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Critical Congenital Heart Disease Beyond HLHS and TGA: Neonatal Brain Injury and Early Neurodevelopment

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Abstract

Background: Characterization of brain injury and neurodevelopmental (ND) outcomes in critical congenital heart disease (cCHD) has primarily focused on hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA). This study reports brain injury and ND outcomes among patients with heterogeneous cCHD diagnoses beyond HLHS and TGA.

Methods: This prospective cohort study included infants with HLHS, TGA, or heterogenous "Other cCHD" including left- or right-sided obstructive lesions, anomalous pulmonary venous return, and truncus arteriosus. Brain injury on perioperative brain MRI and ND outcomes on the Bayley-II at 30 months were compared.

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Shabnam Peyvandi: Substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; drafting/revising article critically for important intellectual content; final approval of the version to be published

Dawn Gano: Substantial contributions to conception and design, analysis and interpretation of data; revising article critically for important intellectual content; final approval of the version to be published

Stephany Cox: Substantial contributions to acquisition of data, analysis and interpretation of data; revising the article critically for important intellectual content; final approval of the version to be published

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Consent: All subjects included in this research project consented to participation in this IRB-approved study. Specific consent for inclusion in this sub-analysis was not performed as no direct contact with participants was required.

Results: A total of 218 participants were included (HLHS=60; TGA=118; "Other cCHD"=40, including 8 with genetic syndromes). Pre-operative (n=209) and post-operative (n=189) MRI showed similarly high brain injury rates across groups, regardless of cardiopulmonary bypass exposure. At 30 months, participants with "Other cCHD" had lower cognitive scores (p=0.035) compared to those with HLHS and TGA, though worse ND outcome in this group was driven by those with genetic disorders.

Conclusion: Frequency of brain injury and neurodevelopmental delay among patients with "Other cCHD" is similar to those with HLHS or TGA. Patients with all cCHD lesions are at risk for impaired outcomes; developmental and genetic screening is indicated.

Introduction:

Critical congenital heart disease (cCHD) is defined practically by the need for surgery in the neonatal period and includes many cardiac diagnoses. As surgical and perioperative care have improved, survival with cCHD has increased, shifting the focus onto risk for neurodevelopmental (ND) impairment.[1] Prenatal cerebral circulation is altered in two of the most common neonatal cCHD diagnoses – hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA), and is associated with dysmature brain development,[2,3] quantifiable even in utero.[4] Postnatally, cCHD neonates may experience low cardiac output and/or hypoxemia during the transitional period, before surgery, and during surgical intervention. Neonatal cardiac surgery may involve various cardiopulmonary bypass strategies, each with associated risks including emboli or hypoxia-ischemia. Postoperatively, cCHD neonates may experience hypoxemia, hypotension, low cardiac output syndrome, or cardiac arrest resulting in brain injury.

In the past decade, our group and others have undertaken perioperative neuroimaging studies that identified high rates of acquired neonatal brain injury and altered brain development in term newborns with cCHD.[5,2,6,7,] Most neuroimaging studies have focused exclusively on neonates with TGA[8,9 10] or cohorts dominated by TGA and HLHS.[9,11,12,13,14,15,16] When other cCHD diagnoses are included in the studies they are either excluded from statistical analyses[16], combined and analyzed as a single group[14,17], or analyzed using functional characterization based upon number of cardiac ventricles and presence of aortic arch obstruction.[11,13,15] Decisions to group cCHD diagnoses are understandable as most neonatal cCHD neuroimaging studies are relatively small cohort studies. Combining or excluding other cCHD diagnoses with more common cCHD types (TGA and HLHS) precludes determination of injury risk in these other diagnoses. Neurodevelopmental outcome studies after neonatal repair of cCHD have comparatively larger cohorts with granular data available for most of the common cCHD diagnoses including TGA[18], HLHS[19], and Tetralogy of Fallot (TOF)[20,21]. Studies that combine neonatal brain imaging with ND outcomes beyond one year are rare.

In this study, we took advantage of the relatively large size of a neonatal neuroimaging cohort enrolled over two decades. We sought to describe rates of brain injury and comparative ND outcomes in other cardiac diagnoses beyond HLHS and TGA. We hypothesized that the infants with other cCHD diagnoses may have different risk profiles

compared with infants with HLHS and TGA owing to unique effects on prenatal circulation, intraoperative support, and postoperative course.

Methods:

Infants born ≥36 weeks gestational age (GA) between 2001-2018 with cCHD were recruited and enrolled for this prospective study to obtain pre- and post-operative brain MRI and subsequent ND testing at the University of California-San Francisco Benioff Children's Hospital (UCSF) and University of British Columbia (UBC). cCHD was defined as a congenital heart defect with expected surgical intervention within the first month of life. Individuals were excluded if congenital infection was suspected or if a known chromosomal duplication, genetic or malformation syndrome was identified prior to enrollment. A small number of participants received a genetic diagnosis based on chromosomal microarray after enrollment, and for this analysis we considered subgroups both with and without a genetic diagnosis. Informed consent was obtained from parents of all participants, and the institutional committee on human research approved the study protocol at both locations.

Participants were grouped based on presence of 1) HLHS or variants- defined as a hypoplastic left ventricle with varying degrees of hypoplasia or atresia of the mitral and aortic valves that underwent single ventricle palliation; 2) TGA-defined as two ventricles with mal-positioned aorta and pulmonary artery undergoing an arterial switch procedure, or 3) Other cCHD lesions requiring neonatal surgery but not fitting into one of the first two categories. Within the Other group, neonates were sub-classified based on left-sided obstructive lesion with biventricular physiology (LSOL-2V), right-sided obstructive lesion with biventricular physiology (RSOL-2V), right-sided obstructive lesion with single ventricle physiology (RSOL-1V), and truncus arteriosus (TA). Anatomy was determined based on postnatal echocardiograms performed by pediatric cardiologists and by direct visual inspection in the operating room. Detailed clinical data was collected from all participants during their initial hospitalization and cardiac surgery.

Brain MRI:

Neonates underwent pre-operative MRI as soon as clinically stable; post-operative imaging was performed following surgical intervention and prior to discharge from the hospital. Imaging was performed both with and without pharmacologic sedation largely determined by era with a transition to non-sedated scans in the more recent time period. Imaging was reviewed by two pediatric neuroradiologists blinded to clinical status and outcomes. Brain injury was categorized as intraventricular hemorrhage (IVH), white matter injury (WMI), or stroke as previously described.[2,6,7,22] Only newly acquired brain injury on the post-operative MRI was reported as "post-operative injury". A cumulative assessment of brain injury across both the pre-and postoperative scans was also noted. If two MRIs were performed pre-operatively, the second one was chosen, and if more than one post-operative brain MRI was performed, the MRI closest to the surgery date was used to quantify burden of pre- vs post-operative brain injury.

Neurodevelopmental assessment:

Participants were invited for follow-up ND assessment at age 30 months. The Bayley Scales of Infant and Toddler Development was administered as a developmental assessment; different versions of the BSID were administered during the study period. The BSID-II was administered to each participant until 2012; after that it was phased out gradually as the BSID-III became available for neurodevelopmental follow-up through 2018. All participants with BSID-II data were included for primary analysis; secondary analysis included all with BSID-II or BSID-III data. Testing was administered by a single qualified examiner (licensed psychologist or experienced psychometrician) at each site, who was blinded to the diagnoses, neuroimaging, and other clinical data. Initial analyses were performed using BSID-II follow-up data, as most patients underwent ND testing with the BSID-II, which consists of the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). BSID-II scores were categorized as Normal (>85), Mild-moderate impairment (1-2SD below the mean, scores of 70-84), or Severe impairment (2SD below the mean, scores <70). The BSID-III consists of cognitive, language, and motor components. To incorporate participants evaluated with BSID-III, the average value of cognitive and language composite scores was calculated as a cognitive/language composite score, comparable to the BSID-II MDI. BSID-II/III scores were categorized as Normal or “High Risk” based on studies looking at equivalencies between BSID-II and BSID-III, with a High Risk score corresponding to moderate-severe impairment.[23,24] High Risk motor score was classified as BSID-II PDI <70 or BSID-III motor score <85, and High Risk cognitive/language score was classified as BSID-II MDI <70 or BSID-III cognitive/language composite score <80.

Statistical analysis:

Demographic and clinical variables were compared among subcategories of participants in the Other cCHD group, as well as compared to patients with HLHS and TGA. Fisher’s exact tests and Pearson’s chi-square tests were used for comparison of categorical variables; the Kruskal-Wallis test was used for continuous variables to compare median values. A p-value of $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Version 27.[25]

Results:

Demographics:

A total of 221 neonates were enrolled during the study period. Parents of three neonates subsequently withdrew from the study during the neonatal period, resulting in 218 infants who met inclusion criteria for further analysis, including, 60 infants with HLHS, 118 infants with TGA, and 40 infants with Other lesions. Baseline demographics are listed for all groups in Table 1. There was a male predominance in all groups, most notably in the TGA group (75%), and least notably in the Other group (55%). Prenatal diagnosis was lowest for the TGA group. Birthweight was lowest in the Other group compared to HLHS or TGA ($p<0.001$), despite no difference in GA-at-birth. There was a higher prevalence of genetic diagnoses in the Other group, including 22q11.2 deletion syndrome (n=7, 18%) and 7q11.23 deletion syndrome (n=1, 3%). Participants with Other lesions were significantly

more likely to undergo repair without cardiopulmonary bypass (CPB) (30%, p<0.001), and were significantly older at age of operation (median age 11 days of life), compared to the HLHS group (median 7 days of life), and TGA group (median 8 days of life, p=0.012). Length of stay was longest in patients with HLHS (median 35.5 days, p<0.001), and similar in patients with TGA (median 20 days) and Other lesions (median 21 days). No significant differences were observed in rates of ECMO based on lesion type. Of all eligible participants, 103 were available for neurodevelopmental follow-up at 30mo (Figure 1). Specific cardiac lesions within the Other group are listed in Table 2. Baseline demographics were not different across sub-categories within the Other group.

Structural brain MRI

Brain MRI was performed pre-operatively in 209 participants, including 57 in the HLHS group, 116 in the TGA group, and 36 in the Other group (Table 3). Among patients in the Other group with pre-operative brain MRI, 22% had an injury identified; 8% had IVH, 17% had WMI, and 3% had stroke, similar to frequency of brain injuries observed in the HLHS or TGA group, though there was a trend towards a lower frequency of stroke in the Other group (p=0.050).

Brain MRI was performed post-operatively in 189 participants, including 50 in the HLHS group, 107 in the TGA group, and 32 in the Other group (Table 4). Post-op MRI was performed was later in the HLHS group compared to the Other and TGA groups (p=0.004), but there was no significant difference in uncorrected GA at time of post-op MRI among the three groups. Among patients in the Other group with post-operative brain MRI, 41% had an injury identified; 6% had IVH, 25% had WMI, and 13% had stroke, not significantly different from the HLHS and TGA groups. Brain injury rates on MRI at any timepoint (pre- or post-operatively) were not significantly different among the three groups, ranging from 42% in the Other group to 62% in the HLHS group. Participants with genetic syndromes had no significant difference in rate of pre- or post-operative brain injury compared to those without genetic syndromes. Additionally, rates of pre- and post-operative brain injury of all types were not significantly different among those who came for ND follow-up compared to those who were not available.

Within the Other group, post-op brain injury rates were further analyzed based on exposure to CPB intra-operatively, and there was no significant difference in frequency of IVH, WMI, stroke, or any injury in the participants that required CPB (Table 4). The patients in the Other group who did not receive CPB included seven with isolated aortic coarctation repair and five with systemic to pulmonary shunts (BT shunt N=4, aortopulmonary window N=1).

Overall neurodevelopmental outcomes

Neurodevelopment was assessed at 30 months in 79 participants (HLHS n=11, TGA n=54, Other n=14) who returned for BSID-II testing; an additional 24 participants had BSID-III testing (Table 5). Rates of developmental follow-up among living children varied significantly based on cCHD lesion. The highest follow-up was observed in the TGA group (61%) and lowest in the HLHS group (38%, p<0.001). No other demographic differences

were noted among those available for ND follow-up versus those who did not attend follow-up.

The Other group had significantly lower median BSID-II MDI score (82.5) compared to the HLHS group (95.0) and TGA group (93.5, p=0.035). The HLHS group had lowest median PDI score (77.0), followed by the Other group (85.5), with the highest median PDI score in the TGA group (91.0, p=0.008) compared to the TGA group. Excluding patients with genetic diagnoses, the Other, HLHS, and TGA groups had no significant difference in BSID-II MDI scores, but the HLHS group had significantly lower PDI score compared to the Other and TGA groups (p=0.012). Within the Other group, excluding those with genetic syndromes, 50% had MDI scores >1SD below the mean, and 30% had PDI scores >1SD below the mean, suggesting at least mild-moderate impairment. Including all participants with 30mo ND BSID-II and BSID-III data (n=103), the Other group had 21% with High Risk cognitive/language scores and 16% with High Risk motor scores, though almost exclusively in those with genetic conditions. In comparison, High Risk cognitive/language scores occurred in 20% of the HLHS group, and 6% of the TGA group. High Risk motor scores occurred in 27% of the HLHS group and 6% of the TGA group.

Within the Other group, there was no association between exposure to CPB and BSID-II/III scores at 30mo. Within the full cohort, no significant ND differences were noted in patients born 2001-2009 vs. 2010-2018.

Genetic syndromes and outcomes

Within the Other group at 30mo, participants with a known genetic syndrome had significantly lower median MDI score (58.5) and PDI score (54.5) compared to those with no known syndrome (median MDI 85; median PDI 91.5), though findings were limited by very small sample size (Table 5). None of the four had scores within the normal range; one (25%) had scores within 1-2SD below the mean, and the other three (75%) had scores >2SD below the mean in all domains.

Discussion:

Neurodevelopmental impairment is common among children born with cCHD but cohort studies neonates with perioperative neuroimaging have focused primarily on the most common types of lesions including HLHS and TGA. This study suggests that children with cCHD beyond these two diagnoses have similarly high rates of acquired brain injury and ND impairment, particularly in children with comorbid genetic syndromes. Risk of brain injury and ND impairment in infants with Other cCHD lesions may be due to alterations in prenatal circulation and neonatal hemodynamic instability, similar to proposed mechanisms of injury in infants with HLHS and TGA. Historically, the non-HLHS, non-TGA group has been a challenging group of patients to study due to heterogeneity of cardiac disease and the high association with co-morbid genetic conditions. Our long-standing prospective cohort study allows for a description of common neuroimaging and ND outcomes in this patient population.

The unique demographics profile of the Other group may be due to distinctive etiology for their cCHD and further highlights how patients with non-HLHS, non-TGA lesions represent a distinct cohort. Most importantly, this group included subjects with genetic syndromes (specifically, 22q11.2 and 7q11.23 deletion syndromes (n=1, 3%). In addition, we observed in the Other group a lower median birthweight, higher proportion of females, older age at time of surgery, and less use of CPB. The overall male predominance in cCHD, though with lesion-specific differences in sex ratios, has previously been observed but is not well understood.[2,7,26]

Pre-operative brain injury was observed in 22% of patients with Other lesions, not significantly different than in the HLHS and TGA groups, though there was a trend towards lower incidence of pre-operative stroke in the Other group. Prior studies have found that postnatal diagnosis of cCHD, longer time to surgery, and need for septostomy can predispose patients to higher rates of brain injury, likely related to hemodynamic instability, acidosis, and hypoxia.[7] Non-cardiac complications such as infection, as well as exposure to enteral feeds and sedatives have also been found to increase risk for pre-operative brain injury.[27] Relatively high rate of postnatal cCHD diagnosis and longer wait time to surgery may have contributed to the incidence of pre-operative brain injury in the Other group. Other clinical factors such as infection and medication use were not specifically studied in this cohort but deserve additional consideration. Further studies are warranted to better understand the factors that contribute to pre-operative brain injury with the goal of reducing its prevalence.

Within the Other group, the rate of newly observed, post-operative injury was substantial and not significantly different than in the HLHS and TGA groups, despite the significant differences in use and duration of CPB. Similar risk factors for pre-operative brain injury (e.g. hypoxemia, hypotension, low cardiac output, intracardiac shunt) remain relevant in the post-operative period, likely with additional contribution from peri-operative hemodynamic fluctuations, though this deserves additional research. It is notable that use of CPB and duration of CPB and cross-clamp time did not seem to be associated with higher frequency of post-operative brain injury in this cohort. In summary, though the Other group included types of cCHD lesions previously thought of as less vulnerable to brain injury, the Other group had a high overall rate of peri-operative injury identified on brain MRI, including WMI in 25%. The association between specific types of perioperative brain injury and later neurodevelopment is complex, as not all injury is necessarily associated with worse prognosis.[9] For example, extent of WMI has been found to be associated with worse motor scores at 30mo, whereas presence of small ischemic strokes may have less ND significance.[9]

It has become well established that children born with cCHD have higher risk of ND impairment[5,28], but the majority of neonatal imaging studies have been limited to a relatively narrow definition of cCHD. Only recently have diagnoses such as coarctation of the aorta or truncus arteriosus been included in studies of cCHD and neurodevelopment, and these lesions were previously thought to have a lower burden of associated impairment than HLHS or TGA. This study demonstrates a high rate of ND impairment in the Other group, with median BSID-II MDI and PDI scores 1-2 SDs below the overall population average. When including patients with genetic syndromes, the Other group appeared most similar

to the HLHS group in ND scores. Excluding patients with identified genetic syndromes, ND outcomes in the Other group were similar to the TGA group. This non-syndromic Other group includes patients such as those undergoing arch repair, often without CPB, and highlights the risk for ND impairment in this population previously thought to have more favorable outcomes, similar to observations by Simon et al. in patients with coarctation of the aorta.[29]

This study implements a method of combining BSID-II and BSID-III data to increase number of patients with ND follow-up data and translate findings into a metric that may be more tangible for conversations of prognosis. The BSID-III scores may underestimate rates of subtle impairment in cCHD[30,31], but this method of categorizing BSID-II/III data may help to identify patients at the highest risk for severe impairment in cohorts that span multiple decades and versions of the Bayley. The category of “High Risk” motor and cognitive/language scores, as implemented in this paper, suggests at least a moderate degree of impairment and may not include patients with milder deficits. As families often tend to focus most on severe impairment in discussions of prognosis, this dichotomous scoring system may be more helpful for discussions of risk to clinicians and families than an average developmental score with an associated range. Consistent use of a patient and family-centric, clinically relevant, standardized metric of ND outcomes will be critical to improving our understanding of outcomes in cCHD and to inform clinicians’ counseling to families about risk of ND impairment in this population.

Including both BSID-II and BSID-III scores at 30 months, among the Other group, presence of High Risk cognitive/language and motor scores was overall similar to the HLHS group, though cases of High Risk development were primarily noted in those with concomitant genetic syndromes. Overall, ND testing at 30mo has been shown to correlate with perioperative brain injury[9], and is a better predictor of school-age development than testing at 12mo.[9,32] Studies with long-term follow-up are needed to further understanding of the relationship between between neonatal brain injury, early neurodevelopment, and later functional outcomes in cCHD, as cognitive deficits may become more apparent as children approach school age and are challenged with more complex task requiring attention and executive function.. This study highlights the relatively high rate of early ND impairment within the population of patients with cCHD beyond HLHS and TGA.

At least 30% of all infants with cCHD have an identifiable genetic anomaly [33,34], and this percentage continues to rise with improved access to genetic testing and new identification of cCHD-related genes.[35] Despite this, patients with an identified genetic etiology for their cCHD are often excluded from studies on imaging and outcomes. Genetic syndromes are more common in certain cCHD lesions such as aortic coarctation, truncus arteriosus, and Tetralogy of Fallot[36], lesions with less overall ND outcome data than HLHS and TGA. Limited data exists on outcomes in patients with concomitant cCHD and genetic syndromes beyond well described chromosomal anomalies (e.g. Trisomy 21), and the few studies that do exist tend to focus on neonatal/perioperative complications and associated outcomes such as neonatal survival rates rather than on neurodevelopment.[33,37,38,39]. Immediate neonatal outcomes after cCHD surgery are worse in patients with genetic syndromes including 22q11.2 deletion.[37,38] Patients with 22q11.2 deletion syndrome have a high burden of

neuropsychiatric symptoms and developmental delay regardless of presence of cCHD[40], but cCHD likely increases this risk further. Several studies have shown worse ND outcomes in neonates with concomitant genetic syndromes and cCHD compared to non-syndromic cCHD peers.[41,42] These studies, similar to this current study, are limited due to small cohorts with genetic syndromes and by homogenous grouping of participants with genetic syndromes, despite known diversity in genotype and phenotype in non-cCHD populations. Our cohort included a small number of patients with identified genetic syndromes but adds to the growing data on the high incidence of severe impairment in this population. Patients with cCHD and genetic syndromes may demonstrate a two-hit model of risk for neurocognitive dysfunction both from cCHD and chromosomal differences. To better understand the combined effect of genetic syndromes and cCHD on long-term neurologic function, studies with larger cohorts of diverse patients with a variety of genetic conditions are ongoing.[43,44]

This study's primary strength is its focus on a cohort of patients with non-HLHS, non-TGA lesions that have often been excluded from cCHD studies regarding neonatal brain injury and, to a lesser extent, neurodevelopment. Additional strengths include the large number of patients with peri-operative neuroimaging and the longitudinal follow-up through 30mo. Limitations include the long recruitment period for this study over two decades, during which clinical practice has evolved and neurodevelopmental testing has changed. Over the study period, improvements in prenatal diagnosis of CHD and specific clinical interventions aimed at neuroprotection may be associated with lower frequency of perioperative brain injury and deserves further study beyond the scope of paper. Tools to measure neurodevelopment have also evolved over two decades, with the Bayley-4 now favored as the standard clinical neurodevelopmental assessment, but there is limited data on how Bayley-4 scores correlate with BSID-II/III scores, particularly in the CHD population. Rates of ND follow-up were relatively low (54%), owing to wide geographic dispersion of our clinical population, which may limit external validity or incorrectly estimate overall rate of impairment. Additionally, socioeconomic status has known associations with ND outcomes in cCHD,[45] but was not explicitly quantified in this study and may have influenced availability for follow-up. Reassuringly, rates of perioperative brain injury were similar in the cohort seen for follow-up compared to those unavailable for follow-up, which would suggest similar risk profile for later ND impairment. It is unclear why the TGA patients had such higher rates of return for ND follow up compared to the HLHS patients, possibly limiting external validity of ND outcomes disproportionally in the HLHS group. Unfortunately, we are unable to know outcomes of those who did not return to follow up.

Despite a relatively large number of patients overall, the Other population included only 40 patients with a wide variety of lesion types, with limited power to calculate statistical differences in patterns of injury or outcome between each type of Other lesion. Further studies of larger populations would be needed to better understand patterns of injury and ND outcomes in specific lesions or genetic syndromes that have traditionally been excluded from cCHD research.

Conclusion:

Critical congenital heart disease confers a relatively high risk of perioperative brain injury and subsequent ND impairment. This large, heterogenous cohort of patients with cCHD adds to the growing literature on associations between specific lesions, patterns of brain injury, and early functional outcomes. To inform prognostication and decrease burden of ND impairment, ongoing research is needed with a focus on patients with less common cCHD lesions and patients with comorbid cCHD and genetic syndromes.

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Data availability:

The datasets generated and analyzed during the current study are not publicly available due to protected health information that, if shared, would compromise the privacy of the individuals. Data are available from the corresponding author on reasonable request.

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Impact:

- This study adds to literature on risk of brain injury in patients with critical congenital heart disease (cCHD) diagnoses other than hypoplastic left heart syndrome (HLHS) and transposition of the great arteries (TGA), a heterogenous cohort of patients that has often been excluded from imaging studies
- Children with cCHD beyond HLHS and TGA have similarly high rates of acquired brain injury
- The high rate of neurodevelopmental impairment in this heterogenous group of cCHD diagnoses beyond HLHS and TGA is primarily driven by patients with comorbid genetic syndromes such as 22q11.2 deletion syndrome

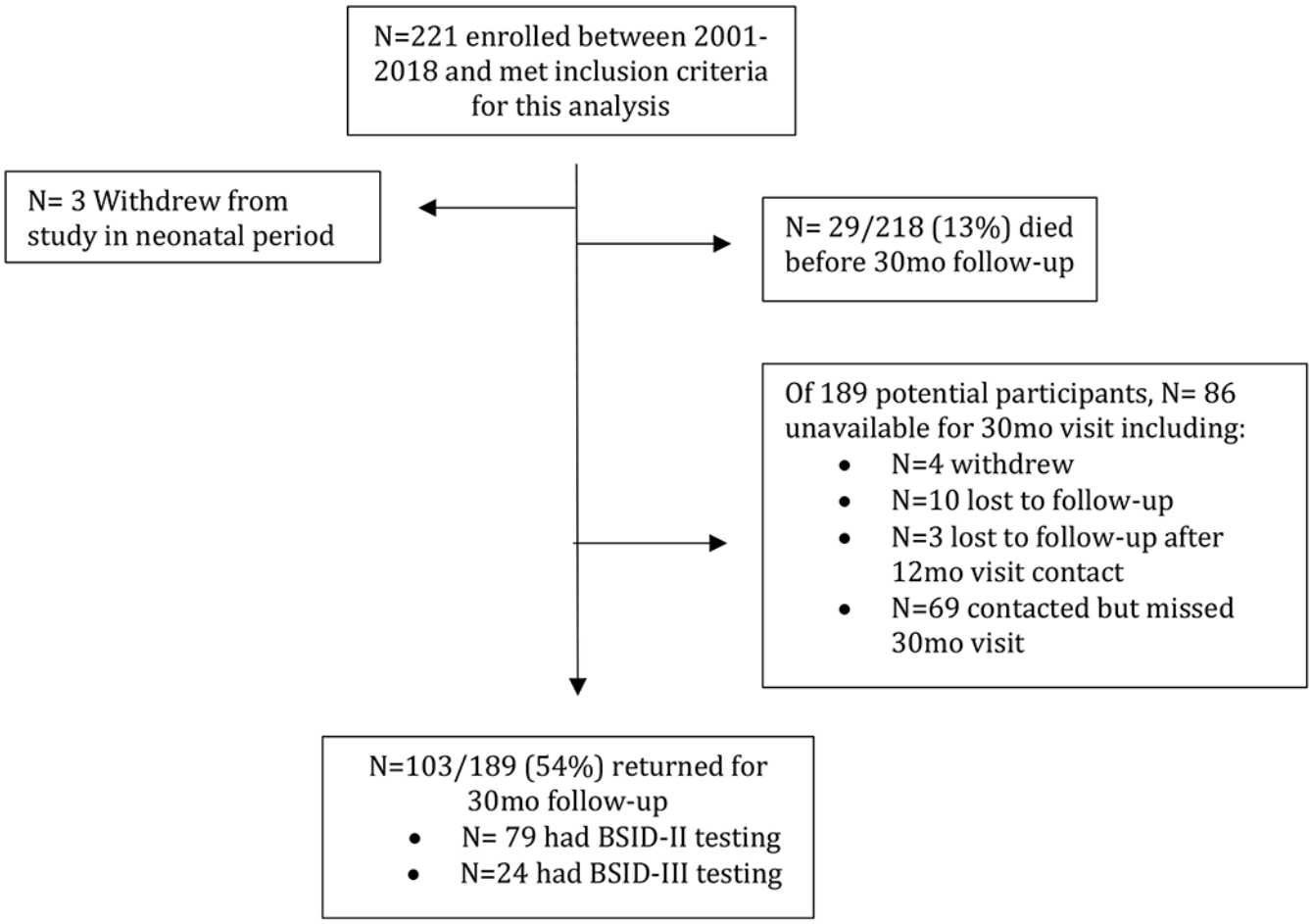

Figure 1:
Consort diagram of participant enrollment and follow-up data

Table 1:

Neonatal demographics of participants with hypoplastic left heart syndrome (HLHS), transposition of the great arteries (TGA), and Other critical congenital heart disease (cCHD) lesions

	HLHS N=60	TGA N=118	Other N=40	p-value
Sex				
Female, n (%)	24 (40%)	29 (25%)	18 (45%)	
Male, n (%)	36 (60%)	89 (75%)	22 (55%)	0.021
Gestational age at birth, wks, median (IQR)	38.7 (38.0-39.6)	39.1 (38.1-40.0)	38.9 (38.1-39.4)	0.063
Birth weight, kg, median (IQR)	3.2 (3.0-3.6)	3.4 (3.0-3.7)	3.0 (2.8-3.3)	<0.001
Head circumference, cm, mean (SD)	34.0 (33.5-34.0)	34.0 (33.0-35.0)	34.0 (32.8-35.0)	0.472
Delivery				
Vaginal, n (%)	37 (62%)	88 (75%)	26 (65%)	
C-Section, n (%)	23 (38%)	30 (25%)	14 (35%)	0.171
Apgar				
1 min, median (IQR)	8 (7.5-8)	8 (6-8)	8 (7-8)	0.014
5 min, median (IQR)	9 (9-9)	8 (8-9)	9 (8-9)	<0.001
Genetic syndrome, n (%)	0 (0%)	0 (0%)	8 (20%)	<0.001
Diagnosis timing:				
Prenatally, n (%)	44 (73%)	42 (36%)	23 (58%)	
Postnatally, n (%)	16 (27%)	76 (64%)	17 (42%)	<0.001
Age at operation, days, median (IQR)	7 (5-10)	8 (6-11)	11 (7-16)	0.012
No cardiopulmonary bypass, n (%)	2 (3%)[a]	0 (0%)	12 (30%)	<0.001
Cardiopulmonary bypass time, mins, median (IQR)	132 (106-157)	151 (127-186)	112 (95-157)	<0.001
Cross-clamp time, mins, median (IQR)	49 (41-67)	75 (60-95)	54 (42-72)	<0.001
Extracorporeal membrane oxygenation during hospitalization, n (%)	9 (15%)	6 (5%)	3 (8%)	0.074
Length of hospital stay, median (IQR)	35.5 (24.5-57)	20 (17-32)	21 (14-32.5)	<0.001

[a]Two HLHS patients had hybrid procedures (one had PA banding and PDA/transverse arch stent and the other had PA banding, PDA ligation and division) without CPB

Table 2:

Diagnoses within the Other critical congenital heart disease lesions

Sub-categories within Other group (n=40)	**Specific Other lesions**
Left-sided obstructive lesion (n=19)	VSD with interrupted aortic arch (9) Interrupted aortic arch type A with A-P window (1) Aortic coarctation/arch hypoplasia (7) Critical aortic stenosis (2)
Right-sided obstructive lesion, two ventricle physiology (n=7)	Tetralogy of Fallot (5) Tetralogy of Fallot + total anomalous pulmonary venous connection (1) Double outlet right ventricle (1)
Right-sided obstructive lesion, single-ventricle physiology (n=9)	Pulmonary atresia, intact ventricular septum (2) Unbalanced common atrioventricular canal, total anomalous pulmonary venous connection (2) Tricuspid atresia/pulmonary atresia (1) Other single ventricle with pulmonary atresia (1) Ebstein's anomaly (1) Unbalanced common atrioventricular canal, pulmonary atresia (1) Double inlet left ventricle, pulmonary atresia (1)
Truncus arteriosus (n=5)	Truncus Arteriosus (TA) Type I (1) TA Type II (3) TA Type III (1)

Table 3:

Frequency of pre-operative injury on brain MRI

	HLHS N=57	**TGA N=116**	**Other N=36**
Gestational age at MRI, weeks, median (IQR)	39.4 (38.5-40.1)	40.0 (39.0-40.9)	39.4 (38.7-40.8)
p=			0.101
Days of life (DOL) at MRI, median (IQR)	5 (3-7)	5 (4-7)	6 (3-11)
p=			0.196
Intraventricular hemorrhage, n (%)	7 (12%)	11 (9%)	3 (8%)
p=			0.790
White matter injury, n (%)	15 (26%)	25 (22%)	6 (17%)
p=			0.541
Stroke, n (%)	9 (16%)	23 (20%)	1 (3%)
p=			0.050
Any injury, n (%)	22 (39%)	46 (40%)	8 (22%)
p=			0.151

Table 4:

Frequency of post-operative and any (pre- or post-operative) injury on brain MRI

	HLHS N=50	**TGA N=107**	**Other N=32**		
			Total	**No bypass N=10**	**Bypass N=22**
Gestational age at MRI, median (IQR)	42.2 (41.3-43.4)	42.1 (40.8-43.4)	41.2 (40.2-43.7)	40.4 (39.6-43.2)	42.3 (40.7-43.8)
p=			0.397		0.217
Days of life (DOL) at MRI, median (IQR)	24 (20-31)	19 (15-26)	20 (16-32)	18 (13-28)	21 (17-35)
			0.004		0.140
Intraventricular hemorrhage, n (%)	2 (4%)	9 (8%)	2 (6%)	1 (10%)	1 (5%)
p=			0.589		0.534
White matter injury, n (%)	16 (32%)	26 (24%)	8 (25%)	2 (20%)	6 (27%)
p=			0.583		1.000
Stroke, n (%)	13 (26%)	13 (12%)	4 (13%)	0 (0%)	4 (18%)
p=			0.073		0.283
Any injury, n (%)	26 (52%)	36 (34%)	13 (41%)	3 (30%)	10 (45%)
p=			0.090		0.467
All participants w/ any neonatal brain MRI (pre- or post-op)					
	N=60	**N=117**	**N=38**	**N=11**	**N=27**
Any injury (pre-or post-op), n (%)	37 (62%)	64 (55%)	16 (42%)	5 (45%)	11 (41%)
p=			0.166		1.00

Table 5:

Neurodevelopmental outcomes at 30 months of age in children with heterogenous critical congenital heart disease

	HLHS	TGA	Other		
			All	Genetic syndrome	No syndrome
Participants with BSID-II follow-up, n=	11	54	14	4	10
Age at follow-up, years, median (IQR)	2.6 (2.5-2.7)	2.6 (2.5-2.7)	2.7 (2.6-2.9)	2.7 (2.7-2.8)	2.7 (2.6-3.0)
p=			0.042		0.515
Mental Developmental Index, median (IQR)	95.0 (81.5-96.0)	93.5 (84.0-104.0)	82.5 (67.0-88.0)	58.5 (50.0-75.5)	85.0 (81.0-101.0)
p=			0.035		0.047
Normal, n= (%)	7 (64%)	40 (74%)	5 (36%)	0 (0%)	5 (50%)
Mild-moderate, n= (%)	2 (18%)	13 (24%)	5 (36%)	1 (25%)	4 (40%)
Severe, n= (%)	2 (18%)	1 (2%)	4 (29%)	3 (75%)	1 (10%)
Psychomotor Developmental Index, median (IQR)	77.0 (71.5-83.5)	91.0 (84.0-102.0) (n=52)	85.5 (76.0-98.0)	54.5 (50.0-68.0)	91.5 (83.0-98.0)
p=			0.008		0.007
Normal, n= (%)	3 (27%)	39 (75%)	7 (50%)	0 (0%)	7 (70%)
Mild-moderate, n= (%)	6 (55%)	10 (19%)	4 (29%)	1 (25%)	3 (30%)
Severe, n= (%)	2 (18%)	3 (6%)	3 (21%)	3 (75%)	0 (0%)