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Prenatal to postnatal trajectory of brain growth in complex congenital heart disease

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ABSTRACT

Altered brain development is a common feature of the neurological sequelae of complex congenital heart disease (CHD). These alterations include abnormalities in brain size and growth that begin prenatally and persist postnatally. However, the longitudinal trajectory of changes in brain volume from the prenatal to postnatal environment have not been investigated. We aimed to evaluate the trajectory of brain growth in a cohort of patients with complex CHD (n = 16) and healthy controls (n = 15) to test the hypothesis that patients with complex CHD would have smaller total brain volume (TBV) prenatally, which would become increasingly prominent by three months of age. Participants underwent fetal magnetic resonance imaging (MRI) at a mean of 32 weeks gestation, a preoperative/neonatal MRI shortly after birth, a postoperative MRI (CHD only), and a 3-month MRI to evaluate the trajectory of brain growth. Three-dimensional volumetric analysis was applied to the MRI data to measure TBV, as well as tissue-specific volumes of the cortical gray matter (CGM), white matter (WM), subcortical (deep nuclear) gray matter (SCGM), cerebellum, and cerebrospinal fluid (CSF). A random coefficients model was used to investigate longitudinal changes in TBV and demonstrated an altered trajectory of brain growth in the CHD population. The estimated slope for TBV from fetal to 3-month MRI was 11.5 cm^3 per week for CHD infants compared to 16.7 cm^3 per week for controls ($p = 0.0002$). Brain growth followed a similar trajectory for the CGM ($p < 0.0001$), SCGM ($p = 0.002$), and cerebellum ($p = 0.005$). There was no difference in growth of the WM ($p = 0.30$) or CSF ($p = 0.085$). Brain injury was associated with reduced TBV at 3-month MRI ($p = 0.02$). After removing infants with brain injury from the model, an altered trajectory of brain growth persisted in CHD infants ($p = 0.006$). These findings extend the existing literature by demonstrating longitudinal impairments in brain development in the CHD population and emphasize the global nature of disrupted brain growth from the prenatal environment through early infancy.

1. Introduction

The key pathways to adverse neurological outcomes in infants with congenital heart disease (CHD) continue to be investigated in order to frame approaches for neuroprotection. Such insights require an understanding of the nature, timing, and neurobiological underpinnings of not only brain injury, but also alterations in brain development. To date, cohort studies have identified that alterations in brain

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development begin prenatally and include impairments in brain volume (Limperopoulos et al., 2010; Sun et al., 2015). These volumetric deficits exist before cardiac surgery, persist postoperatively, and are even present into adolescence and adulthood (Cordina et al., 2014; Rollins et al., 2017; von Rhein et al., 2015; 2014; Heye et al., 2018). Importantly, reductions in tissue- and region-specific brain volumes have been associated with adverse neurodevelopmental outcomes in cognitive, motor, language, and executive function domains (Rollins et al., 2017; von Rhein et al., 2014; Heye et al., 2018; Latal et al., 2016).

Despite evidence of reduced brain volume in CHD patients across multiple stages of childhood development, there are limited data investigating longitudinal brain growth within a single cohort. This type of analysis may provide information regarding the timing of total and tissue-specific alterations in brain volume, which may lend insight to the underlying pathophysiologic processes and/or critical period(s) for neurologic risk. Our laboratory has previously performed repeated two-dimensional (2D) MRI measures of brain size in infants with CHD and identified preoperative deficits across multiple regions, which persisted at three months of age (Ortinau et al., 2012a; 2012b). While these biometric methods can be readily applied at the bedside, they are limited to 2D global brain region measurements, as opposed to three-dimensional (3D) volumetric methods, which can also generate specific tissue-type measures (Gholipour et al., 2011). Furthermore, 2D biometry has variable correlation with 3D volumetry, depending on whether global or tissue-specific measures are being evaluated (Kyriakopoulou et al., 2017; Nguyen The Tich et al., 2009). Thus, application of 3D volumetric methods provide more detailed tissue assessments that may be more relevant for untangling the neurobiological processes of altered brain development in CHD.

The only studies to date that have investigated longitudinal 3D brain volumes in infants with CHD have focused on postnatal comparisons. These data have demonstrated diminished total brain growth perioperatively, over two weeks, in infants with hypoplastic left heart syndrome (HLHS) compared to infants with transposition of the great arteries (TGA) (Peyvandi et al., 2018a). MRI at approximately one year of age demonstrated smaller total brain volume (TBV) in children with single ventricle physiology or TGA when compared to controls. At three years of age, these deficits only persisted in those children with single ventricle physiology (Ibuki et al., 2012). While fetal imaging in CHD has clearly suggested a disruption in brain development prenatally, no data have evaluated the progression of brain volume from the fetal to postnatal environment. Additionally, the interplay between brain development and brain injury pre- and post-natally has yet to be fully defined.

This study was a pilot investigation that aimed to extend the existing literature by determining the trajectory of brain growth in patients with complex CHD, beginning during pregnancy and continuing through the perioperative period and into early infancy. We hypothesized that the CHD population would have smaller TBV than the control population, that the volume difference would exist prenatally, and that volume reduction would become more prominent by three months of age. We also hypothesized that brain injury would be associated with smaller TBV by three months of age.

2. Materials and methods

2.1. Patient population

Pregnant women with a known diagnosis of fetal complex CHD were recruited from the Fetal Care Center at Barnes Jewish Hospital/St. Louis Children's Hospital from 2012 to 2015. Specific lesions targeted for recruitment included HLHS, dextro-transposition of the great arteries (d-TGA), pulmonary atresia (PA), tetralogy of Fallot (TOF), double outlet right ventricle (DORV), truncus arteriosus, and complex single ventricle physiology. The control population included pregnant women cared for in the Obstetrics Clinic at Barnes Jewish Hospital who had an otherwise healthy pregnancy. These women were approximately matched to the CHD population on fetal gestational age (GA) at MRI, fetal sex, and maternal race. Exclusion criteria included fetal diagnosis of a genetic syndrome or chromosomal abnormality known to affect clinical outcome, congenital anomalies (outside of CHD for the study population), suspected or proven congenital infection, or multiple gestation pregnancy. The local Institutional Review Board approved all aspects of the study. Adult participants provided informed, written consent for prenatal study evaluations and data collection. Both parents provided informed, written consent for infant postnatal study evaluations and data collection.

2.2. Demographic and clinical variables

Demographic and clinical variables were collected after informed consent was obtained. Demographic variables included maternal age, maternal and paternal race, and infant sex. Clinical variables included pregnancy, delivery, and hospitalization characteristics. Pregnancy data included co-morbid conditions and new pregnancy diagnoses. Delivery characteristics included mode and indication for delivery, Apgar scores, and delivery complications. GA at birth and anthropometric measures at birth and at each MRI were also collected. Hospitalization variables for CHD subjects included medical variables related to the CHD diagnosis (i.e., need for preoperative prostaglandins or atrial septostomy), cardiac surgical data, extracorporeal life support, length of hospital stay, and survival.

2.3. Magnetic resonance imaging

Brain MRI was performed at four time points for the CHD population and at three time points for the control population. These included: 1) a fetal brain MRI performed during the second or third trimester of pregnancy for both groups, 2) a neonatal brain MRI that occurred preoperatively for CHD subjects and within the first week of life for control subjects, 3) a postoperative MRI for CHD subjects only, and 4) a 3-month MRI for all subjects. The preoperative and postoperative MRIs were used to evaluate for perioperative brain injury in the CHD population. Two raters experienced in neonatal neuroimaging (J.S. and C.S.) who were blinded to the subject's group and clinical history reviewed each MRI and a consensus was formed for presence of brain injury and qualitative abnormalities in brain development. Brain injury was defined as white matter injury, intraventricular hemorrhage, hemorrhagic or ischemic infarct, or other hemorrhage (i.e., cerebellar hemorrhage). A standardized scoring system was applied to evaluate the severity of white matter injury (minimal, moderate, or severe) and to calculate an overall brain injury severity score (0–3) (Dimitropoulos et al., 2013; McQuillen et al., 2007). Qualitative abnormalities in brain development included increased extra-axial space, open Sylvian Fissure, and delayed myelination patterns.

2.3.1. Fetal magnetic resonance imaging acquisition

Pregnant women underwent fetal MRI on a 1.5 Tesla Magnetom Avanto (Siemens Healthcare, Erlangen, Germany) without sedation. The acquisition parameters included a T2 half-fourier acquisition single-shot turbo spin-echo (HASTE) sequence acquired in the axial, coronal, and sagittal planes with a field of view (FOV) of 320 millimeters (mm), repetition time (TR) of 1450 milliseconds (ms), echo time (TE) of 140 ms, flip angle of 180°, and slice thickness of 3.0 mm. To address the possibility of fetal motion and improve the success of volumetric reconstruction, multiple acquisitions were acquired in each plane (Kuklisova-Murgasova et al., 2012; Gholipour et al., 2010). The MR scanner and acquisition protocol utilized were identical for both the CHD and control groups.

2.3.2. Postnatal magnetic resonance imaging acquisition

Postnatal imaging (preoperative, postoperative, and 3-month MRIs)