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Original Article

White Matter Injury in Newborns With Congenital Heart Disease: A Diffusion Tensor Imaging Study

Sarah B. Mulkey MD [a,*], Xiawei Ou PhD [b], Raghu H. Ramakrishnaiah MBBS [b], Charles M. Glasier MD [b], Christopher J. Swearingen PhD [a], Maria S. Melguizo MS [a], Vivien L. Yap MD [c], Michael L. Schmitz MD [d], Adnan T. Bhutta MBBS [e]

[a] *Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas*
[b] *Department of Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas*
[c] *Department of Pediatrics, NewYork-Presbyterian–Weill Cornell Medical College, New York, New York*
[d] *Department of Anesthesiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas*
[e] *Department of Pediatrics, University of Maryland, Baltimore, Maryland*

ABSTRACT

BACKGROUND: Brain injury is observed on cranial magnetic resonance imaging preoperatively in up to 50% of newborns with congenital heart disease. Newer imaging techniques such as diffusion tensor imaging provide sensitive measures of the white matter integrity. The objective of this study was to evaluate the diffusion tensor imaging analysis technique of tract-based spatial statistics in newborns with congenital heart disease. **METHODS:** Term newborns with congenital heart disease who would require surgery at less than 1 month of age were prospectively enrolled ($n = 19$). Infants underwent preoperative and postoperative brain magnetic resonance imaging with diffusion tensor imaging. Tract-based spatial statistics, an objective whole-brain diffusion tensor imaging analysis technique, was used to determine differences in white matter fractional anisotropy between infant groups. Term control infants were also compared with congenital heart disease infants. Postmenstrual age was equivalent between congenital heart disease infant groups and between congenital heart disease and control infants. **RESULTS:** Ten infants had preoperative brain injury, either infarct or white matter injury, by conventional brain magnetic resonance imaging. The technique of tract-based spatial statistics showed significantly lower fractional anisotropy ($P < 0.05$, corrected) in multiple major white matter tracts in the infants with preoperative brain injury compared with infants without preoperative brain injury. Fractional anisotropy values increased in the white matter tracts from the preoperative to the postoperative brain magnetic resonance imaging correlating with brain maturation. Control infants had higher fractional anisotropy in multiple white matter tracts compared with infants with congenital heart disease. **CONCLUSION:** Tract-based spatial statistics is a valuable diffusion tensor imaging analysis technique that may have better sensitivity in detecting white matter injury compared with conventional brain magnetic resonance imaging in term newborns with congenital heart disease.

Keywords: white matter injury, congenital heart disease, diffusion tensor imaging, brain magnetic resonance imaging, tract-based spatial statistics, newborn brain injury, fractional anisotropy

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Introduction

Newborns with congenital heart disease (CHD) are at risk for brain injury, both preoperatively and postoperatively. The increased preoperative risk can be explained, at least in part, by the structural immaturity of the brain in newborns with CHD.[1,2] Conventional brain magnetic resonance imaging (MRI) may reveal preoperative injury in the form of ischemic infarcts, white matter injury, and other injury

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* Communications should be addressed to: Dr. Mulkey; Department of Pediatrics; Section of Pediatric Neurology; University of Arkansas for Medical Sciences; 1 Children's Way; Slot 512-15; Little Rock, Arkansas 72202.
E-mail address: mulkeysarah@uams.edu

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types in up to 50% of newborns requiring surgery as neonates.[1,3,4] New or increased injury may also be observed postoperatively in 30-40%.[1,5,6] These injuries may appear fairly small on conventional imaging and may resolve over time.[6,7]

Diffusion tensor imaging (DTI) is a quantitative MRI technique that can assess the structural integrity of the cerebral white matter, providing a valuable method to quantify microstructural brain changes with injury.[8] Fractional anisotropy is one parameter that can be measured by DTI. Fractional anisotropy reflects the directionality of water molecule diffusion and thus provides a measure of microstructural integrity, because water molecules tend to diffuse along the direction of axonal tracts while diffusion is restricted by the myelin sheath in the direction perpendicular to axonal tracts. Fractional anisotropy values rise as a newborn's brain matures correlating with increasing structural complexity.[9-11] Fractional anisotropy values, however, are reduced with white matter injury.[12-14] In an MRI study of newborns with CHD, fractional anisotropy values in many white matter tracts were found to be lower compared with control newborns, but there was no difference between CHD newborns with and without brain injury using a region-of-interest analysis technique.[15] In another study, infants with preoperative brain injury had a lower rate of fractional anisotropy increase postoperatively compared with infants with normal preoperative brain MRIs, suggesting delayed development of the white matter tracts in these newborns.[16] Fractional anisotropy values may also vary as a function of cardiac anatomy. For example, among infants with a single-ventricle type of CHD, a smaller ascending aortic diameter was associated with lower fractional anisotropy values in brain white matter compared with infants with a larger ascending aortic diameter.[17]

A newer DTI analysis technique is known as tract-based spatial statistics. This technique allows for an objective measure of the brain white matter tracts using a "white matter skeleton" built by the combined subject images, thus removing any subjective selection of brain regions.[18] In preterm newborns, this technique has revealed areas of white matter injury outside of areas visualized by conventional brain MRI.[19] A recent study using this technique was able to demonstrate widespread changes in major white matter tracts in ex-preterm neonates known to have punctate lesions on previous MRI images.[12] These changes in white matter microstructure were significantly different when compared with gestation- and sex-matched controls without a history of punctate lesions on MRI. The distribution of reduced fractional anisotropy in the corticospinal tracts with punctate lesions using this technique was more widespread than the visible extent of the lesions on conventional MRI.[12] In addition, findings at term-equivalent age correlate with neurodevelopment at the age of 2 years, thus raising the possibility of using tract-based spatial statistics in preterm newborns as a biomarker of neurodevelopmental outcome.[20] This technique, however, has not been well explored in newborns with CHD.

The objectives of this study were to (1) evaluate the DTI technique of tract-based spatial statistics in studying the white matter of newborns with CHD, (2) determine how brain injury in CHD newborns affects fractional anisotropy values in the major white matter tracts, and (3) correlate fractional anisotropy values with brain maturity in CHD newborns. We hypothesized that tract-based spatial statistics would be a valuable technique to analyze white matter injury and brain maturity in newborns with CHD.

Methods

Subjects

After receiving informed consent, newborns with CHD were prospectively enrolled into a pilot observational study at Arkansas Children's Hospital between June 1, 2012 and April 30, 2013. Subjects had to have CHD expected to require surgery at less than 1 month of age. Infants were excluded if their gestation at birth was <36 weeks or if they had a major genetic syndrome. Recorded baseline characteristics included demographics, birth history (i.e., birth weight, gestation, and Apgar scores), and type of CHD. For each infant, details pertaining to the surgery included age at surgery, type of surgery, Risk Adjustment for Congenital Heart Surgery (RACHS-1) category,[21] use of cardiopulmonary bypass including total bypass time, and the degree of hypothermia. The RACHS-1 is a consensus-based method for risk adjustment for in-hospital mortality in CHD and is based on the surgical procedure performed.[21] In addition, data from 11 healthy infants born at term gestation recruited for other brain MRI research projects were included in this study to serve as control subjects. This study received institutional review board–approval before initiation.

Brain magnetic resonance imaging

All subjects underwent a brain MRI, preoperatively, on a 1.5-T Achieva scanner (Philips Healthcare, Best, the Netherlands) using an MRI protocol that consisted of three-dimensional T_1-weighted images, axial T_2-weighted images, T_1 inversion recovery, fluid-attenuated inversion recovery, diffusion-weighted images, susceptibility-weighted images, and DTI. The three-dimensional T_1-weighted sequence was obtained for anatomic evaluation and volumetric analysis and the T_1-weighted inversion recovery was obtained to assess myelination. A single-shot spin echo planar imaging sequence with acquisition voxel size 2 mm × 2 mm × 3 mm and diffusion-weighting gradients ($b = 700$ s/mm^2) uniformly distributed in 15 directions was used to acquire the DTI data. Infants were sedated by a pediatric cardiovascular anesthesiologist based on the individual need of each infant, because the MRI was performed immediately before transfer to the operating room for CHD surgery, in most cases. Three infants had a preoperative clinical cardiac MRI during which the brain MRI was performed.

Postoperatively, infants had a brain MRI with the same protocol using a nonsedated technique of swaddling the infant to achieve sleep[22] using a MedVac Infant Immobilizer (CFI Medical Solutions, Fenton, MI). During the MRI, infants were monitored using an MRI-compatible pulse oximeter, and an MRI-compatible camera was attached to the head coil and connected to a screen outside the scanner room to watch for infant movement. For some infants, sequences were repeated because of movement artifact. Most of the MRIs occurred when the infant was stable and close to hospital discharge. One infant had a clinical procedure requiring anesthesia during which the postoperative brain MRI was obtained under sedation. For two infants, the postoperative brain MRI was obtained because of the attending physician's clinical concern about a neurological problem and was performed under sedation. The control infants had similar MRI examinations including DTI at 0-2 weeks of age (postmenstrual age 39-41 weeks).

The brain MRIs were interpreted by board-certified pediatric neuroradiologists (C.M.G. and R.H.R.) and scored using the CHD MRI Injury Score as reported previously.[4] The score incorporates the relative size and number of areas involved in 11 types of imaging abnormalities, including white matter injury, gray matter injury, focal cerebral infarction, watershed infarcts, hemorrhages, changes in susceptibility-weighted imaging, and brain atrophy, which are observed in newborns with CHD. Brain injury was defined as having an infarct, white matter injury, and/or deep gray matter injury. The isolated finding of a subdural hemorrhage, preoperatively, was considered as "no brain injury" since

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