Cortical Folding Is Altered before Surgery in Infants with Congenital Heart Disease

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Infants with congenital heart disease have altered brain development. We characterized cortical folding, a critical part of brain development, in congenital heart disease infants and demonstrated an overall decrease in cortical surface area and cortical folding with regional alterations in the right lateral sulcus and left orbitofrontal region, cingulate region, and central sulcus. These abnormalities were present prior to surgery. *(J Pediatr 2013;163:1507-10).*

Infants with congenital heart disease (CHD) requiring surgery in early infancy are at increased risk for impaired neurodevelopment. Magnetic resonance imaging (MRI) has demonstrated alterations in brain development and growth in this population.[1,2] Recent advances in MRI techniques have improved characterization of brain development in the newborn and may provide insights into potential mechanisms of adverse neurological outcomes. One such technique is surface-based analysis, which depicts cortical folding and sulcation, a vital part of brain development. Measures of cortical growth appear to be predictive of neurocognitive outcome in later childhood,[3] and preliminary data in a small number of infants with CHD revealed less curvedness and concavity within the operculum, with subtle differences existing between infants with hypoplastic left heart syndrome and transposition of the great arteries.[4] Surface-based analysis of the fetus has also suggested delayed cortical development across multiple regions of the brain in infants with hypoplastic left heart syndrome.[5] The aim of this study was to quantify global brain cortical folding and regional sulcal depth differences in infants with CHD prior to surgery. The hypothesis was that infants with CHD would exhibit reduced cortical folding compared with healthy, term-born infants.

Methods

Fifteen term infants with CHD requiring surgery in early infancy who were part of a larger prospective cohort from Starship Children's Hospital in Auckland, New Zealand were included in the analysis. Control infants included 12 healthy term-born infants from Washington University in St. Louis. Informed consent was obtained from all parents, and the study was approved by the local ethics committees at both hospitals.

MRI scans were performed as previously described.[6] The T2-weighted image acquisitions were used in this analysis. For infants with CHD, coronal (2-mm slice thickness) and transverse (3-mm slice thickness) T2-weighted images were acquired. The coronal and transverse T2-weighted images were co-registered, averaged, and resampled to 1-mm isotropic spatial resolution. The control data were acquired at 1-mm isotropic resolution. Post-processing was the same for both the CHD and control population, allowing for comparison between the groups. Post-processing analysis was undertaken as described by Hill et al.[7] The images were aligned along the anterior and posterior commissures and cropped into left and right hemispheres. A semi-automated algorithm, LIGASE, was applied and segmentations were manually edited using CARET software (http://brainvis.wustl.edu)[8] to generate three-dimensional cortical mid-thickness surface reconstructions. Cortical surface area (CSA) was calculated from the cortical mid-thickness surface. A cerebral hull surface was then generated that runs along the margins of the gyri and does not dip into the sulci. The gyrification index (GI), the ratio of the cortical mid-thickness surface area to the cerebral hull surface area, was calculated for each hemisphere. Surfaces were registered to the population-average, landmark- and surface-term 12 v. 2 atlas by using the "Core Six" landmarks: the central sulcus, the Sylvian fissure, the anterior portion of the superior temporal gyrus, the calcarine sulcus, and the dorsal and ventral portions of the medial wall, as previously described.[7,9] All image processing was reviewed by a single rater (D.A.).

CHD	Congenital heart disease
CSA	Cortical surface area
GI	Gyrification index
MRI	Magnetic resonance imaging

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Statistical Analyses

Statistical analysis was conducted using SPSS v. 19.0 (SPSS Inc, Chicago, Illinois). Baseline characteristics were compared using a 2-sample *t* test for continuous variables and a Fisher exact test for comparing the proportion of males in each group. MRI measures of CSA and GI were analyzed using a 2-sample *t* test. Although there was not a difference in head circumference between the groups, brain size may be affected by head size and, therefore, head circumference was controlled for in all analyses. An ANCOVA was performed to control for head circumference. CSA and GI were the dependent variables, group (CHD vs control) was a fixed factor, and head circumference was a covariate. Alpha of <0.05 was used as the level of significance for this portion of the analysis. Sulcal depth maps were computed for each hemisphere, where depth is the Euclidean distance between each vertex on the cortical mid-thickness surface and the nearest vertex on the cerebral hull surface.[9] Then a *t* test was performed using methods similar to Hill et al,[7] except that we used a 2-sample *t* test rather than a paired *t* test. Alpha of <0.025 per hemisphere was used as the level for significance for multiple comparisons correction.

Results

Fifteen infants with CHD were included in this study. Five infants had transposition of the great arteries, 4 had right-sided lesions requiring a Blalock–Taussig shunt, 5 had hypoplastic left heart syndrome requiring a Norwood procedure, and 1 infant had transposition of the great arteries with tricuspid atresia and interrupted aortic arch and underwent a Norwood procedure. Baseline characteristics between control and infants with CHD were similar (Table). The infants with CHD had an MRI an average of 5 days (range 2-9 days) after birth.

After controlling for head circumference, infants with CHD had reduced CSA and GI compared with control infants for both the left and right hemispheres (Table). Individual cortical mid-thickness reconstructions are displayed in Figure 1. Regional sulcal depth analyses (Figure 2) demonstrated differences in the left hemisphere in the orbitofrontal region, superior portion of the central sulcus, and the cingulate gyrus. infants with CHD had less sulcation in the orbitofrontal region, specifically within the olfactory sulcus. Regions in the dorsal prefrontal sulcus and the superior temporal sulcus showed a trend towards differences, with the sulcus for control infants deeper than infants with CHD. For the right hemisphere, infants with CHD displayed less sulcation in the posterior ascending limb of the lateral sulcus. In contrast, there were 2 regions that appeared deeper in infants with CHD attributable to a simpler, broader cortical surface—the cingulate gyrus and the superior portion of the central sulcus.

Of the 15 infants included in this study, 7 (46%) had focal signal abnormalities in the white matter. None of the infants had any other signal abnormalities. There was no difference in CSA or GI between infants with or without focal signal abnormalities.

Discussion

This study demonstrates preoperative alterations in global cerebral development in infants with CHD, including reductions in total CSA and gyration. Such global reductions display regional variability, with greater alterations seen in the orbitofrontal region, cingulate, and central sulcus of the left hemisphere. Alterations in the right hemisphere involve the posterior ascending limb of the lateral sulcus.

Preoperative alterations in brain development in infants with CHD have been previously demonstrated. Delay in neuronal and axonal development has been suggested in studies employing diffusion tensor imaging and magnetic resonance spectroscopy.[2] Additionally, smaller brain volumes and more immature measures of spectroscopy are present in the third trimester of pregnancy.[1] Fetuses with hypoplastic left heart syndrome had delayed cortical developmental in the superior frontal, postcentral, occipital, cingulate, calcarine, collateral, superior temporal, and sylvian regions.[5] Assessment of cortical folding after birth but before

Table. Baseline characteristics and cortical folding measures

	Controls (n = 12)	CHD (n = 15)	Unadjusted *P* value	Adjusted *P* value*
Baseline Characteristics				
Gestational age, wk: mean (SD)	39.4 (0.91)	39.1 (1.3)	.43	-
Birth weight, kg: mean (SD)	3.50 (0.38)	3.33 (0.68)	.45	-
Head circumference, cm: mean (SD)	34.2 (1.1)	34.8 (1.4)	.17	-
Sex, male: n (%)	7 (58)	5 (33)	.26	-
Ethnicity:			.002	-
Caucasian: n (%)	5 (42)	8 (53)		
African American: n (%)	7 (58)	0		
Maori: n (%)	0	5 (33)		
Other	0	2 (14)		
MRI measures				
Left CSA, cm^2: mean (95% CI)	316 (301-330)	279 (266-292)	.06	.001
Right CSA, cm^2: mean (95% CI)	322 (306-337)	287 (274-301)	.10	.002
Left GI: mean (95% CI)	2.06 (2.00-2.11)	1.88 (1.83-1.92)	.001	<.001
Right GI: mean (95% CI)	2.10 (2.03-2.16)	1.93 (1.88-1.99)	.008	.001

*Adjusted for head circumference at birth for CSA and GI using ANCOVA. The mean (95% CI) values displayed in each MRI measure represent the values for the adjusted model.