Altered Gray Matter in Adolescents with d-Transposition of the Great Arteries

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Objective To investigate the structural brain characteristics of adolescent patients with d-transposition of the great arteries (d-TGA), repaired with the arterial switch operation in early infancy, using quantitative volumetric magnetic resonance imaging.

Study design Ninety-two patients with d-TGA from the Boston Circulatory Arrest Study (76% male; median age at scan 16.1 years) and 49 control subjects (41% male; median age at scan 15.7 years) were scanned using a 1.5-Tesla magnetic resonance imaging system. Subcortical and cortical gyral volumes and cortical gyral thicknesses were measured using surface-based morphometry. Group differences were assessed with linear regression.

Results Compared with controls, patients with d-TGA demonstrated significantly reduced subcortical volumes bilaterally in the striatum and pallidum. Cortical regions that showed significant volume and thickness differences between groups were distributed throughout parietal, medial frontoparietal, cingulate, and temporal gyri. Among adolescents with d-TGA, volumes and thicknesses correlated with several perioperative variables, including age at surgery, cooling duration, total support time, and days in the cardiac intensive care unit.

Conclusions Adolescents with d-TGA repaired early in life exhibit widespread differences from control adolescents in gray matter volumes and thicknesses, particularly in parietal, midline, and subcortical brain regions, corresponding to white matter regions already known to demonstrate altered microstructure. These findings complement observations made in white matter in this group and suggest that the adolescent d-TGA cognitive profile derives from altered brain development involving both white and gray matter. *(J Pediatr 2016;169:36-43)*.

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Advances in prenatal diagnosis, surgical treatment, and postoperative management of children born with congenital heart disease (CHD) have dramatically improved their survival. Currently, the number of adults with CHD in the US has been estimated to be as high as 2.9 million.[1] However, survivors often demonstrate neurodevelopmental morbidity for which the neuroanatomic correlates remain unclear.[2]

Ample evidence supports a relationship between CHD and adverse sequelae in the developing brain. Neuropathologic evaluation in neonates who died shortly after cardiac surgery has demonstrated both white and gray matter injury, including cerebral cortex, subcortical gray matter, hippocampus, and cerebellum.[3] Interestingly, the pattern of gray matter injury included both infarction and neuronal dropout, suggesting that in surviving children with CHD, not all gray matter injury will be evident as chronic infarction.

Magnetic resonance imaging (MRI) of infants before and after corrective surgery for CHD has revealed evidence of cerebral injury. These studies demonstrate a relationship between injury or diminished gray matter volume, particularly in frontal and parietal lobes, and predisposing risk factors including low preoperative cerebral blood flow, severity of perioperative hypoxia, lower mean systemic blood pressure in the first postoperative day, and type of CHD.[4-7] Preoperatively, neonates with single ventricle defects and d-transposition of the great arteries (d-TGA) have imaging features of delayed cerebral maturation of both white matter and gray matter.[8,9] We have previously demonstrated alteration of deep white matter microstructure not apparent on conventional clinical MRI in adolescents

CHD	Congenital heart disease
d-TGA	d-Transposition of the great arteries
MRI	Magnetic resonance imaging
TIV	Total intracranial volume

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with d-TGA surgically corrected in early infancy.[10] As has been found in the premature infant, white matter injury can adversely affect the development of cortical gray matter, reflected in altered thickness.[11,12] Evidence for compromised gray matter beyond the perioperative period has been reported. Of note, morphometric study of a group of adolescents with surgically corrected CHD revealed reduction of total cortical gray matter and subcortical gray matter volumes.[13,14]

Our group has previously reported the cognitive and behavioral deficits of children and adolescents with repaired d-TGA.[15] We have now employed quantitative volumetric analysis of brain MRI data to compare parcellated gray matter volumes and cortical thicknesses in a group of adolescents with d-TGA repaired in early infancy with those of healthy control adolescents.

Further, we explored associations between medical covariates and gray matter measures within the group with d-TGA.

Methods

In the Boston Circulatory Arrest Study, infants <age 3 months with d-TGA undergoing the arterial switch operation were randomly assigned to 2 methods of vital organ support during hypothermic cardiopulmonary bypass (predominant deep hypothermic circulatory arrest vs predominant low-flow cardiopulmonary bypass) between April 1988 and February 1992. We have previously published trial methods and neurodevelopmental findings in the perioperative period and at ages 1, 4, 8, and 16 years.[15-19]

Adolescents recruited to the control group met criteria adapted from the National Institutes of Health MRI study of normal brain development.[20,21] Children with known risk factors for brain disorders (eg, intra-uterine exposure to toxicants; histories 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 neurologic examination) were excluded. We also excluded control subjects for whom MRI was contraindicated (eg, pacemaker, metal implants), those with trisomy 21, adolescents with other forms of CHD requiring surgical correction, and subjects whose primary language was not English. This study was approved by the Boston Children's Hospital Institutional Review Board and adhered to institutional guidelines. Parents provided informed consent, and adolescents provided assent.

MRI Acquisition

Subjects were scanned on identical GE Twin 1.5T systems (General Electric, Milwaukee, Wisconsin) at either Boston Children's Hospital or Beth Israel Deaconess Medical Center. Volumetric series for each subject were acquired using a spoiled proton gradient recalled 3-dimensional sequence, with imaging parameters: acquisition matrix = 256 × 256, field of view = 220 mm, slice thickness = 1.5 mm, repetition time/echo time = 35 ms/6 ms, flip angle = 45 degrees, resulting in a voxel size of 0.8594 × 0.8594 × 1.5 mm^3. Slices were obtained axially, aligned parallel to the anterior commissure-posterior commissure plane.

Structural brain MRIs were blindly interpreted by a neuroradiologist for quality of MRI data and the presence of structural abnormalities. Abnormalities were classified with respect to origin (acquired or developmental), type (infarction, mineralization, iron deposition, myelination delay, ventriculomegaly, abnormal signal characteristics), extent (focal or diffuse), and anatomic location in the brain. These data are a subset of those reported on in a previous article.[15]

MRI Analysis and Anatomic Classification

Images were processed using the fully-automated tools in Freesurfer v 5.0 (A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, Massachusetts). The technical details are described elsewhere.[22-27] Briefly, this procedure involves partitioning volumetric MRI images into white matter, gray matter, and cerebrospinal fluid. The deep gray matter in each hemisphere is segmented into 7 discrete subcortical structures with corresponding calculated volumes: thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens. Next, the outer pial surface of the brain is delineated, as is the surface comprising the white matter/gray matter junction. Cortical thickness is obtained by taking the distance between these 2 surfaces. Finally, the cortical surface is parcellated into distinct units based on gyral and sulcal structure. Mean cortical thickness and volume is obtained for 30 gyri in each hemisphere. All images were inspected for image processing errors and manually corrected when necessary.

We classified parcellated regions according to position along their respective arterial trees using a standard atlas of cerebral vasculature.[28,29] Each region was assigned to 1 of 3 groups (proximal, middle, or terminal) based on location in the arterial tree relative to the origin of the main cerebral arterial trunk supplying it blood. Consequently, anterior cingulate cortex (which receives blood flow from branches of the proximal anterior cerebral artery) was classified as a proximal volume, and posterior cingulate cortex was classified as a terminal volume (because it is perfused by distal branches of the anterior cerebral artery). In order to minimize multiple comparisons, clusters were created by averaging adjacent volumes or thicknesses as well as homologous volumes or thicknesses across hemispheres. This resulted in 24 subcortical and cortical volume clusters and 20 cortical thickness clusters (**Table I**; available at www.jpeds.com).

Statistical Analyses

Wilcoxon or Fisher exact tests were used to compare d-TGA and control groups with respect to demographic variables and structural MRI findings. For subjects with d-TGA, medical variables measured before or during the arterial switch operation included presence of a ventricular septal defect, age at surgery (>30 days vs ≤30 days), cooling duration for the first cycle, total duration of deep hypothermic circulatory