Brain Volume and Neurobehavior in Newborns with Complex Congenital Heart Defects

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Objective To investigate the relationship between tissue-specific alterations in brain volume and neurobehavioral status in newborns with complex congenital heart defects preoperatively.

Study design Three-dimensional volumetric magnetic resonance imaging was used to calculate tissue-specific brain volumes and a standardized neurobehavioral assessment was performed to assess neurobehavioral status in 35 full-term newborns admitted to the hospital before cardiopulmonary bypass surgery. Multiple linear regression models were performed to evaluate relationships between neurobehavioral status and brain volumes.

Results Reduced subcortical gray matter (SCGM) volume and increased cerebrospinal fluid (CSF) volume were associated with poor behavioral state regulation (SCGM, $P = .04$; CSF, $P = .007$) and poor visual orienting (CSF, $P = .003$). In cyanotic newborns, reduced SCGM was associated with higher overall abnormal scores on the assessment ($P = .001$) and poor behavioral state regulation ($P = .04$), and increased CSF volume was associated with poor behavioral state regulation ($P = .02$), and poor visual orienting ($P = .02$). Conversely, acyanotic newborns showed associations between reduced cerebellar volume and poor behavioral state regulation ($P = .03$).

Conclusion Abnormal neurobehavior is associated with impaired volumetric brain growth before open heart surgery in infants with complex congenital heart defects. This study highlights a need for routine preoperative screening and early intervention to improve neurodevelopmental outcomes. *(J Pediatr 2014;164:1121-7)*.

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Brain injury and neurodevelopmental impairments have emerged as salient comorbidities of congenital heart defects (CHDs), especially in newborns with complex cardiac lesions.[1-4] Moreover, there is increasing awareness of neurologic compromise presenting even before corrective or palliative surgery, with up to 60% of newborns demonstrating neuroimaging abnormalities[1-3,5,6] and up to 70% showing signs of neurobehavioral impairment.[7-10] Studies using advanced magnetic resonance imaging (MRI) techniques are adding to this growing body of literature by providing quantitative in vivo measurements of brain structure.[11-15] For instance, recent studies using 3-dimensional (3D) volumetric MRI have shown that fetuses with CHD have progressively lower total and tissue-specific brain volumes as well as delayed gyrification in the third trimester compared with healthy controls.[14,15]

The high prevalence of neurologic and neurobehavioral abnormalities, in addition to more recent quantitative indicators of impairment, points to a need for routine monitoring of neurologic status in these high-risk infants. Moreover, a better understanding of the association between early brain structure and function may help to determine the most appropriate methods for evaluating this high-risk population. Very few studies have investigated the relationship between neurologic status and brain injury in newborns with complex CHD, and available data are equivocal.[8,9] Furthermore, no study to date has examined the association between clinical neurobehavioral status and volumetric brain growth in newborns with CHD before open heart surgery. Therefore, the objective of this study was to examine the association between preoperative neurobehavioral status, as measured with a standardized

3D	Three-dimensional
CGM	Cortical gray matter
CHD	Congenital heart defect
CSF	Cerebrospinal fluid
ENNAS	Einstein Neonatal Neurobehavioral Assessment Scale
MRI	Magnetic resonance imaging
mWM	Myelinated white matter
SCGM	Subcortical gray matter
SNAP-II	Score for Neonatal Acute Physiology-II

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neurobehavioral assessment, and global and tissue-specific brain volumes, as measured using 3D volumetric MRI.

Methods

The study cohort included full-term newborns (>36 weeks' gestational age) diagnosed with complex CHD requiring corrective or palliative cardiopulmonary bypass surgery. Subjects were enrolled prospectively, either antenatally or postnatally. Mothers of fetuses with confirmed complex CHD following a fetal echocardiogram were enrolled as part of a larger, longitudinal study of brain development in fetuses and infants with CHD. Postnatally, newborns were enrolled following admission to the cardiac intensive care unit at our center with complex CHD confirmed by echocardiography.

Newborns were excluded when there was evidence of central nervous system dysfunction that could be plausibly attributed to causes that were unrelated to complications of CHD. This included subjects with central nervous system infections; congenital malformations, known chromosomal anomalies, or syndromes; or documented perinatal insults. Informed, parental consent was obtained before acquiring any patient information. This study was approved by the institutional review board at our center as part of the longitudinal study protocol.

Preoperative brain MRI studies were conducted for enrolled newborns as per the standard clinical protocol at our center for newborns undergoing cardiopulmonary bypass surgery. In certain cases, surgery was scheduled beyond the neonatal period and studies were performed strictly for research purposes. Studies took place as soon as the clinical care team determined that the newborn was stable enough to be transported to the MRI scanner or at the parents' earliest convenience when newborns were scanned as outpatients.

No sedation was used during the MRI scan unless it was necessary for clinical reasons. Newborns who were not clinically sedated were quieted by feeding and swaddling and were immobilized through using an Infant Vacuum Immobilizer (Newmatic Medical, Caledonia, Michigan). All infants were provided with 2 layers of hearing protection: ear plugs (Mighty Plugs; Beneficial Products Inc, Ashland, Oregon) and Neonatal Noise Guards (Natus Medical Inc, Seattle, Washington). Oxygen saturation, heart rate, and temperature were monitored and recorded throughout the scanning process by a nurse using a Veris MR vital signs monitoring system (MEDRAD, Inc, Indianola, Pennsylvania).

MRI pulse sequences were acquired on a 3-T magnetic resonance scanner (Discovery MR750, GE Healthcare, Milwaukee, Wisconsin) with a 32-channel receive-only head coil (MR Instruments, Inc, Minneapolis, Minnesota). Two sequences were required to compute brain volumes: a T1-weighted fluid attenuated inversion recovery sequence with periodically rotated overlapping parallel lines with enhanced reconstruction, 2-mm contiguous axial slices, 38.6-ms echo time, 1525-ms repetition time, 565.42-ms inversion time, 256 × 256 matrix, 1 excitation, and 25.6-cm field of view, as well as a 2-mm axial T2-weighted periodically rotated overlapping parallel lines with enhanced reconstruction sequence with 83.72-ms echo time, 9640-ms repetition time, 256 × 256 matrix, 2 excitations, and 25.6-cm field of view. A pediatric neuroradiologist blinded to clinical diagnosis and neurobehavioral findings reviewed each MRI study.

Image processing was performed on Linux workstations. A previously validated automatic segmentation software program[16,17] was used to segment each brain volume into 5 major tissue classes and the cerebellum (**Figure 1**). The resulting images were inspected and corrected manually using MINC software (www.bic.mni.mcgill.ca/software/minc). Manual corrections were performed by a single investigator, and intrarater reliability was assessed by performing the manual corrections a second time for 5 cases. Using the intraclass correlation coefficient, intrarater reliability was calculated as 0.998 overall: total brain volume, 0.96; cortical gray matter (CGM), 0.89; myelinated white matter (mWM), 0.77; unmyelinated white matter, 0.97; subcortical gray matter (SCGM), 0.91; and cerebellar volume, 0.91. Following automatic segmentation and manual corrections, each tissue volume was determined by multiplying the number of voxels in the appropriate tissue's segmentation mask (eg, CGM) by the volume of each voxel (www.bic.mni.mcgill.ca/software/minc).

The Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS)[18] was administered by 1 of 2 evaluators trained in assessing neonatal neurobehavioral status and blinded to clinical neurologic findings and MRI results. The ENNAS was selected as a comprehensive yet efficient assessment of neonatal neurologic and neurobehavioral status, which has been previously used to evaluate newborns with CHD.[4,7,19,20] It takes approximately 20 minutes to perform at the newborn's bedside and consists of 20 test items, which evaluate muscle tone, passive and active movements, primitive reflexes, as well as visual and auditory orienting. In addition, 4 summary items assess overall impression of "cuddliness," spontaneous movements, tonus, and tremor (both incidence and quality). Of the 24 scored items, 19 contribute to an overall score reflecting the number of failed items, with the remaining items informing the summary scores. The infant's behavioral state is also observed throughout the assessment, with predominant state documented independently of the scored items. Assessments with up to 2 failed items were classified as normal, 3-6 failed items constituted a suspect assessment, and >6 failed items was considered abnormal.

The ENNAS has excellent concurrent validity with the standard neonatal neurologic examination.[20] The negative predictive value of this instrument is very good (83%-92%) for intellectual function, communication, and socialization and good (64%-83%) for neuromotor status and daily living skills at school age.[21] The sensitivity of the ENNAS is also good, ranging from 64% to 78%, although positive predictive value and specificity remain limited due to a susceptibility