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Fetal brain growth and risk of postnatal white matter injury in critical congenital heart disease

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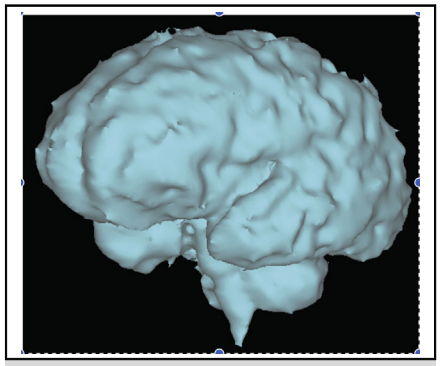
ABSTRACT

Objective: To test the hypothesis that delayed brain development in fetuses with d-transposition of the great arteries or hypoplastic left heart syndrome heightens their postnatal susceptibility to acquired white matter injury.

Methods: This is a cohort study across 3 sites. Subjects underwent fetal (third trimester) and neonatal preoperative magnetic resonance imaging of the brain to measure total brain volume as a measure of brain maturity and the presence of acquired white matter injury after birth. White matter injury was categorized as no-mild or moderate-severe based on validated grading criteria. Comparisons were made between the injury groups.

Results: A total of 63 subjects were enrolled (d-transposition of the great arteries: 37; hypoplastic left heart syndrome: 26). White matter injury was present in 32.4% (n = 12) of d-transposition of the great arteries and 34.6% (n = 8) of those with hypoplastic left heart syndrome. Overall total brain volume (taking into account fetal and neonatal scan) was significantly lower in those with postnatal moderate-severe white matter injury compared with no-mild white matter injury after adjusting for age at scan and site in d-transposition of the great arteries (coefficient: 14.8 mL, 95% confidence interval, −28.8 to −0.73, $P = .04$). The rate of change in total brain volume from fetal to postnatal life did not differ by injury group. In hypoplastic left heart syndrome, no association was noted between overall total brain volume and change in total brain volume with postnatal white matter injury.

Conclusions: Lower total brain volume beginning in late gestation is associated with increased risk of postnatal moderate-severe white matter injury in d-transposition of the great arteries but not hypoplastic left heart syndrome. Rate of brain growth was not a risk factor for white matter injury. The underlying fetal and perinatal physiology has different implications for postnatal risk of white matter injury. (J Thorac Cardiovasc Surg 2020;■:1-8)



Fetal brain volumetry in a fetus with CHD. Segmentation of a 3-dimensional, steady-state, free-precession acquisition was performed to measure TBV. The image depicted is the final volumetric image of the fetal brain.

CENTRAL MESSAGE

Smaller brain volume beginning in utero is associated with clinically significant acquired WMI after birth among those with d-TGA.

PERSPECTIVE

Patients with CHD have delayed brain development and are at risk for brain injury after birth. In this longitudinal study from fetal to neonatal life, we identify an association between brain immaturity and acquired brain injury in d-TGA but not HLHS, highlighting the importance of cardiac physiology in our understanding of brain health in CHD.

See Commentary on page XXX.

CONG

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Abbreviations and Acronyms

CHD = congenital heart disease
CI = confidence interval
d-TGA = d-transposition of the great arteries
HLHS = hypoplastic left heart syndrome
MRI = magnetic resonance imaging
TBV = total brain volume
UBC = University of British Columbia
UCSF = University of California San Francisco
UT = University of Toronto
WMI = white matter injury

Scanning this QR code will take you to the article title page to access supplementary information.

Brain injury in the form of white matter injury (WMI) and stroke is common in the full-term neonate with critical congenital heart disease (CHD),[1] such as hypoplastic left heart syndrome (HLHS) or d-transposition of the great arteries (d-TGA). Studies have shown that approximately one-third of newborns with critical CHD have evidence of WMI even before the neonatal operation.[2] Of note, moderate to severe WMI in the newborn period is associated with impairments in motor outcomes in late infancy.[3] Brain magnetic resonance imaging (MRI) studies in the fetus and neonate with CHD have revealed delays in global brain volumes, microstructure, and metabolic brain development.[4,5]

The mechanism of postnatal WMI in the patient with CHD is thought to be related to brain immaturity similar to mechanisms observed in the premature population. In particular, hypoxic and ischemic events are thought to affect selectively vulnerable cell populations including preoligodendrocytes leading to WMI. Although replenishment occurs in this progenitor cell population, maturation is arrested in preoligodendrocytes resulting in impaired myelination.[6] The relationship between brain immaturity and WMI in the CHD population has been difficult to elucidate given the myriad of risk factors in the postnatal period that are associated with neurologic outcomes.[7-9]

To design effective preventative strategies in this patient population, understanding the causal pathway to acquired neonatal brain injury is crucial. In this study, we sought to determine the association between fetal and neonatal brain size and growth as a measure of maturational state with the risk of postnatal preoperative WMI using longitudinal MRI from fetal to postnatal life. We chose moderate to severe WMI as the primary outcome because of the clinically relevant association with impaired motor outcomes in infancy noted in prior studies.[3] We studied 2 well-characterized groups of patients (d-TGA and HLHS) to account for varying cardiac anatomy and physiology that can influence both our primary predictor and outcome of interest.

MATERIALS AND METHODS

Between 2010 and 2018, pregnant mothers with a fetal diagnosis of critical CHD at 3 sites (University of California San Francisco [UCSF], University of British Columbia [UBC], and University of Toronto [UT] Hospital for Sick Children) were invited consecutively to participate in a prospective protocol using MRI to study brain development and brain injury in CHD. Fetuses with a suspected congenital infection, clinical evidence of a congenital malformation or syndrome, or a suspected or confirmed genetic or chromosomal anomaly were excluded. Once written informed consent was received, subjects underwent a fetal brain MRI in the third trimester of pregnancy followed by a postnatal brain MRI of the neonate before cardiac surgery. The institutional committee on human research approved the study protocol at each site. Written informed consent was obtained from each pregnant mother and postnatal infant's parents.

Subjects diagnosed as having d-TGA or HLHS with both a fetal and neonatal brain MRI were included in this study. Ten subjects (HLHS = 5; d-TGA = 5) had a fetal brain MRI but did not return for a neonatal brain MRI and were not included in the study. There were no significant differences between the subjects included in the study and the subjects who did not have repeat imaging after birth. d-TGA was defined as great vessel malposition with the aorta arising from the right ventricle and pulmonary artery arising from the left ventricle with or without a ventricular septal defect. HLHS was defined as the presence of 1 functioning right ventricle with varying degrees of severe left heart hypoplasia requiring a palliative surgical intervention for survival (stage I operation) in the newborn period. In all subjects, the cardiac diagnosis was confirmed with postnatal echocardiography.

Magnetic Resonance Imaging Study

A fetal brain MRI was performed in the third trimester (median, 35 weeks; interquartile range, 32.6-36). Similar imaging protocols were used at each site. The fetal scans were performed on a 1.5-T (Siemens Avanto, Erlangen, Germany, UBC and UT) or 3-T (GE Healthcare, Waukesha, WI, UCSF) MRI system. A 3-dimensional steady-state free-precession acquisition (UT, UBC) or T2-weighted images (UCSF) were used to measure fetal brain volume. Imaging parameters used at each site are detailed in the Supplementary Methods. All scans were postprocessed at 1 site (UT). Postprocessing of the acquisition to segment the fetal brain was performed by use of a combination of threshold, cutting, and filling tools with a commercial software package (Mimics, Materialize, Leuven, Belgium) as previously described[10] (Figure 1).

Postnatal MRI studies before cardiac surgery were performed as soon as the baby could be safely transported to the MRI scanner as determined by the clinical team. Imaging parameters at each site are detailed in the Supplementary Methods. Brain volume was measured on the postnatal scan as was done on the fetal scan (postprocessing of scans and measurement of brain volumes were performed at a single site). A neuroradiologist at each site reviewed each MRI for focal, multifocal, or global changes blinded to clinical variables. For this study, brain injury in the form of WMI was collected. WMI was further classified as mild (1 to 3 foci each <2 mm), moderate (>3 foci or any foci >2 mm), or severe (>5% of WM volume).[2] We have previously demonstrated high inter-rater reliability of the neuroradiology scores applied to grade the severity of brain injury,[11] as well as consistent findings when compared with quantitative measures of WMI.[3] Other forms of brain injury were also recorded

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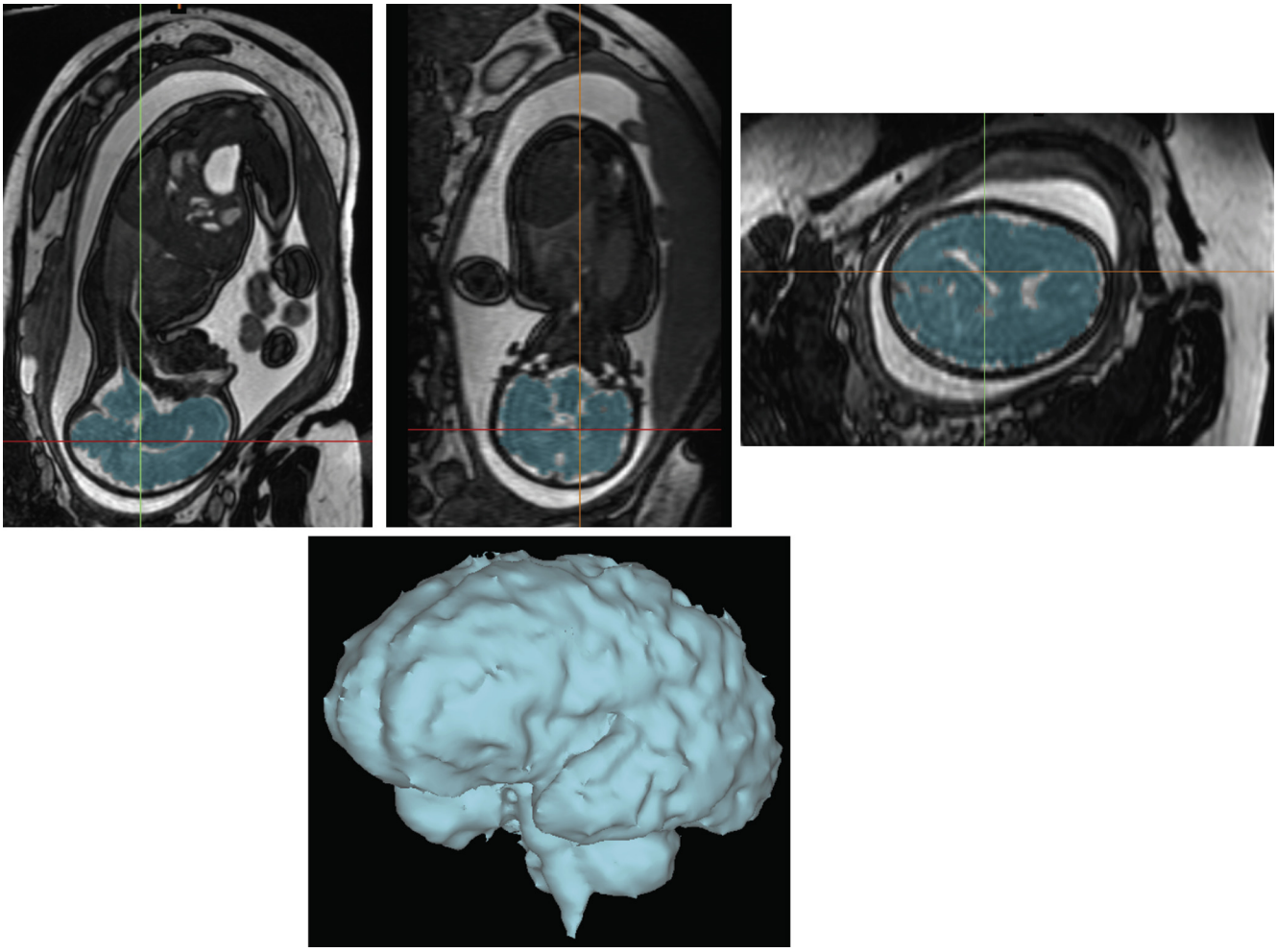

FIGURE 1. Fetal brain volumetry in a fetus with CHD with segmentation of a 3-dimensional, steady-state, free-precession acquisition to measure TBV. Three orthogonal planes are depicted with the final volumetric image of the fetal brain.

including stroke, although all were small and not analyzed as part of the present study.

Clinical Variables

Clinical data (including fetal, delivery, and postnatal variables) were prospectively collected from the medical records by the study physicians or a team of trained neonatal research nurses and reviewed by investigators at each site blinded to all neuroimaging findings.

Statistical Analysis

Our primary outcome was prospectively defined as the presence of moderate to severe WMI on the postnatal preoperative MRI as defined earlier. Baseline demographics were compared between those with and without WMI within each cardiac group (d-TGA or HLHS). Our primary exposure was total brain volume (TBV) on the fetal and neonatal MRI. We identified a significant interaction with cardiac diagnostic group in the relationship between our primary predictor and outcome; thus, the analysis was stratified by cardiac diagnosis (HLHS and d-TGA). To take into account 2 imaging time points and within-subject correlation, we conducted a repeated-measures analysis using generalized estimating equations to assess the relationship between TBV at both the fetal and neonatal time points with the prevalence of moderate to severe WMI after birth. The final model included an adjustment for both time at MRI (postmenstrual age at scan) and site. All analyses were performed on Stata 14.0 software (StataCorp, LP, College Station, Tex).

RESULTS

A total of 63 subjects were enrolled who had both fetal and neonatal brain MRI scans (d-TGA = 37, HLHS = 26). Baseline demographics are presented in Table 1 by WMI severity. Gestational age at birth was on average 1 week earlier for those with moderate-severe WMI on the postnatal preoperative MRI, although not statistically significant (GA birth: d-TGA: 38.8 weeks, 95% confidence interval [CI], 38.2-39.4 vs 39.1 weeks, 95% CI, 38.7-39.5 weeks, $P = .5$; HLHS: 38.1 weeks, 95% CI, 37.6-38.5 vs 39.1 weeks, 95% CI, 38.5-39.9 weeks, $P = .07$). No other clinical or demographic factors were different by WMI severity for either cardiac group. Anatomic details are included in Table 1. Among the d-TGA group, the percentage of patients with a ventricular

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TABLE 1. Baseline demographics of study population by cardiac group and white matter injury severity (comparing those with no/mild white matter injury with those with moderate/severe white matter injury)

	d-TGA (n = 37)			HLHS (n = 26)		
	No/mild WMI (n = 33)	Moderate/severe WMI (n = 4)	*P* value	No/mild WMI (n = 21)	Moderate/severe WMI (n = 5)	*P* value
GA fetal scan Mean, 95% CI	35.1 (34.4-35.8)	34.5 (31.7-37.3)	.58	34.7 (33.7-35.7)	32.8 (30.1-35.4)	.07
Male	20 (60.6%)	4 (100%)	.28	17 (81%)	3 (60%)	.25
GA birth Mean, 95% CI	39.1 (38.7-39.5)	38.8 (38.2-39.4)	.5	39.1 (38.5-39.7)	38.1 (37.6-38.5)	.07
Birth weight, kg Mean, 95% CI	3.4 (3.2-3.5)	3.3 (2.8-3.9)	.86	3.2 (3.0-3.5)	3.0 (2.6-3.3)	.34
Birth HC, cm Mean, 95% CI	34.2 (33.8-34.7)	34 (31.7-36.2)	.72	34.1 (33.2-34.9)	33.7 (33.1-34.2)	.65
pH on first arterial blood gas Mean, 95% CI	7.29 (7.26-7.33)	7.29 (7.21-7.38)	.98	7.30 (7.25-7.35)	7.33 (7.24-7.41)	.58
Lowest preoperative oxygen saturation	69.1 (61.6-76.5)	64.5 (34.5-94.5)	.68	80.5 (73.0-87.9)	85.4 (80.1-90.7)	.48
Preoperative cardiac arrest, N (%)	1 (3.0%)	0	1.0	1 (4.8%)	0	1.0
BAS, N (%)	26 (78.8%)	2 (50%)	.28	3 (14.3%)	0	1.0
VSD, N (%)	11 (33.3%)	3 (75%)	.13			
Aortic atresia, N (%)				10 (47.6%)	5 (100%)	.05
Retrograde flow in aortic arch, N (%)				14 (66.7%)	5 (100%)	.29
GA postnatal scan, Mean, 95% CI	39.6 (39.2-40.0)	39.3 (38.4-40.2)	.62	39.8 (39.3-40.4)	38.5 (37.9-39.1)	.02
Site			.42			.46
UCSF	4 (12.1%)	1 (25%)		10 (47.6%)	4 (80%)	
UBC	6 (18.2%)	1 (16.7%)		1 (4.8%)	0	
Toronto	23 (69.7%)	2 (50%)		10 (47.6%)	1 (20%)	

D-TGA, D-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome; *WMI*, white matter injury; *GA*, gestational age; *CI*, confidence interval; *HC*, head circumference; *BAS*, balloon atrial septostomy; *VSD*, ventricular septal defect; *UCSF*, University of California San Francisco; *UBC*, University of British Columbia.

septal defect was similar in those with no/mild WMI compared with those with moderate-severe WMI. In addition, 4 subjects had an associated coarctation of the aorta, one of which had moderate-severe WMI. Among the HLHS group, a significantly higher percentage of patients had aortic atresia in the moderate/severe WMI group. The prevalence and severity of preoperative neonatal brain injury are presented in Table 2. In the d-TGA group, 12 subjects (32.4%) had WMI, of whom 4 (10.8%) had moderate to severe WMI. In the HLHS group, 8 (34.6%) had WMI, of whom 5 (19.2%) had moderate to severe WMI. A small number of patients had evidence of stroke on the neonatal MRI (d-TGA: n = 3, 8.1%; HLHS: n = 2, 7.7%), all of which were small.

TABLE 2. Prevalence and severity of preoperative brain injury by cardiac group

	d-TGA (n = 37)	HLHS (n = 26)
Total WMI, N (%)	12 (32.4%)	8 (34.6%)
Mild WMI	8 (18.9%)	3 (11.5%)
Moderate-severe WMI	4 (10.8%)	5 (19.2%)
Stroke, N (%)	3 (8.1%)	2 (7.7%)

d-TGA, D-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome; *WMI*, white matter injury.

The average TBV on the fetal MRI and neonatal MRI are listed in Table 3 by cardiac group and WMI severity. The trajectory of TBV from the fetal to neonatal time period by WMI severity is depicted in Figure 2, *A* and *B*. In subjects with d-TGA, overall TBV was significantly lower in the group with acquired neonatal moderate to severe WMI after adjusting for postmenstrual age at scan and site (overall TBV was 14.8 mL (95% CI, −28.8 to −0.73) lower each week from fetal to neonatal life in those with moderate to severe WMI compared with those with no/mild WMI, $P = .04$) (Table 4). However, the rate of change in TBV (ie, rate of growth) did not differ by injury group. TBV increased at a rate of 15.5 mL/week (95% CI, 11.8-19.1) in the subjects with no/mild WMI, whereas it increased at a rate of 13.8 mL/week (95% CI, 7.9-19.5) in those with moderate-severe WMI ($P = .74$). To account for differences in anatomy, a sensitivity analysis was performed removing the 4 d-TGA subjects with associated coarctation of the aorta. We observed a similar trend of a lower TBV among those with acquired neonatal moderate/severe WMI after adjusting for age at scan and site (overall TBV was 14.7 mL (95% CI, −31.7 to 2.2) lower each week from fetal to neonatal life in those with moderate-severe WMI compared with those with no/mild WMI, $P = .08$). In

TABLE 3. Fetal and neonatal total brain volume by white matter injury severity on the preoperative neonatal magnetic resonance imaging in each cardiac group

	d-TGA (n = 37)		HLHS (n = 26)	
	No/mild WMI N = 33	Moderate-severe WMI N = 4	No/mild WMI N = 21	Moderate-severe WMI N = 5
Fetal TBV, mL Mean, 95% CI	267.6 (254.1-281.1)	244.1 (176.2-311.9)	250.0 (231.3-268.7)	225.1 (162.2-288.0)
Neonatal TBV, mL Mean, 95% CI	336.6 (323.7-349.6)	312.0 (292.6-331.4)	330.1 (311.9-358.3)	325.8 (276.4-375.1)

d-TGA, D-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome; *WMI*, white matter injury; *TBV*, total brain volume; *CI*, confidence interval.

subjects with HLHS, no significant difference was noted in overall TBV between those with no/mild WMI and those with moderate-severe WMI (coefficient 14.8, 95% CI, −14.4 to 44.1, $P = .32$), and there was no difference noted in rate of change in TBV between the groups (15.1 mL/week, 95% CI, 11.9-18.4 in no/mild WMI vs 19.1 mL/week, 95% CI, 9.7-28.5 in moderate-severe WMI, $P = .27$).

Finally, we noted no difference in the rate of growth from fetal to neonatal life by cardiac diagnosis. TBV increased by 15.3 mL/week in d-TGA and 15.9 mL/week in HLHS. The difference in slopes per 1 week increase in postmenstrual age was minimal at 1.6 mL, 95% CI, −0.61 to 3.8, $P = .16$ (Figure 3).

DISCUSSION

In this prospective longitudinal study across 3 sites, we demonstrate that lower TBV as a measure of brain maturity beginning in the third trimester of fetal life is associated with increased risk of acquired moderate to severe WMI in the neonatal preoperative period in patients with d-TGA, but not in HLHS. The rate of perinatal brain growth, although similar between d-TGA and HLHS, was not a risk factor for injury in either group. Our results identify important differences between HLHS and d-TGA with regard to acquired postnatal brain injury that brings to light several physiologic considerations that are unique to the fetus with complex CHD.

The overall model that informed our study design is the concept that fetuses with CHD and restricted oxygen/nutrient delivery have delayed brain development[4,10] that heightens their postnatal susceptibility to WMI via instability during the perinatal transitional period. The mechanism of acquired WMI in term neonates with complex CHD is thought to be secondary to hypoxic-ischemic injury to susceptible immature premyelinating oligodendrocytes similar to the mechanism seen in premature infants.[6] As in prior studies, we did not identify WMI on fetal MRI; thus, we designed our study to determine whether brain immaturity beginning in the fetal time period is associated with postnatal acquired brain injury. Given the myriad of risk factors associated with WMI in the CHD population after birth,[7-9] isolating the relationship between brain maturity and WMI has been challenging with varying results in the literature. Semiquantitative techniques have suggested that brain immaturity is a risk factor for WMI,[12,13] whereas other studies using quantitative diffusion weighted imaging have not found similar results.[8] As a crude measure of brain immaturity, relative prematurity (ie, early term birth) has been associated with increased risk of preoperative WMI in patients with CHD,[14,15] which was a trend observed in our study. In the present study, we found that in subjects with d-TGA, fetal TBV is lower and continues to remain low after birth among those who go on to acquire postnatal moderate to severe WMI compared with those who do not.

A piglet CHD model demonstrates that hypoxia impairs the generation and migration of neural progenitors destined to become forebrain interneurons and reduces overall cortical growth.[16] It is possible, that within the d-TGA group, there are varying degrees of impaired oxygen and nutrient delivery to the brain such that a certain subset of patients have a greater decline in cortical growth, overall brain volumes, and maturation. Those with the most brain immaturity may be particularly vulnerable to hemodynamic instability that occurs after placental separation and is often difficult to predict prenatally[17] leading to significant WMI. Preoperative brain injury is more common in d-TGA compared with new postoperative brain injury,[18] suggesting that fetal, perinatal, and neonatal risk factors play an important role in the development of acquired injury.

Perinatal brain ischemia may be a significant contributor to risk of WMI in the setting of brain immaturity. Animal models support a role for cerebral ischemia in acquired WMI in addition to hypoxemia. In particular, systemic hypotension and cerebral hypoperfusion resulting from umbilical cord occlusion in the fetal lamb model result in periventricular WMI and injury to the cerebral cortex.[19,20] In the normal newborn, the transitional circulation results in a 3- to 5-fold increase in left ventricular output due to the decline in pulmonary vascular resistance and increase in pulmonary blood flow. This is mirrored by dramatic reductions in output from the right ventricle with removal of the umbilical circulation.[21,22] In contrast to the normal fetus, in d-TGA, cerebral circulation is largely driven by output from the right ventricle and is thus more dependent on systemic venous return. These hemodynamic aberrations

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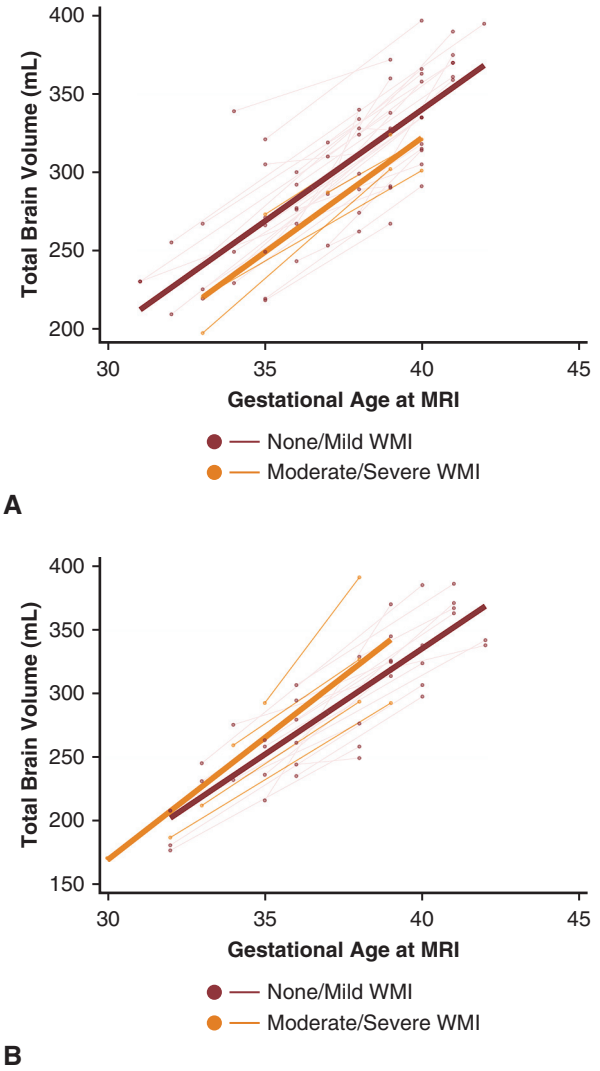

FIGURE 2. Rate of change in TBV from fetal to postnatal life in subjects with d-TGA (A) and HLHS (B) by WMI severity. The plots include fetal and neonatal brain MRI measures with a line connecting the fetal to neonatal measurement for each subject (*light orange* and *light red*) and a best-fitted line. The *orange* and *light orange lines* represent those with moderate to severe WMI, and the *red* and *light red lines* represent those with no or mild WMI. The *x-axis* represents gestational age at the time of MRI and the *y-axis* represents TBV in milliliters. A, Among subjects with d-TGA, overall TBV is significantly lower among those with acquired neonatal moderate to severe WMI after adjusting for gestational age at scan and site ($P = .04$) with no difference noted in rate of growth between the 2 time points by injury status ($P = .27$). B, Among subjects with HLHS, there was no significant difference in overall TBV or rate of growth by injury status. *MRI*, Magnetic resonance imaging; *WMI*, white matter injury.

unique to the fetus with d-TGA may lead to varying degrees of cerebral ischemia during the transitional period from fetal to neonatal life further contributing to acquired perinatal WMI. In addition, lower partial pressure of oxygen levels before corrective cardiac surgery has been associated

TABLE 4. Results from the repeated-measures analysis assessing the relationship between total brain volume on both the fetal and neonatal scans with white matter injury severity on the postnatal scan in each cardiac group

	d-TGA		HLHS	
WMI severity	Coefficient (95% CI)*	*P* value	Coefficient (95% CI)*	*P* value
No-mild	Ref		Ref	
Moderate-severe	−14.8 (−28.8 to −0.73)	.04	14.8 (−14.4 to 44.1)	.32

WMI, White matter injury; *d-TGA*, d-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome; *CI*, confidence interval. *The coefficient represents the difference in overall TBV between those with moderate to severe WMI and those with no or mild white matter injury after accounting for gestational age at scan and site.

with WMI in d-TGA.[9] In the setting of an immature brain, these patients may be even more sensitive to relatively low partial pressure of oxygen levels supporting timely interventions for those with a restrictive atrial communication or earlier corrective surgery.[18] Given that all of the subjects in this cohort were prenatally diagnosed, this cohort is likely generally healthier with regard to perinatal clinical characteristics and brain health compared with postnatally diagnosed patients.[23,24] Despite this advantage, a significant percentage of subjects with d-TGA in our cohort had evidence of postnatal WMI before surgery, highlighting the

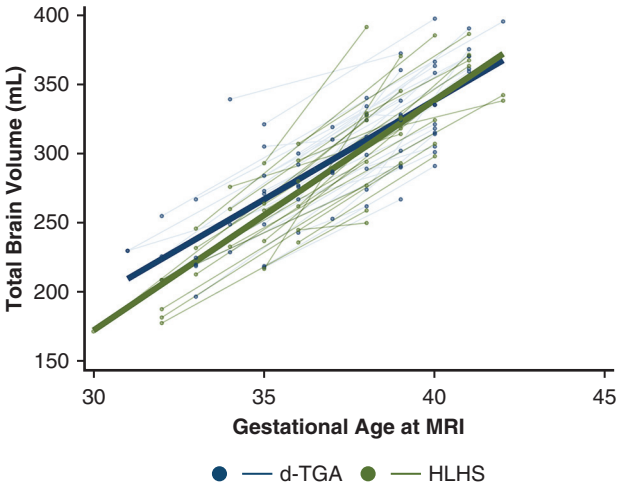

FIGURE 3. Rate of change in TBV from fetal to postnatal life by cardiac diagnosis group: d-TGA or HLHS. The plots include fetal and neonatal brain MRI measures with a line connecting the fetal to neonatal measurement for each subject (*light blue* and *light green*) and a best-fitted line. The *blue* and *light blue lines* represent those with d-TGA and the *green* and *light green lines* represent those with HLHS. The *x-axis* represents gestational age at the time of MRI, and the *y-axis* represents TBV in milliliters. No difference was noted in overall TBV or the rate of change from fetal to neonatal life between the 2 cardiac groups ($P = .16$). *MRI*, Magnetic resonance imaging; *d-TGA*, d-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome.

potential significance of the transitional circulation as it pertains to perinatal/delivery room and preoperative management to protect cerebral blood flow and minimize ischemia. Our findings potentially provide a mechanism to prenatally identify d-TGA subjects who are the most vulnerable to ischemia and thus at highest risk of acquired WMI after birth to allow for clinical care that provides the highest degree of neuroprotection.

Perinatal brain growth from the fetal to postnatal time period did not differ by cardiac group, similar to a prior study.[25] Oxygen and nutrient delivery to the fetal brain are thought to be similar between HLHS and d-TGA as seen by lower oxygen saturation levels in the ascending aorta by fetal cardiac MRI. In addition, both subgroups demonstrate trends toward decreased cerebral oxygen delivery and significantly lower cerebral oxygen consumption compared with controls.[10] Despite the similarity in perinatal brain growth, the 2 groups diverged in the association between brain immaturity and acquired postnatal WMI. No significant association was identified between brain immaturity and acquired postnatal WMI in HLHS suggesting that the underlying fetal and perinatal physiology has different implications for postnatal risk of WMI in this group compared with d-TGA. In particular, anatomic factors within the HLHS group may contribute more to susceptibility to WMI during the perinatal transitional period. As described earlier, changes during transitional circulation such as a decline in pulmonary vascular resistance and increase in pulmonary blood flow lead to a significant increase in left ventricular output with a decline in right ventricular output in the normal neonate. In the setting of HLHS with varying degrees of left heart hypoplasia, cerebral blood flow and risk of ischemia might be more variable in the transitional period depending on the presence or absence of antegrade flow across the aorta. Thus, those at the extreme end of the spectrum with aortic atresia and lack of any antegrade flow to the brain are likely at highest risk of ischemia and acquiring WMI during the transitional period. In fact, all 5 subjects with HLHS with moderate to severe WMI had aortic atresia in our cohort. Postnatal studies have demonstrated an association between aortic atresia and smaller ascending aorta size with impairments in white matter microstructure both at birth[26] and later in life.[27] Our findings for both d-TGA and HLHS suggest

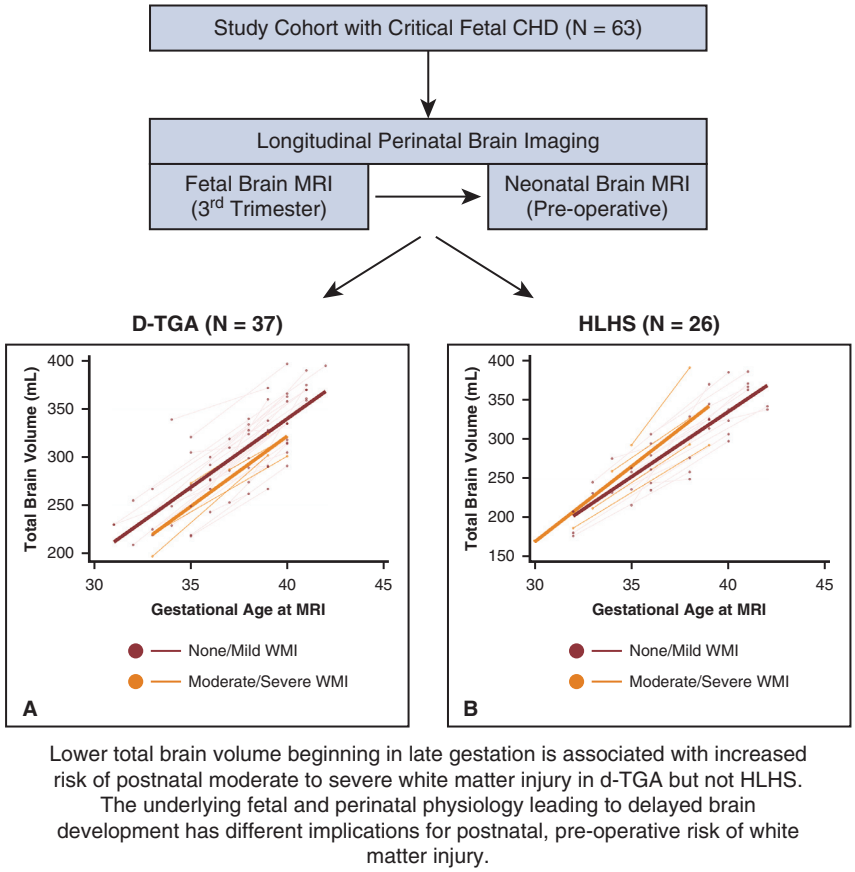

FIGURE 4. Graphic summary of study findings. A total of 63 subjects were included, of whom 37 had d-TGA and 26 had HLHS. Subjects underwent a fetal brain MRI in the third trimester followed by a neonatal MRI before their cardiac operation. *CHD*, Congenital heart disease; *MRI*, magnetic resonance imaging; *d-TGA*, d-transposition of the great arteries; *HLHS*, hypoplastic left heart syndrome.

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that future studies should focus on the transitional circulation and its impact on cerebral blood flow and risk of WMI including incorporation of anatomic details to tailor possible interventions.

Study Strengths and Limitations

Our study was strengthened by the prospective design with longitudinal fetal and neonatal MRI scans. In addition, our study reports findings within homogeneous groups of patients with HLHS or d-TGA allowing for analysis by cardiac physiology. However, our findings are limited by the relatively small sample size, making it challenging to determine causality in the relationship between brain maturity and injury. The multicenter nature of this study may lead to unmeasured confounders that can influence the relationship between brain maturity and WMI; however, this was addressed by adjusting for site in our analysis.

CONCLUSIONS

Perinatal brain development appears to be related to the risk of clinically significant acquired postnatal WMI, particularly in patients with d-TGA (Figure 4). Given the association between moderate to severe WMI and poor motor outcomes in infancy,[3] these findings aid in identifying imaging markers before birth to predict neurologic outcomes. In addition, our results can help inform clinical trials on perinatal interventions aimed at optimizing brain development and minimizing clinically significant brain injury in the CHD population.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: brain development, brain injury, congenital heart disease, neurodevelopment

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APPENDIX E1. SUPPLEMENTARY METHODS

Fetal Magnetic Resonance Imaging Parameters

UT: The following imaging parameters were acquired during a single maternal breath hold: echo time, 1.74 ms; repetition time, 3.99 ms; slice thickness, 2 mm; matrix size, 256 × 205 × 80; field of view, 400 mm; signal average, 1; parallel imaging factor, 2; and average scan time, 13 seconds.

UCSF: T2-weighted anatomic images of the fetal brain were acquired using SSFSE with the real-time platform: TE = 100 ms, TR = 4 s, slice thickness = 3 mm, 256 × 192 with a field of view of 28-32 cm depending on the orientation and lipid artifacts in the field of view.

UBC: T2-weighted anatomic images of the fetal brain were acquired using SSFSE: TE = 94 ms, TR = 1000 ms, slice thickness = 4 mm, flip angle = 165, voxel size: 0.6348 × 0.6348 × 3.0094 mm^3.

Neonatal Magnetic Resonance Imaging Parameters

UCSF: Studies were performed with pharmacologic sedation, as needed, on a 3T GE MR750 system (GE Healthcare, Waukesha, WI) and included 3D isotropic 1 mm T1-weighted IR-SPGR (TE/TR 3.5/8.7 ms, TI 450 ms), 2-mm thickness T2-weighted fast spin echo (TE/TR 120/2000 ms) with 2 mm in-plane resolution. Additional 3D 1 mm isotropic T2 (TE/TR 93/3000 ms) scans were also acquired when conditions permitted.

UBC: Studies were carried out without pharmacologic sedation on a Siemens 1.5 Tesla Avanto (Siemens AG, Healthcare Sector, Erlange, Germany) using a VB 13A software (Siemens AG, Healthcare Sector) and included 3-dimensional coronal volumetric T1-weighted images (TR, 36 msec; TE, 9.2 msec; field of view, 200 mm; slice thickness, 1 mm; section gap, 0) and axial fast spin-echo T2-weighted images (TR, 4610 msec; TE, 107 msec; field of view 160 mm; slice thickness, 4 mm; section gap, 0.2 mm).

UT: Studies were carried out without pharmacologic sedation on a Siemens 1.5 Tesla Avanto (Siemens AG, Healthcare Sector, Erlange, Germany) and included volumetric 3D T1-weighted imaging (TE/TR of 3/1920 ms, field of view of 200 × 200 × 200 mm, matrix size of 256 × 256 mm, slice thickness of 0.8 mm), and axial T2-weighted imaging (TE/TR of 210/9970 ms, field of view of 140 × 140 × 114 mm, matrix size of 218 × 320 mm, slice thickness of 4 mm).

Image acquisitions were optimized at each site with a consistent scanning protocol for the duration of the study.

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000 Fetal brain growth and risk of postnatal white matter injury in critical congenital heart disease

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Smaller brain volume beginning in utero is associated with clinically significant acquired WMI after birth among those with d-TGA.