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Growth Asymmetry, Head Circumference and Neurodevelopmental Outcomes in Infants with Single Ventricles

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Abstract

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Objectives—To assess the variability in asymmetric growth and its association with neurodevelopment in infants with single ventricles (SV).

Study design—We analyzed weight for age z-score (WAZ) minus head circumference for age z-score (HCAZ), relative head growth (cm/kg), along with individual growth variables in subjects prospectively enrolled in the Infant Single Ventricle (ISV) trial. Associations between growth indices and scores on the Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI) of the Bayley Scales of Infant Development-II (BSID-II) at 14 months were assessed.

Results—Of the 230 subjects enrolled in the ISV trial, complete growth data and BSID-II scores were available in 168 (73%). Across the cohort, indices of asymmetric growth varied widely at enrollment and before superior cavopulmonary connection (SCPC) surgery. BSID-II scores were not associated with these asymmetry indices. In bivariate analyses, greater pre-SCPC HCAZ correlated with higher MDI ($r=0.21$, $p=0.006$) and PDI ($r=0.38$, $p<0.001$) and a greater HCAZ increase from enrollment to pre-SCPC with higher PDI ($r=0.15$, $p=0.049$). In multivariable modeling, pre-SCPC HCAZ was an independent predictor of PDI ($p=0.03$), but not MDI.

Conclusions—In infants with SV, growth asymmetry was not associated with neurodevelopment at 14 months, but pre-SCPC HCAZ was associated with PDI. Asymmetric growth, important in other high risk infants, is not a brain sparing adaptation in infants with SV.

Trial registration—Clinicaltrials.gov: NCT00113087

Keywords

Congenital heart disease; neurodevelopment; somatic growth

Poor somatic growth is common in infants with single ventricle (SV) physiology and has been linked to increased morbidity, prolonged hospitalization and impaired neurodevelopment.^{1–5} To date, most analyses of growth in SV patients have focused on weight, length and head circumference with little attention paid to growth asymmetry. Asymmetry in growth restriction (preservation of head growth in the setting of low weight) is an important distinction in predicting outcomes in premature and intrauterine growth restricted (IUGR) infants.^{6, 7} Although the presence of growth asymmetry for populations with SV heart disease has been well documented during gestation and at birth,^{1, 8, 9} the individual variability and association with post-natal outcomes is not known.

In the setting of SV heart disease (with reduced oxygenation and compromised blood flow to the brain), changes in fetal regional vascular resistance theoretically preserve cerebral blood flow, nutrient delivery and brain growth.^{10, 11} Although similar changes in fetal regional resistance indices occur in both SV and IUGR fetuses, SV fetuses do not exhibit the same preservation of brain growth.^{12–14} Reports on the association of ‘brain-sparing’ vascular changes in fetuses with congenital heart disease and neurodevelopmental outcomes are conflicting with improved testing scores at 12 and 14 months of age but worse cognitive developmental scores at 18 months of age.^{15–17} Regardless, the disparity between the growth outcomes of SV and IUGR fetuses with similar vascular changes highlights the impact of multiple factors on somatic growth in the setting of structural heart disease.

The combination of maternal, placental and fetal factors that contribute to development and growth potential is arguably different for every individual with SV physiology. Even though multiple studies have shown that, as a population, newborns with SV are below average in weight and slightly further below average in head circumference,^{1, 8, 9} our aim was to more closely examine growth asymmetry at the individual subject level within this population. We utilized the well characterized cohort of infants with SV enrolled in a prospective, multicenter, randomized trial assessing the impact of treatment with an angiotensin converting enzyme inhibitor on somatic growth (ISV trial) conducted by the National Heart, Lung, and Blood Institute sponsored Pediatric Heart Network (PHN).¹ This study previously found that at 14 months of age, the treatment group had a lower head circumference for age z-score (HCAZ), but there were otherwise no differences in somatic growth, symptoms or indices of ventricular function between the two groups.¹ We hypothesized that indices of growth asymmetry for individuals would be indicative of brain sparing adaptations and predictive of neurodevelopmental outcomes.

METHODS

The study design and primary results of the ISV trial have been published.^{1, 18} In brief, 230 subjects between the ages of 1 week and 45 days were enrolled at 10 North American centers. Subjects were randomized in this double-blind trial to enalapril or placebo and followed to 14 months of age with a primary outcome of weight for age z-score (WAZ) and secondary outcomes of other indices of somatic growth, heart function, and developmental indices.¹⁸ The study protocol was approved by the Institutional Review or Ethics Board at each participating center, and written informed consent was obtained from parents prior to trial enrollment.

Data collected at the time of study enrollment included age, race, ethnicity, sex, socioeconomic status and detailed anatomic diagnosis. Anthropometric measurements of weight, height and head circumference were collected prospectively at 7 time points: study enrollment, 4 days after enrollment, 2 weeks after enrollment, prior to the superior cavopulmonary connection (SCPC), 7 days after restarting the study drug after SCPC, age 10 months and age 14 months.¹⁸ All study coordinators performing anthropometric measurements at PHN centers underwent training specifically designed to ensure accurate and reliable measurements by using training modules from the Health Resources and Service Administration Maternal and Child Health Bureau. Quality assurance measures included using dedicated, appropriately calibrated scales, duplicate measurements and third measurements when the first two were not in agreement. Anthropometric measurements were converted to age-specific z-scores based on World Health Organization (WHO) standards¹⁹ to determine WAZ, length-for-age z-score (LAZ), and HCAZ. For the purposes of this study, markers of asymmetry included weight-for-length z-score (WLZ, also determined by WHO standards), asymmetry between standardized weight and head circumference (WAZ minus HCAZ) and relative head growth defined as change in head circumference in cm divided by change in weight in kg.⁶

Neurodevelopmental testing included the Bayley Scales of Infant Development (BSID)-II at 14 months of age. Testing was performed by trained personnel at each study site certified by

the Data Coordinating Center's neuropsychological testing consultant. The BSID-II was administered in either English or Spanish depending on the dominant language spoken at home. We utilized two components of the BSID-II: the Psychomotor Developmental Index (PDI), which assesses gross motor and fine motor skills, and the Mental Developmental Index (MDI), which measures cognitive functioning through assessment of memory, problem solving, number concepts, vocalization, language and social interaction skills. The mean PDI and MDI score for the normal population is 100, with a standard deviation (SD) of 15, and a minimum score of 50. Subjects who were too impaired to complete neurodevelopmental testing (0.6% for MDI and 7.7% for PDI) were assigned a score of 50.

Data were described as both means with SD and medians with 25th and 75th percentile values (IQR). Associations between growth and BSID-II results were tested using unadjusted linear regression models. The linearity of association was also assessed using generalized additive models. Spearman correlations were calculated to provide a non-parametric test of the association between growth and outcomes. Multivariable modeling was performed using a backward stepwise regression. Stepwise regression included $p=0.15$ as the criterion for entry into the model and $p=0.05$ as the criterion to stay in the model. Bootstrapping was utilized to estimate the reliability of each independent variable entering into stepwise regression, equivalent to the percentage of models out of 1000 that contain the variable of interest with a p-value of 0.05 or less.

RESULTS

Of the 230 infants with SV enrolled in the ISV trial between August 2003, and May 2007, 168 (73%) had complete biometric data at both the enrollment and pre-SCPC visits and valid PDI and MDI scores. Subjects were enrolled at a mean age of 21 days and 100/168 (60%) had HLHS. There were no differences in the baseline characteristics between subjects who did and did not have complete data for this analysis except for age at enrollment (Table I).

The distribution of growth and asymmetry indices are summarized in Figures 1 and 2, respectively. At the cohort level, this study population was small at enrollment (mean WAZ -1.26 ± 1.3), short (mean LAZ -1.05 ± 1.3) and had even smaller head circumference (mean HCAZ -1.71 ± 1.44). Within subjects, the asymmetry followed a similar pattern with proportionally small head circumference for weight (mean WAZ-HCAZ 0.43 ± 1.02) and lower weight for length (mean WLZ -0.82 ± 1.32). The range of this asymmetry across the cohort was wide (Figure 2). At enrollment WAZ-HCAZ ranged from -2.75 to 4.84 (IQR -0.26 to 0.95) and WLZ ranged from -6.31 to 2.70 (IQR -1.60 to 0.03). From enrollment to the pre-SCPC visit, the cohort as a whole demonstrated improvement in head size (mean HCAZ -1.34 ± 1.24 , $p<0.001$ compared with enrollment) but a drop in weight (mean WAZ -1.58 ± 1.2 , $p<0.001$ compared with enrollment). This was reflected within subjects as well, with a reversal in head-to-body asymmetry (ie, proportionally large heads for weight, mean WAZ-HCAZ -0.23 ± 1.21 , $p<0.001$ compared with enrollment). Similar to the findings at enrollment, the variation in this marker of growth asymmetry across the cohort was wide (range -4.45 to 3.00 , IQR -0.98 to 0.39). The relative change in HC also varied widely (range 0.50 to 8.00 cm/kg, IQR 1.89 to 2.74).

The study population scored below normative averages on BSID-II testing for both the PDI (mean z-score -1.3 ± 1.2) and MDI (mean z-score -0.3 ± 1.0). Growth asymmetry indices at enrollment and pre-SCPC, as well as relative head growth between the two time points, were not associated with BSID scores. In regards to the PDI, on bivariate analysis, increased growth measures that were associated with a higher PDI score included LAZ, WAZ and HCAZ at enrollment, pre-SCPC and 14 months. Additional continuous and categorical variables associated with PDI are listed in Table II. In multivariable analysis, higher HCAZ at pre-SCPC ($p=0.006$, reliability 79.8%) and LAZ at 14 months ($p<0.001$, reliability 94.8%) were the only growth measures independently associated with PDI. Additional factors independently associated with PDI included ECMO ($p=0.046$, reliability 52.3%) and neonatal hospital length of stay ($p=0.01$, reliability 72.4%). The percent variance in PDI attributed to the pre-SCPC HCAZ was 3%. Factors that predicted pre-SCPC HCAZ were HCAZ at enrollment (slope 0.45, $p<0.001$; 37% of the variance), Hispanic ethnicity and a diagnosis of HLHS. Predicted pre-SCPC HCAZ was lower for Hispanics (by -0.81 , $p<0.001$) and for subjects with HLHS (by -0.39 , $p=0.016$).

In regards to the MDI, on bivariate analysis, increased growth variables that were associated with a higher MDI score included LAZ at enrollment, WAZ and LAZ at pre-SCPC, and HCAZ and LAZ at 14 months. Additional continuous and categorical variables associated with MDI are also listed in Table II. In the final multivariable model, higher LAZ at pre-SCPC ($p=0.001$, reliability 86.5%) was the only growth variable independently associated with higher MDI. Additional factors independently associated with the MDI included ECMO ($p=0.01$, reliability 60.3%), number of serious adverse events ($p=0.003$, reliability 75.4%), and clinical site ($p=0.02$, reliability 60.3%).

Additional analyses of associations between BSID scores and growth asymmetry included testing for non-linear associations. Although there were a small number of cases of non-linear associations between growth asymmetry and BSID scores, the curves fitted using generalized additive models and the scatter plots did not suggest the presence of any meaningful associations. The non-linearity was triggered by one or two outliers. Furthermore, careful analysis of the scatter plots did not reveal any patterns within subsets of the cohort such as those on the low or high end of the scoring ranges or on the low or high end of the asymmetry distribution. Similarly, removing outliers did not create a pattern of association.

DISCUSSION

In this secondary analysis of growth asymmetry, head circumference and relative head growth in infants with SV enrolled in the ISV trial, we found that higher HCAZ prior to SCPC was independently associated with higher PDI but not MDI at 14 months of age. Head sparing, asymmetric growth was not associated with neurodevelopmental outcomes at 14 months in this patient population.

Customary pediatric teaching suggests that brain development in infancy and childhood is always prioritized in times of poor growth. Growth restriction before birth is a complex, multifactorial process driven by the *in utero* environment as well as genetic and epigenetic

factors. Traditionally, the timing of an *in utero* insult has been proposed to drive symmetric versus asymmetric growth restriction with insults in early gestation creating global, symmetric growth restriction and those later in gestation leading to asymmetric, head sparing growth restriction.^{20, 21} The child's prognosis is largely dependent on the etiology, with many of the earlier, more global insults, being of more dire consequence.²² Structural heart disease is a malformation (sometimes isolated, sometimes not) associated with several factors that can limit growth.⁸ These cannot be classified as early gestation versus late gestation insults. First, single ventricle anatomy is associated with genetic abnormalities that predispose the infant to worse growth outcomes.²³ Moreover, alterations in regional oxygenation and blood flow in fetuses with single ventricle may affect brain growth starting in the late second trimester.^{24, 25} Although regional adaptations in vascular resistance, similar to those seen in uteroplacental insufficiency, occur in single ventricle heart disease,^{10, 26} they appear to be inadequate to preserve head growth.¹² Finally, the single ventricle population may be exposed to heterogeneity in uteroplacental function.²⁷ Growth restriction from uteroplacental insufficiency predisposes the heart to dysfunction^{28, 29} and may affect post-natal morbidity and growth.

Given the myriad of contributors to fetal and post-natal growth, we anticipated wide variation in the degree of growth asymmetry in our population. Even though our results confirmed such variability, growth asymmetry was not associated with neurodevelopmental outcomes at 14 months of age as we had hypothesized. We therefore conclude that the concept of cerebral autoregulation as a means to preserve brain growth and development is an oversimplification in infants with complex cardiac anatomy. The weak association of HCAZ at the pre-SCPC visit with neurodevelopmental testing, however, does underscore the importance of overall brain growth regardless of its proportionality to the rest of the body. The relative importance of normal versus catch-up growth, as well as predetermined versus modifiable growth, remains uncertain. Recently, decreased brain volume, as measured by MRI, has been associated with impaired pre-operative neurobehavioral assessments in infants with complex congenital heart disease.³⁰ We found that higher pre-SCPC HCAZ was associated with higher PDI scores at 14 months of age and that enrollment HCAZ was the strongest predictor of pre-SCPC HCAZ. Relative head growth and change in HCAZ from baseline to pre-SCPC were not independently associated with the BSID scores.

Similar to the congenital heart disease population, the literature on post-natal growth in premature infants is conflicting on the importance of catch-up, relative and normal growth.^{6, 31–33} Such complexity makes it difficult to define clinical growth objectives and suggests that forcing somatic growth with caloric supplementation is an oversimplified approach. Weight gain without a proportional increase in length may be detrimental. Indeed, in patients with single ventricle physiology, catch-up in weight gain is more achievable than maintenance of normal length.^{34, 35} In our study, length and head circumference, but not weight, were independent predictors of neurodevelopmental testing results. Although our study focused on head circumference and asymmetry, it is important to note that length was the only growth variable that demonstrated significant association on bivariate analysis at all three time points (enrollment, pre-SCPC and 14 months) with both BSID tests (MDI and PDI) in addition to being an independent predictor at two time points. The association of

length with neurodevelopmental outcomes and quality of life in patients with single ventricles has become a recurring theme.^{5, 36} Further work is needed to understand what drives linear growth and whether or not it is modifiable.

This study had some important limitations. In regards to neurodevelopmental testing, while infants with a recognizable genetic or phenotypic syndrome were excluded from the ISV trial, most subjects did not undergo formal genetic evaluation. Therefore, unrecognized genetic abnormalities that may have affected both growth and neurodevelopment may have been a confounding factor in our cohort. The average age at enrollment of 3 weeks also complicates inferences about *in utero* versus post-natal growth. Given that many patients were enrolled after their neonatal palliative surgery, significant weight gain or loss related to the peri-operative course may have skewed the asymmetry measures. Similarly, HCAZ as a surrogate for brain growth ignores other factors such as edema, hydrocephalus and extra-axial fluid. For this reason drawing conclusions about the HCAZ at 14 months, after the SCPC, is difficult. Finally, our study was designed to identify growth measures that were associated with neurodevelopmental outcomes at 14 months but we cannot make causal inferences.

Although variability in asymmetric growth was considerable in our population of SV infants, the degree of asymmetry was not associated with neurodevelopmental testing outcomes. Regardless of the proportionality, head circumference and length, but not weight, were associated with outcomes. These findings reinforce the fact that neurodevelopment is affected by multiple factors and targeting weight gain alone in this population is not adequate to improve outcomes.

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Figure 1.

Summary of Individual Anthropometric Distribution. Box and whisker plots display the median, 25–75th percentile, minimum and maximum for the study cohort at the two time points. WAZ=weight for age z-score, LAZ=length for age z-score, HCAZ=head circumference for age z-score, SCPC=superior cavopulmonary connection. * p<0.001 for same measure at pre-SCPC compared to enrollment.

Figure 2.

Summary of Individual Anthropometric Asymmetry Distribution. Box and whisker plots display the median, 25–75th percentile, minimum and maximum for the study cohort at the two time points. WLZ=weight for length z-score, WAZ-HCAZ = weight for age z-score minus head circumference for age z-score, SCPC=superior cavopulmonary connection, Rel HG= relative head growth. * $p < 0.001$ for same measure at pre-SCPC compared to enrollment.

Table 1

Baseline characteristics of patients who were enrolled in ISV with and without complete biometric and BSID-II data for this analysis. HLHS (hypoplastic left heart syndrome), WAZ=weight for age z-score, LAZ=length for age z-score, HCAZ=head circumference for age z-score, WLZ=weight for length z-score, SCPC=superior cavopulmonary connection.

Characteristic	Complete Data	Incomplete Data	p
n	168	62	
Mean Age at Enrollment (days)	21.1 (± 9.3)	18.5 (± 8.1)	0.05
Male (n)	119 (71%)	43 (69%)	0.87
Caucasian (n)	134 (80%)	50 (80%)	1.00
Median Gestational Age	38 (IQR 37,39)	38 (IQR 38,39)	0.42
HLHS	100 (60%)	44 (71%)	0.13
WAZ at Enrollment	-1.27 (± 1.31)	-1.28 (± 1.18)	0.95
LAZ at Enrollment	-1.04 (± 1.31)	-1.06 (± 1.18)	0.94
HCAZ at Enrollment	-1.70 (± 1.44)	-1.71 (± 1.19)	0.97
WAZ-HCAZ at Enrollment	0.43 (± 1.02)	0.44 (± 0.99)	0.98
WLZ at Enrollment	-0.82 (± 1.32)	-0.88 (± 1.14)	0.76
1 Serious Adverse Event(s) (n)	125 (74.6%)	50 (80.7%)	0.39

Table 2

Continuous and categorical variables associated on bivariate analysis with psychomotor development index and mental development index ($p < 0.05$). Continuous variables with a negative association are shown in italics. Variables that were significant on multivariable modeling are underlined. WAZ=weight for age z-score, LAZ=length for age z-score, HCAZ=head circumference for age z-score, WLZ=weight for length z-score, SCPC=superior cavopulmonary connection, SAE=serious adverse events.

	Psychomotor Development Index	Mental Development Index
Continuous Variables	<i>Length of neonatal hospital stay</i> Enrollment WAZ, LAZ and HCAZ Pre-SCPC WAZ, LAZ and <u>HCAZ</u> 14 months WAZ, <u>LAZ</u> and HCAZ HCAZ change from enrollment to pre-SCPC <i>Number of SAE</i>	<i>Length of neonatal hospital stay</i> Enrollment LAZ Pre-SCPC WAZ, <u>LAZ</u> and HCAZ 14 months LAZ, HCAZ <u>Number of SAE</u>
Categorical Variables	Number SAE (<2, 2–4, >4) Ross class I at pre-SCPC and 14 month Ross class I at 14 months # other cardiac procedures at SCPC (0, >0) <u>ECMO</u>	Number SAE (<2, 2–4, >4) Ross class I at pre-SCPC and 14 month Ross class I at pre-SCPC Feeding mechanism Site <u>ECMO</u>