

Original Article

## Aortic morphometry and microcephaly in hypoplastic left heart syndrome

Amanda J. Shillingford,<sup>1</sup> Richard F. Ittenbach,<sup>4</sup> Bradley S. Marino,<sup>1</sup> Jack Rychik,<sup>1</sup> Robert R. Clancy,<sup>3</sup> Thomas L. Spray,<sup>2</sup> J. William Gaynor,<sup>2</sup> Gil Wernovsky<sup>1</sup>

*Divisions of <sup>1</sup>Cardiology, <sup>2</sup>Cardiothoracic Surgery, <sup>3</sup>Neurology, and the <sup>4</sup>Biostatistics and Data Management Core, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America*

**Abstract** Microcephaly is a marker of abnormal fetal cerebral development, and a known risk factor for cognitive dysfunction. Patients with hypoplastic left heart syndrome have been found to have an increased incidence of abnormal neurodevelopmental outcomes. We hypothesized that reduced cerebral blood flow from the diminutive ascending aorta and transverse aortic arch in the setting of hypoplastic left heart syndrome may influence fetal growth of the brain. The purpose of our study, therefore, was to define the prevalence of microcephaly in full-term infants with hypoplastic left heart syndrome, and to investigate potential cardiac risk factors for microcephaly. We carried out a retrospective review of full-term neonates with hypoplastic left heart syndrome. Eligible patients had documented indexes of birth weight, and measurements of length, and head circumference, as well as adequate echocardiographic images for measurement of the diameters of the ascending aorta and transverse aortic arch. We used logistic regression for analysis of the data. A total of 129 neonates met the criteria for inclusion, with 15 (12%) proving to have microcephaly. The sizes of their heads were disproportionately smaller than their weights ( $p$  less than 0.001) and lengths ( $p$  less than 0.001) at birth. Microcephaly was associated with lower birth weight ( $p$  less than 0.001), lower birth length ( $p$  equal to 0.007), and a smaller diameter of the ascending aorta ( $p$  equal to 0.034), but not a smaller transverse aortic arch ( $p$  equal to 0.619), or aortic atresia ( $p$  equal to 0.969). We conclude that microcephaly was common in this cohort of neonates with hypoplastic left heart syndrome, with the size of the head being disproportionately smaller than weight and length at birth. Microcephaly was associated with a small ascending aorta, but not a small transverse aortic arch. Impairment of somatic growth may be an additional factor in the development of microcephaly in these neonates.

**Keywords:** Hypoplasia of the left heart; aortic atresia; deep hypothermic circulatory arrest; central nervous system; cerebral blood flow

**H**YPOPLASTIC LEFT HEART SYNDROME OCCURS when the systemic or left ventricle fails to develop adequately. It is associated with varying degrees of hypoplasia of the aorta, aortic valve, mitral valve, and left ventricle. It is the second most common critical cardiac defect to present in the first week of life, and is fatal in infancy if palliative surgery is not performed.<sup>1</sup> Genetic syndromes and

non-cardiac malformations have been reported in up to three-tenths of neonates with the syndrome.<sup>2</sup> Early survival has now improved, due to prompt diagnosis and stabilization in the neonatal period, as well as advances in surgical techniques and perioperative management.<sup>3,4</sup> Studies to date, however, have indicated that survivors of both reconstructive surgery and transplantation have a greater likelihood of decreased intelligence, delays in speech and language, attentional and behavioural difficulties, and an increased need for special services in school.<sup>5–9</sup> Accordingly, greater attention has been directed toward understanding factors that may influence undesirable outcomes.

Correspondence to: Amanda J. Shillingford, MD, Division of Cardiology, The Children's Hospital of Philadelphia, 34th & Civic Center Boulevard, Philadelphia, Pennsylvania 19104, United States of America. Tel: +215 590 3548; Fax: +215 590 5825; E-mail: shillingford@email.chop.edu

Accepted for publication 7 April 2006

Microcephaly is defined as a condition in which the circumference of the head is significantly smaller than average for the age and gender of an individual, and is considered a surrogate for the size of the underlying brain. The presence of microcephaly suggests either under- or mal-development of the central nervous system.<sup>10</sup> Indeed, Glauser et al.<sup>11</sup> found microcephaly, defined as a brain of abnormally low weight at autopsy, in one-quarter of a cohort of deceased patients with hypoplastic left heart syndrome. Abnormally small circumferences of the head have previously been reported in patients with congenital cardiac disease, including those with hypoplastic left heart syndrome.<sup>11–14</sup> The aetiology of this microcephaly is uncertain, but we hypothesized that reduced flow of blood to the brain, in consequence of severe hypoplasia of the aortic arch in fetuses with hypoplastic left heart syndrome, is associated with poor cerebral growth. Thus, the purpose of our study was, first, to define the prevalence of microcephaly in a population of full-term infants with hypoplastic left heart syndrome, and second, to identify potential cardiac anatomic risk factors for the presence of microcephaly.

## Materials and methods

We performed a retrospective review of charts from full term neonates with hypoplastic left heart syndrome who were enrolled in one of two separate trials of neurological outcome at the Children's Hospital of Philadelphia. The first trial enrolled patients between 1992 and 1997,<sup>13</sup> while the second trial enrolled patients between 1998 and 2003.<sup>13,15</sup> Consent-waived approval to review the information was provided by the Institutional Review Board. Patients were eligible for the present analysis if they had an estimated gestational age greater than or equal to 37 weeks, carried a diagnosis of hypoplastic left heart syndrome, defined as underdevelopment of the left ventricle in conjunction with severe mitral valve stenosis or atresia, severe aortic valve stenosis or atresia, and hypoplasia of the aortic arch, and had documented measurements of weight, length, and head circumference at birth, as well as adequate preoperative echocardiographic images for ascertainment of the diameters of the ascending aorta and transverse aortic arch. All anthropometric data were adjusted for gestational age and gender according to the most recent guidelines outlined by the Growth Charts for 2000 from the Centers for Disease Control.<sup>16</sup> Microcephaly was defined as a head circumference less than or equal to the third percentile. Two sonographers blinded to the anthropometric data reviewed the echocardiographic images, and directly measured the diameter of the ascending aorta just distal to the sinotubular junction, and that of the transverse aortic arch between the

origins of the brachiocephalic and left carotid arteries, using a system for offline measurement.

## Statistics

Analysis of data occurred in three distinct phases. In the first, we summarized the data using measures of central tendency, variability, and association, calculation of frequency tables, and graphing relevant categorical and continuous variables. Student's t-test was used when appropriate. The second phase consisted of specifying and testing our two primary hypotheses, seeking a statistically significant relationship between the diameter of ascending aorta and presence or absence of microcephaly, and between the diameter of the transverse aorta and presence or absence of microcephaly. Finally, in the third phase, secondary hypotheses were also specified and tested. As with the second phase, the outcome of interest was presence or absence of microcephaly. In the third phase, we examined gender, gestational age, aortic valvar anatomy in terms of atresia or stenosis, birth weight by kilogram and percentile, birth length by centimetres and percentile, and body surface area as covariates of interest. Simple logistic regression equations were used to test the models in all phases. The experiment-wise error rate for the two primary hypotheses was held constant at the level of 0.05, with an adjusted hypothesis-wise error rate of 0.036 for each hypothesis, individually.<sup>17</sup> Hypothesis-wise error rates for all secondary hypotheses were not adjusted beyond the level of 0.05 of significance. Attempts to control statistically for anthropometric indexes, including birth weight and small for gestational age infants, were unsuccessful because these variables, being collinear with microcephaly, meant that the specified logit equations could not be calculated. We did not use values of the Z-scores of the diameters of the ascending and transverse aorta, indexed to body surface area, as the exponential relationship of these scores at very low values of both head circumference and ascending aorta have not been validated. Small differences in measurements will result in large differences in Z-scores at very low values. All data were analyzed using STATA 9.0 (STATA Corp, College Station, TX).

## Results

In all, a total of 129 neonates met the criteria for inclusion (Table 1). In general, head circumference percentiles for the entire cohort were clustered toward lower values (Fig. 1). Mean head circumference for the microcephalic group was 30.7 plus or minus 1.1 centimetres, and the mean head circumference for the non-microcephalic group was 34.3 plus or minus 1.2 centimetres. The cumulative probability curves (Fig. 2)

Table 1. Cohort characteristics, N = 129.

Gender	
(female:male)	43:86
Gestational age (weeks)	
average $\pm$ standard deviation	38.9 $\pm$ 1.3
Birth weight (kg)	
average $\pm$ standard deviation	3.2 $\pm$ 0.5
Birth weight (%)	
average $\pm$ standard deviation	36.7 $\pm$ 27.0
Small for gestational age ( $\leq$ 10th% birth weight)	25 (19.4%)
Birth length (cm)	
Average $\pm$ standard deviation	49.8 $\pm$ 3.2
Birth length (%)	
Average $\pm$ standard deviation	49.7 $\pm$ 31.4
Body surface area (m <sup>2</sup> )	
average $\pm$ standard deviation	0.21 $\pm$ 0.02
Head circumference (cm)	
average $\pm$ standard deviation	33.9 $\pm$ 1.6
Head circumference (%)	
average $\pm$ standard deviation	26.5 $\pm$ 20.7
Aortic valve	
(atresia:stenosis)	78:51

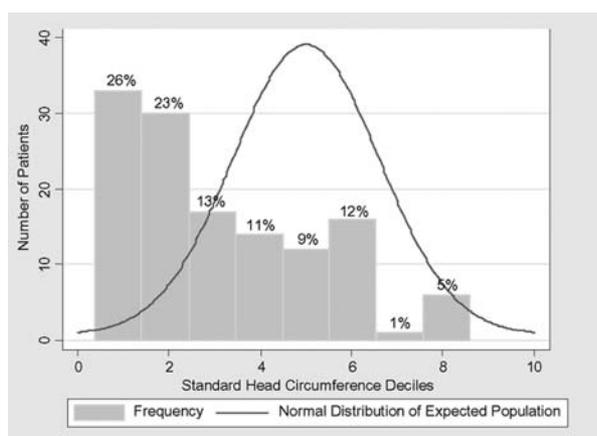


Figure 1.

The histogram demonstrates the distribution of head circumferences by deciles. The proportion of the entire cohort represented in each decile is also displayed above the bar. The bell shaped curve illustrates the expected distribution of head circumference percentiles in the general population. Note that the head circumferences in the study population are clustered toward the lower deciles.

show the relative distributions of head circumference, weight, and length in the population. Head circumference percentiles for the cohort were disproportionately smaller than both weight percentiles ( $p$  less than 0.001) and length percentiles ( $p$  less than 0.001).

For the entire group, the mean and standard deviation of the ascending aortic diameter was 3.2 plus or minus 1.5 millimetres, and the mean transverse aortic diameter was 3.7 plus or minus 0.9 millimetres

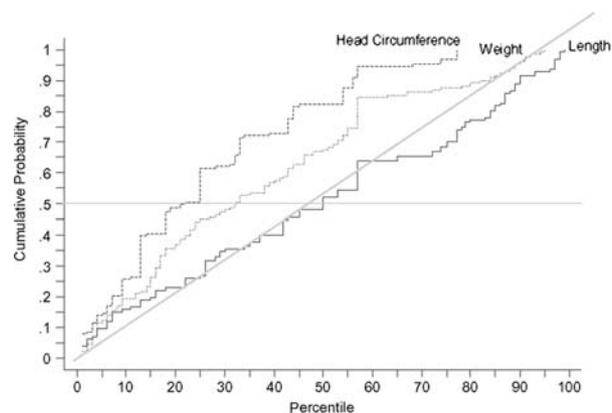


Figure 2.

These curves show the cumulative anthropometric data for the study population. The horizontal line shown at 0.5 on the y-axis represents the median values for each measurement. The diagonal line represents a normally distributed set of values. The curve for head circumference is shifted leftward toward the smaller percentiles with the median value occurring at the 22nd percentile. The curve for weight is also shifted to the left, but to a lesser degree with the median value occurring at the 34th percentile. The curve for length falls along the expected distribution.

(Table 1). We found that 15 neonates (12%) had microcephaly, with 9 having aortic atresia, and 6 having aortic stenosis. Only 4 of these 15 neonates also had a weight less than or equal to the third percentile, and only three neonates had a length less than or equal to the third percentile. Microcephalic patients had significantly smaller birth weights ( $p$  equal to 0.001) and birth lengths ( $p$  equal to 0.007), as well as a smaller body surface area ( $p$  equal to 0.024). A significant association between microcephaly and a smaller ascending aortic diameter was identified ( $p$  equal to 0.034), and the difference between the mean ascending aortic diameter in those with microcephaly (2.4 plus or minus 1.2 millimetres), as compared to those with normal circumferences (3.3 plus or minus 1.6 millimetres), was 0.9 millimetres. We failed to find any statistically significant associations between microcephaly and transverse aortic size or aortic atresia. The patients with aortic atresia had a smaller mean ascending aortic diameter of (2.5 plus or minus 1.2 millimetres) compared to the patients with aortic stenosis (4.2 plus or minus 1.5 millimetres) ( $p$  less than 0.001), but no significant difference between mean transverse aortic size in aortic atresia (3.8 plus or minus 1.5 millimetres) and in aortic stenosis (3.6 plus or minus 0.8 millimetres) was present. In addition, no statistically significant associations between microcephaly and the presence of aortic atresia ( $p$  equal to 0.969) or the size of the transverse aorta ( $p$  equal to 0.619) (Table 2) were observed. The results of all single covariate analyses are shown in Table 2.

Table 2. Single covariate predictors of microcephaly.\*

Predictors	Microcephalic N = 15	Non-microcephalic N = 114	$\beta$ coefficient	OR (95% CI)	P
<i>Primary outcomes</i>					
Ascending aorta (mm)	2.4 $\pm$ 1.0	3.3 $\pm$ 1.6	-0.54	0.58 (0.36–0.96)	.034
Transverse aorta (mm)	3.8 $\pm$ 1.3	3.7 $\pm$ 0.9	0.14	1.15 (0.66–2.03)	.619
<i>Secondary outcomes</i>					
Gender (female:male)	8:7	35:79	-0.95	0.39 (0.13–1.52)	.088
Aortic valve (atresia:stenosis)	9:6	69:45	0.02	1.02 (0.34–3.07)	.969
Gestational age (weeks)	39.1 $\pm$ 1.1	38.9 $\pm$ 1.3	0.10	1.11 (0.72–1.7)	.635
Birth weight (kg)	2.67 $\pm$ 0.43	3.31 $\pm$ 0.48	-0.003	0.997 (0.995–0.998)	<.001
Birth weight (%)	11.7 $\pm$ 13.0	40.0 $\pm$ 27.0	-0.08	0.92 (0.88–0.97)	.001
Birth length (cm)	47.6 $\pm$ 3.1	50.1 $\pm$ 3.1	-0.26	0.77 (0.64–0.93)	.007
Birth length (%)	31.2 $\pm$ 25.3	51.7 $\pm$ 32.0	-0.02	0.978 (0.959–0.997)	.024
Body surface area (m <sup>2</sup> )	0.19 $\pm$ 0.02	0.21 $\pm$ 0.02	-61.98	1.2e-27 (1.8e-41–8.1e-41)	<.001

\*Head circumference  $\leq$  3rd percentile, see text for details

The Box and Whisker plots displayed in Figure 3 demonstrate the distribution of values for the aortic diameters in neonates with and without microcephaly. The difference in the distribution of the transverse aortic diameters between the microcephalic and the non-microcephalic groups is minimal. The distribution of ascending aortic diameters in the microcephalic group is clustered toward the smaller sizes, and is noticeably differentiated from those with heads of normal size.

## Discussion

In this retrospective analysis, we found that microcephaly was common in neonates with hypoplastic left heart syndrome as compared to the general population. Of the neonates examined, one-eighth had a head circumferences less than or equal to the third percentile at birth. Low birth weight was also common in this group, but not to the same degree as small head circumference. Microcephaly was significantly associated with a smaller ascending aorta, but not with a smaller transverse aorta or the presence of aortic atresia. The mean ascending aortic diameter from the neonates with microcephaly was almost 1 millimetres smaller than in those with heads of normal size. We were unable further to investigate the relationship between microcephaly and ascending aorta size by adjusting for birth weight or birth length, because the variables were co-linear, and the specified logit equations were incalculable. It is reasonable to conclude that the contribution of impairment of somatic growth may be an additional important factor in the development of microcephaly.

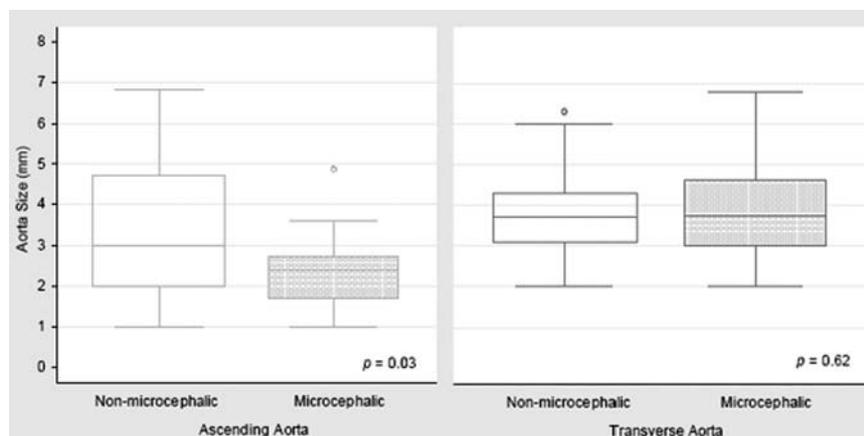
Our central hypothesis focused on the notion that growth of the head and brain is influenced by reduced flow of blood during fetal life due to the anatomic restriction imposed by aortic hypoplasia. Principles

from Poiseuille's equation for flow in a tube have been applied, and therefore blood flow is directly related to the radius of the vessel.<sup>‡</sup> There are limitations to applying this equation to the cardiovascular system, since the original description from Poiseuille was based on a non-pulsatile and rigid system. In addition, the factors affecting prenatal flow of blood to the brain are complex. In the normal fetal circulation, oxygen-rich blood from the placenta is directed across the patent oval foramen into the left heart, and ejected into the head and neck vessels. Thus, the most oxygen-rich blood is delivered to the developing brain. In hypoplastic left heart syndrome, antegrade flow from the left ventricle into the aortic arch is impaired, and left to right flow across the atrial septum results in less favourable streaming than in the normal heart. As the degree of aortic hypoplasia worsens, the flow of blood to the branches of the aortic arch originates predominately via retrograde flow from the arterial duct, resulting in the delivery of desaturated blood to the developing brain. Another important consideration is that cerebral and systemic, or placental, circulations are parallel circuits in the fetus, and therefore the placenta and the fetal brain are "competing" for blood. The relative resistances of the two circuits will determine the volumes of flow, and thus changes in cerebral vascular resistance may compensate for the anatomic obstruction of the ascending aorta.

Direct measurements of prenatal and postnatal flows to the brain are not available for our cohort of patients, but might provide important insights. Recent studies in heterogenous forms of congenital cardiac disease have shown that prenatal cerebral vascular resistance and postnatal cerebral blood flow are

<sup>‡</sup>Poiseuille's equation: Flow =  $\Delta P \pi r^4 / 8 \eta \ell$

$\Delta P$ , pressure difference across the tube;  $r$ , radius of the tube;  $\eta$ , viscosity of the fluid;  $\ell$ , length of tube



**Figure 3.**

The Box and Whisker plots demonstrate the distribution of data for the aorta diameters in microcephalic and non-microcephalic infants. The ascending aorta diameters are shown on the left, and the transverse aorta diameters are shown on the right. The open boxes represent the distributions around the median aortic diameters for non-microcephalic newborns. The grey boxes represent the distributions around the median aortic diameters of the microcephalic newborns. The solid line in the middle of the box corresponds to the median values and the entire box incorporates the data points falling into the lower and upper quartiles. Extreme values are represented by the vertical lines. Open circles represent outliers.

abnormal.<sup>14,18,19</sup> Kaltman et al.<sup>19</sup> found that cerebral vascular resistance was lower than normal for infants with hypoplastic left heart syndrome and higher than normal for infants with right-sided obstructive lesions, while Donofrio et al.<sup>18</sup> showed that fetal hypoxia results in a lower cerebral vascular resistance. The relative influences of changes in cerebral vascular resistance and anatomic obstruction to highly oxygenated blood flow into the cerebral vasculature remain undefined. Bokesch et al.<sup>20</sup> found that glial derived protein S100B, a marker of cerebral ischemia, is elevated in infants with hypoplastic left heart syndrome and significantly associated with the size of the ascending aorta. If growth of the brain is affected by cerebral perfusion, then the association we found between microcephaly and a smaller ascending aorta supports the report from these workers.<sup>20</sup> Still, the interactions between cardiac anatomic factors such as a diminutive aorta, cerebral vascular resistance, cerebral blood flow, and microcephaly at birth remain incompletely understood, but are likely to contribute to the long term disabilities seen in this population.

Fetal studies in both animals and humans have shown that redistribution of cardiac output occurs when a normal fetus is exposed to nutritional or oxygen deficiency.<sup>21–23</sup> The “brain-sparing” effect refers to the phenomenon that, in a growth-restricted infant, the degree of impairment of somatic growth is expected to be more significant than that of the head, due to fetal autoregulatory mechanisms which cause preferential distribution of cardiac output to the most vital organs. In a normal circulatory system, most nutritional deficiency results in sparing of the brain. The finding in our cohort that head circumference is

disproportionately smaller than birth weight is inconsistent with the “brain-sparing” effect, and suggests that growth of the brain may be differentially impaired in the fetus with hypoplastic left heart syndrome.

Rosenthal<sup>24</sup> extensively described the fetal growth parameters in infants with transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart syndrome, and coarctation of the aorta as compared to the non-congenital heart disease population. He also suspected that restriction of growth reflected altered haemodynamics. Similar to our findings, the infants with hypoplastic left heart syndrome had smaller weights at birth, with a head circumference that was disproportionately smaller than the somatic weight. Infants with coarctation of the aorta, in whom the obstruction to blood flow is distal to the cerebral vessels, and antegrade flow in the ascending aorta is preserved, had smaller weights and lengths at birth, with normal head circumferences when compared to controls. Infants with discordant ventriculo-arterial connections, in whom the flow of blood to the cerebral vessels contains lower proportions of oxygen than normal, were found to be heavier, but to have relatively smaller heads when compared to controls. In a recent report from Manzar et al.,<sup>25</sup> infants with hypoplastic left heart syndrome, and those with transposed arterial trunks, also had smaller head circumferences compared to normal infants. We agree with prior reports that the differences in patterns of growth among various forms of congenital cardiac disease may be influenced by a combination of unique circulatory disturbances and variations in content of oxygen.<sup>21–23</sup> The possibility that abnormal growth of the head is part of the developmental syndrome of

congenital cardiac disease must also be emphasized, and therefore the brain-sparing theory may not be appropriately applied to patients with congenitally malformed hearts.<sup>24</sup>

The high prevalence of microcephaly in neonates with hypoplastic left heart syndrome has important clinical implications. Neurodevelopmental impairments in the population with congenitally malformed hearts has been extensively described, and may be one of the most important late morbidities encountered by survivors of neonatal cardiac surgery.<sup>5–7,9,26–28</sup> The aetiologies of these deficits are likely multifactorial and cumulative, and therefore increasing attention has been directed towards identifying prenatal factors that may influence later neurological states. Although microcephaly in a neonate does not absolutely portend cognitive or developmental impairment, its presence suggests a pathologic disruption of normal fetal growth of the brain, which may lead to an increased risk of later neurological problems.<sup>10,29</sup> Microcephaly is common in children with autism, as well as in children with cerebral palsy and mental retardation.<sup>30–32</sup> Limperopoulos et al.,<sup>12,33–36</sup> reported microcephaly in approximately one third of infants with congenital heart disease, excluding those with hypoplastic left heart syndrome, and the presence of preoperative microcephaly was significantly associated with post-operative microcephaly, as well as abnormal neurological sequels that included fine motor delays and global developmental delay in infancy. Structural congenital abnormalities of the central nervous system are also known to coincide with all forms of congenital cardiac disease.<sup>11,37</sup> In one autopsy study of 41 infants with hypoplastic left heart syndrome, three-tenths were found to have structural abnormalities of the brain.<sup>11</sup> Pre-operative periventricular leukomalacia, a marker of ischemic injury, has been reported in one-sixth of neonates with congenital cardiac disease.<sup>38</sup>

One limitation of our study is a potential bias in selection, since our population was identified retrospectively from two clinical trials performed at a single institution. The size of the heads of the parents, and their ethnicity, may also be important factors when considering the significance of the size of the head in a newborn, and such data were not available for our analysis. The clinical significance of microcephaly in this cohort, and the long term neurodevelopmental state of the subjects, are unknown, but currently under investigation in other studies.

We conclude that microcephaly is common in newborns with hypoplastic left heart syndrome prior to cardiac surgery. Low weight at birth is also common, and significantly associated with microcephaly, but head circumference was disproportionately smaller than birth weight and length. Newborns with hypoplastic left heart syndrome and microcephaly had

a significantly smaller ascending aortas compared to those without microcephaly, with a mean diameter difference of almost 1 millimetres. Our findings, in combination with other reports in the literature, suggest that complex interactions of cerebral vascular dynamics based on anatomic substrate and nutrient delivery may be important in fetal development of the brain in neonates with congenital cardiac disease.

## Acknowledgements

We acknowledge the contributions of Rita Novello and Anysia Fedec, who performed the echocardiographic measurements. In addition, we also acknowledge the previous work of Dr. Lazarus Kochilas and Dr. Jennifer Shores.<sup>39</sup> This work has been supported in part by: National Institute of Neurologic Disorders and Stroke, National Institutes of Health, NS-N01-2315, General Clinical Research Center, NIH MO1-RR00240, American Heart Association National Grant 9950480N, Fannie E. Rippel Foundation.

## References

1. Ferencz C, Rubin JD, McCarter RJ, et al. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. *Am J Epidemiol* 1985; 121: 31–36.
2. Natowicz M, Chatten J, Clancy R, et al. Genetic disorders and major extracardiac anomalies associated with the hypoplastic left heart syndrome. *Pediatrics* 1988; 82: 698–706.
3. Verheijen PM, Lisowski LA, Stoutenbeek P, et al. Prenatal diagnosis of congenital heart disease affects preoperative acidosis in the newborn patient. *J Thorac Cardiovasc Surg* 2001; 121: 798–803.
4. Tworetzky W, McElhinney DB, Reddy VM, Brook MM, Hanley FL, Silverman NH. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation* 2001; 103: 1269–1273.
5. Ikke L, Hale K, Fashaw L, Boucek M, Rosenberg AA. Developmental outcome of patients with hypoplastic left heart syndrome treated with heart transplantation. *J Pediatr* 2003; 142: 20–25.
6. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobs DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatrics* 2000; 105: 1082–1089.
7. Goldberg CS, Schwartz EM, Brunberg JA, et al. Neurodevelopmental outcome of patients after the fontan operation: A comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr* 2000; 137: 646–652.
8. Eke CC, Gundry SR, Baum ME, Chinnock RE, Razzouk AJ, Bailey LL. Neurologic sequelae of deep hypothermic circulatory arrest in cardiac transplant infants. *Ann Thorac Surg* 1996; 61: 783–788.
9. Wernovsky G, Stiles KM, Gauvreau K, et al. Cognitive development after the Fontan operation. *Circulation* 2000; 102: 883–889.
10. Woods CG. Human microcephaly. *Curr Opin Neurobiol* 2004; 14: 112–117.
11. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Congenital brain anomalies associated with the hypoplastic left heart syndrome. *Pediatrics* 1990; 85: 984–990.
12. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurologic status of newborns with congenital heart defects before open heart surgery. *Pediatrics* 1999; 103: 402–408.

13. Clancy RR, McGaurn SA, Goin JE, et al. Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. *Pediatrics* 2001; 108: 61–70.
14. Licht DJ, Wang J, Silvestre DW, et al. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J Thorac Cardiovasc Surg* 2004; 128: 841–849.
15. Gaynor JW, Gerdes M, Zackai EH, et al. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. *J Thorac Cardiovasc Surg* 2003; 126: 1736–1745.
16. US Department of Health and Human Services. Centers for Disease Control and Prevention. National Health and Nutritional Examination Survey. CDC Growth Charts: United States, 2000.
17. Zhang J, Quan H, Ng J, Stepanavage ME. Some statistical methods for multiple endpoints in clinical trials. *Control Clin Trials* 1997; 18: 204–221.
18. Donofrio MT, Bremer YA, Schieken RM, et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol* 2003; 24: 436–443.
19. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005; 25: 32–36.
20. Bokesch PM, Appachi E, Cavaglia M, Mossad E, Mee RB. A glial-derived protein, S100B, in neonates and infants with congenital heart disease: evidence for preexisting neurologic injury. *Anesth Analg* 2002; 95: 889–892.
21. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* 1974; 120: 817–824.
22. Rudolph AM. The fetal circulation and its response to stress. *J Dev Physiol* 1984; 6: 11–19.
23. Lumbers ER, Yu ZY, Gibson KJ. The selfish brain and the barker hypothesis. *Clin Exp Pharmacol Physiol* 2001; 28: 942–947.
24. Rosenthal GL. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. *Am J Epidemiol* 1996; 143: 505–513.
25. Manzar S, Nair AK, Pai MG, Al-Khusaiby SM. Head size at birth in neonates with transposition of great arteries and hypoplastic left heart syndrome. *Saudi Med J* 2005; 26: 453–456.
26. Bellinger DC, Wypij D, Kuban KC, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 1999; 100: 526–532.
27. Bellinger DC, Wypij D, duDuplessis AJ, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 2003; 126: 1385–1396.
28. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. *Circulation* 2002; 106 (12 Suppl 1): I95–I102.
29. Dorman C. Microcephaly and intelligence. *Dev Med Child Neurol* 1991; 33: 267–269.
30. Ivanovic DM, Leiva BP, Perez HT, et al. Head size and intelligence, learning, nutritional status and brain development. *Head, IQ, learning, nutrition and brain. Neuropsychologia* 2004; 42: 1118–1131.
31. Watemala N, Silver S, Harel S, Lerman-Sagie T. Significance of microcephaly among children with developmental disabilities. *J Child Neurol* 2002; 17: 117–122.
32. Miles JH, Hadden LL, Takahashi TN, Hillman RE. Head circumference is an independent clinical finding associated with autism. *Am J Med Genet* 2000; 95: 339–350.
33. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. *J Pediatr* 2000; 137: 638–645.
34. Limperopoulos C, Majnemer A, Shevell MI, et al. Functional limitations in young children with congenital heart defects after cardiac surgery. *Pediatrics* 2001; 108: 1325–1331.
35. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr* 2002; 141: 51–58.
36. Majnemer A, Limperopoulos C, Shevell M, Rosenblatt B, Rohlicek C, Tchervenkov C. Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. *J Pediatr* 2006; 148: 72–77.
37. Miller G, Vogel H. Structural evidence of injury or malformation in the brains of children with congenital heart disease. *Semin Pediatr Neurol* 1999; 6: 20–26.
38. Mahle WT, Tavani F, Zimmerman RA, et al. An MRI study of neurological injury before and after congenital heart surgery. *Circulation* 2002; 106 (12 Suppl 1): I109–I114.
39. Kochilas L, Shores JC, Novello RT, et al. Aortic morphometry and microcephaly in the hypoplastic left heart syndrome. *J Am Coll Cardiol* 2001; 37 (Suppl 1): (Abstract #893–1) 470A.