White Matter Volume Predicts Language Development in Congenital Heart Disease

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Objective To determine whether brain volume is reduced at 1 year of age and whether these volumes are associated with neurodevelopment in biventricular congenital heart disease (CHD) repaired in infancy.

Study design Infants with biventricular CHD (n = 48) underwent brain magnetic resonance imaging (MRI) and neurodevelopmental testing with the Bayley Scales of Infant Development-II and the MacArthur-Bates Communicative Development Inventories at 1 year of age. A multitemplate based probabilistic segmentation algorithm was applied to volumetric MRI data. We compared volumes with those of 13 healthy control infants of comparable ages. In the group with CHD, we measured Spearman correlations between neurodevelopmental outcomes and the residuals from linear regression of the volumes on corrected chronological age at MRI and sex.

Results Compared with controls, infants with CHD had reductions of 54 mL in total brain ($P = .009$), 40 mL in cerebral white matter ($P < .001$), and 1.2 mL in brainstem ($P = .003$) volumes. Within the group with CHD, brain volumes were not correlated with Bayley Scales of Infant Development-II scores but did correlate positively with MacArthur-Bates Communicative Development Inventory language development.

Conclusions Infants with biventricular CHD show total brain volume reductions at 1 year of age, driven by differences in cerebral white matter. White matter volume correlates with language development, but not broader developmental indices. These findings suggest that abnormalities in white matter development detected months after corrective heart surgery may contribute to language impairment. *(J Pediatr 2017;181:42-8).*

Trial registration ClinicalTrials.gov: NCT00006183.

Congenital heart disease (CHD) is among the most common birth defects. Moderate or severe forms of CHD affect 0.5%-1% of all live births[1,2] Children with CHD have an elevated risk of neurodevelopmental impairment, which typically affects attention, executive function, social cognition, and/or language.[3-6] Language in particular was the most common isolated delay in 1 longitudinal study of children with CHD.[7] In biventricular forms of CHD, such as transposition of the great arteries (TGA) or tetralogy of Fallot (TOF), over one-half of children require special services such as special education or early intervention[4,8] Thus, neurodevelopmental impairments significantly influence quality of life and daily functioning.[9-12]

Brain magnetic resonance imaging (MRI) has demonstrated both overt brain injury and subtle quantitative differences in the brain structures of children and adolescents with CHD. Cerebral white matter abnormalities are the most frequently reported neuroimaging abnormality in this population, though diffusely scattered punctate hemorrhages are also common.[13,14] Subtle differences in cerebral white matter microstructure and cortical thickness are measurable in adolescents with TGA even without overt brain injury by qualitative MRI.[15,16] Abnormalities in brain development are thought to precede surgery with reduced cortical folding, smaller cerebral volumes, and abnormal metabolism apparent in newborns and infants prior to surgery and even in utero.[17-19] Recent studies in adolescents indicate a relationship between brain MRI findings and neurodevelopmental functioning.[20,21]

BSID-II	Bayley Scales of Infant Development-II
CDI	MacArthur-Bates Communicative Development Inventories
CHD	Congenital heart disease
MDI	Mental developmental index
MRI	Magnetic resonance imaging
PDI	Psychomotor developmental index
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot

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In the present study, we sought to determine whether brain volumes are reduced following corrective surgery for biventricular CHD, and to determine the relationship between quantitative brain volumes and neurodevelopment in infancy. The study sample is unique in that the corrective heart surgery was performed in infancy, and the MRI was performed at approximately 1 year of age, allowing for a period of recovery and growth after surgical correction. In addition, we specifically evaluated language, given that it is commonly affected by CHD and may be more sensitive to subtle cognitive differences not detectable with instruments that assess global development. We hypothesized that both cerebral white and gray matter volumes would be smaller in infants with CHD than control infants, and that cerebral volumes would be more closely associated with language scores than with broader neurodevelopmental measures.

Methods

Cardiac subjects for these analyses were participants in a clinical trial (ClinicalTrials.gov: NCT00006183) comparing 2 hematocrit strategies during cardiopulmonary bypass surgery in infants. Detailed trial methods were previously published.[22] Briefly, the trial sample consisted of infants who underwent biventricular repair at less than 9 months of age with a diagnosis of 1 of the following: (1) TGA, (2) TOF with or without pulmonary atresia or truncus arteriosus, or (3) ventricular septal defect or complete common atrioventricular canal defect. Exclusion criteria were birth weight less than 2.3 kg, recognizable phenotypic syndrome of congenital anomalies detected during routine clinical care, extracardiac anomalies of greater than minor severity that could impede recovery of myocardial or brain function in the perioperative period, previous cardiac surgery, or associated cardiovascular anomalies necessitating aortic arch reconstruction or additional open surgical procedures before the planned developmental follow-up. Genetic testing was not performed for all subjects, but no children with CHD were identified as having chromosomal or genetic problems by 1 year of age by treating clinicians.

A comparison sample of 13 healthy control infants was selected from the National Institutes of Health MRI study of normal brain development, including all infants with neuroimaging performed on the same MRI scanner as the infants with CHD, and who had acceptable imaging quality and were of comparable age. These control infants had no known risk factors for brain disorders such as intrauterine exposure to toxins, history of closed head injury with loss of consciousness, language disorder or axis 1 psychiatric disorder, first degree relative with a lifetime history of an axis 1 psychiatric disorder, or abnormality on neurological examination.[23] This study was approved by the Boston Children's Hospital Institutional Review Board and adhered to both institutional guidelines and the Declaration of Helsinki.

Image Acquisition and Analysis

At approximately 12 months of age, subjects underwent brain MRI with sequences including a standard clinical axial fast spin echo T2-weighted sequence for skull stripping and coronal 3-dimensional spoiled gradient recalled echo for volumetric analyses. Detailed MRI acquisition variables for both the CHD trial subjects and the healthy control infants have been previously published.[14,23]

For volumetric analyses, we applied a whole brain probabilistic segmentation algorithm local MAP PSTAPLE.[24] This innovative algorithm, which was not available at the time primary trial results were published, computes probabilistic segmentations of a target brain simultaneously from multiple templates. Each of the template images is registered to the target image. Label and intensity information from each template is used to compute label probabilities of the target image. An expectation maximization algorithm is used both to estimate the segmentation of the target image and to measure the ability of each template to predict locally the correct segmentation of the target image. The algorithm converges on a local optimum, labeling both cortical and subcortical structures based on information stored in the template library.

This segmentation algorithm yields 134 brain regions. To reduce the problem of multiple comparisons, we selected 22 discrete regions thought likely to be affected by CHD, and from these 22 discrete regions created 6 aggregate regions for group comparisons and correlation analyses. The 22 discrete regions are listed in **Table I** (available at www.jpeds.com). The 6 aggregate regions were total brain, cerebral white matter, cerebral gray matter, subcortical gray matter, cerebellum, and brainstem.

Demographic and Medical Variables

For correlation analyses, we evaluated demographic and medical factors thought to be associated with brain volumes in the subjects with CHD. Demographic characteristics included sex and race. Birth characteristics were weight, gestational age, and Apgar score at 5 minutes. Preoperative variables were catheterizations, balloon atrial septostomy, age at operation, and endotracheal intubation before surgery. Operative variables were hematocrit treatment group, crossclamp time, total support time, total bypass time, low-flow bypass time, duration of circulatory arrest, hematocrit at onset of low-flow, lowest tympanic temperature, lowest pCO_2, pH at lowest pCO_2, highest pCO_2, and lowest pO_2. Of note, the pH-stat blood gas strategy was used during core cooling on cardiopulmonary bypass. Postoperative variables were lactate 60 minutes after bypass, lowest $PaCO_2$, lowest PaO_2, PRISM-III[25] score at 12 and 24 hours postoperative, hours intubated, postoperative intensive care unit length of stay, postoperative hospital length of stay, hypertension, and hypothermia.

Neurologic and Neurodevelopmental Outcomes

A standardized neurologic examination was performed on all subjects with CHD and was an entry criterion for control subjects. Neurodevelopmental evaluation performed at 1 year of age included the Bayley Scales of Infant Development-II (BSID-II)[26] for all subjects; the MacArthur-Bates Communicative Development Inventories (CDI)[27] was completed for subjects with CHD only. We evaluated the Words and Gestures