needed to fully elucidate the role of the glymphatic system in CMH accrual in this population.

Limitations

There are several limitations to this study. Given that our study is a retrospective analysis of a data set from a prospectively enrolled study, both the inclusion and exclusion criteria were established in the recruitment phase of the original study, which aimed to investigate the causes and timing of WMI in this population. Patients with other brain injuries, including stroke, subdural hemorrhage, and intraventricular hemorrhage, were excluded. Additionally, we were limited by the data available from this cohort in our retrospective analysis. Specifically, not all patients received both pre- and postoperative MRI. Only a subset of patients in our cohort (n=82) returned for neurodevelopmental assessment, which could contribute to selection bias. Furthermore, there may be a contribution of genetic syndrome that is separately affecting neurodevelopmental outcomes, which could not be analyzed in this study due to the low numbers of infants with a known genetic diagnosis in our cohort.

We were also limited in our selection of risk factors to demographic factors and medical management factors that were relatively easy to abstract from the clinical record. Neonatal cardiac critical care is highly variable, and we were not able to capture all medications that were used (eg, anticoagulants, pressors, or diuretics) or every clinical event (eg, transient hypoxemia or apnea). There are likely many factors that contribute

to CMH risk that are difficult to quantify. Furthermore, at the time of patient recruitment, the preferred surgical strategy for aortic arch repair involved the use of DHCA, and it is unknown whether antegrade cerebral perfusion strategies are worse (longer CPB times) or protective for CMH.

Finally, our analysis of preoperative risk factors for CMH was underpowered to detect potentially meaningful associations. Future multicenter retrospective and prospective studies are needed to increase the sample size and help in better characterizing the risk of CMH in this population.

CONCLUSIONS

Our data show that CMH is a clinically significant problem in infants with severe CHD. We report both a high postoperative prevalence of CMH and an association between CMH on postoperative MRI and impaired neurodevelopmental outcomes at 18 months of age. Longer duration of CPB was the most significant risk factor associated with new or worsened postoperative CMH. Surgical factors, however, are not the only cause of CMH given the substantial preoperative prevalence observed. Further research is needed to better understand the mechanism of injury and to elucidate preoperative and postoperative CMH risk. The design of neuroprotection strategies to mitigate risk factors for CMH may improve neurodevelopmental outcomes in this vulnerable population.

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Disclosures

None.

Supplemental Material

Table S1

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