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White Matter Injury in Newborns with Congenital Heart Disease-A Diffusion Tensor Imaging Study

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Abstract

BACKGROUND—Brain injury is observed on brain 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. 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.

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METHODS—Term newborns with congenital heart disease that would require surgery at less than one 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 to 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 to 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 showed higher fractional anisotropy in multiple white matter tracts compared to 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 to 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

INTRODUCTION

Newborns with congenital heart disease (CHD) are at risk for brain injury, 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 show preoperative injury in the form of ischemic infarcts, white matter injury, and other injury types in up to 50% of newborns requiring surgery as neonates.[1, 3, 4] New or increased injury may also be seen 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 quantitate 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, since 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 a MRI study of

CHD newborns, fractional anisotropy values in many white matter tracts were found to be lower compared to control newborns, but there was no difference between CHD newborns with and without brain injury using a region of interest analysis technique.[15] In a separate study, infants with preoperative brain injury were found to have a lower rate of fractional anisotropy increase postoperatively compared to 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 to 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 shown 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 to gestational age 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 age 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

Following 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 one month of age. Infants were excluded if their gestational age at birth was <36 weeks or if they had a major genetic syndrome. Recorded baseline characteristics included demographics, birth history (i.e. birth weight, gestational age, 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 CHD 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 gestational age recruited for other brain MRI research projects were included in this study to serve as controls. This study received Institutional Review Board approval prior to initiation.

Brain MR Imaging

All subjects underwent a brain MRI, preoperatively, on a 1.5 Tesla Achieva scanner (Philips Healthcare, Best, the Netherlands) using a MRI protocol that consisted of 3D T1 weighted images, axial T2 weighted images, T1 inversion recovery, fluid attenuation inversion recovery, diffusion weighted images, susceptibility weighted images, and DTI. The 3D T1 weighted sequence was obtained for anatomic evaluation and volumetric analysis and the T1 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, as the MRI was performed immediately prior to 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 non-sedated technique of swaddling the infant to achieve sleep[22] using a MedVac Infant Immobilizer (CFI Medical Solutions, Fenton, MI, USA). During the MRI, infants were monitored using a MRI-compatible pulse oximeter and a 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 due to 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 due to attending physician clinical concern for a neurologic problem and was done 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 read by board-certified pediatric neuroradiologists (CMG and RHR) and scored using the CHD MRI Injury Score as reported previously.[4] The score incorporates the relative size and number of areas involved of 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 seen 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 this can frequently be seen in a newborn due to birth forces following delivery. The level of brain maturity was determined using the validated Total Maturation Score by consensus of the neuroradiologists.[1, 2, 23] A MRI physicist (XO) reviewed all DTI data for quality and performed the DTI tract-based spatial statistics analysis.

DTI Tract-Based Spatial Statistics Analysis

For the DTI tract-based spatial statistics analysis, infants were grouped by brain injury status, with either the presence or absence of brain injury by conventional MRI, preoperatively and postoperatively. Infants were also grouped by preoperative Total Maturation Score, with either Total Maturation Score ≤12 vs. >12, to evaluate the effect of brain maturation on fractional anisotropy. A Total Maturation Score of 12 was chosen since it correlates with a term gestational age (38 to 39 weeks) and provided two CHD subject groups of fairly equal size for tract-based spatial statistics analysis of brain maturation.[23] CHD infants were also compared to control infants.

The tract-based spatial statistics analyses were carried out by the FMRIB Software Library (FSL) tract-based spatial statistics v1.2.[18, 24] First, the fractional anisotropy maps for each subject were computed from the scanner-carried software (Fibertrak, Philips) and were exported to a workstation with FSL installed on a Linux virtual machine (VMware Inc., Palo, Alto, CA, USA). Each fractional anisotropy data set was then aligned to every other fractional anisotropy data set by FSL to identify the one with minimum total warping, and this fractional anisotropy data set was therefore regarded as the most representative one and served as the target fractional anisotropy data set. Nonlinear transforms were then performed to register each fractional anisotropy data set to this target. Afterwards, all fractional anisotropy images were merged, and a fractional anisotropy skeletonization program by FSL was used to create a fractional anisotropy skeleton in which a threshold of fractional anisotropy ≥0.15 was chosen. Subsequent voxel-wise statistics were performed on the normalized and skeletonized fractional anisotropy data.

Statistical Analysis

For demographic and clinical data, the median, lower quartiles, and upper quartiles were computed for continuous variables, frequencies and percentages were computed for ordinal variables. Demographic and clinical similarity between CHD infant groups (preoperative brain injury vs. no brain injury) was estimated using equivalence tests assuming a 20% margin.[25, 26] Postmenstrual age at initial MRI was estimated between controls and CHD patients, with and without brain injury as well as in total, using equivalence tests assuming a 10% margin. R statistical software, R version 2.15.1, was used for the creation of Table 1. For the DTI tract-based spatial statistics analysis, voxel-wise comparisons of fractional anisotropy values were performed by t-tests. Threshold-Free Cluster Enhancement option[18] was used and the results were fully corrected for multiple comparisons. Clusters with $P < 0.05$ (corrected) were regarded as significant.

RESULTS

Nineteen of 31 (61%) eligible infants during the study period were enrolled. The clinical characteristics, timing of brain MRIs, and age at surgery for the 19 infants are described in Table 1. The CHD type and surgical RACHS-1 category for each infant is presented in Table 2. None of the infants had seizures preoperatively. Six of 12 infants that had a normal preoperative neurologic exam had preoperative brain injury (Table 2).

Brain injury, as defined by having a single focal infarct or multi-focal infarcts and/or white matter injury on conventional MRI, was seen preoperatively in 10 CHD infants (52%, Table 2). Five of the 9 CHD infants without brain injury had completely normal brain MRIs, while the other 4 had a small subdural hemorrhage (n=1), small subdural, choroid plexus, and intraventricular hemorrhages (n=1), which are changes that can be found normally in newborns following birth, and cerebral atrophy (n=2). Six infants with brain injury also had cerebral atrophy. The preoperative CHD MRI Injury Score[4] is reported in Table 2. Infants with and without brain injury were equivalent for birth gestational age and postmenstrual age at the preoperative and postoperative brain MRI. Infants with preoperative brain injury had a lower birth weight and lower 1- and 5-minute Apgar scores compared to infants without preoperative brain injury (Table 1).

Following Threshold-Free Cluster Enhancement correction for multiple comparisons, tract-based spatial statistics showed significantly lower fractional anisotropy values in many major white matter tracts including the splenium of the corpus callosum, posterior limb of the internal capsule, the corticospinal tracts, and the optic radiations in infants with preoperative brain injury compared to infants without preoperative brain injury (P <0.05, corrected, Figure 1). These changes did not persist postoperatively. Fractional anisotropy values in all major white matter tracts (projection, association, and callosal fibers), showed a significant increase from the preoperative to the postoperative MRI correlating with increasing brain maturity (P <0.05, corrected, Figure 2).

Total Maturation Scores were equivalent, preoperatively and postoperatively, for infants with and without preoperative brain injury. Two of 3 infants with a preoperative Total Maturation Score of ≤ 10, equivalent to a maturation level or gestational age ≤ 35 weeks, had preoperative brain injury. Infants were grouped by Total Maturation Score ≤12 (correlating with a postmenstrual age of ≤38–39 weeks) vs. >12 (correlating with a postmenstrual age of >39 weeks) for DTI analysis.[23] The mean (standard deviation) postmenstrual age at MRI was slightly lower in the Total Maturation Score ≤12 vs. >12 groups, 38.8(0.4) vs. 40.1(0.3) weeks, P = 0.038. There was no difference in white matter fractional anisotropy values for the 12 infants with a Total Maturation Score of ≤12 vs. the 7 infants with a preoperative Total Maturation Score >12. A cutoff value of Total Maturation Score ≤11 vs. >11 was also tried, without finding a significant difference between brain maturation groups. Eight of 10 (80%) infants with preoperative brain injury had a Total Maturation Score ≤12 compared to 4 of 9 (44%) infants without preoperative brain injury (odds ratio 5, 95% confidence interval 0.6553, 38.1532, P = 0.109).

The postmenstrual age for control infants at MRI was statistically equivalent within a 10% margin to CHD with brain injury, CHD infants without brain injury, and CHD infants overall at the time of the preoperative brain MRI. Control infants showed higher fractional anisotropy values in the splenium of the corpus callosum, posterior limb of the internal capsule, the corticospinal tracts, and the optic radiations compared to all CHD infants (P <0.05, corrected). When CHD infants were grouped by preoperative brain injury status, infants with brain injury had widespread areas of lower fractional anisotropy values in the white matter tracts compared to controls, however CHD infants without brain injury had more limited areas of lower fractional anisotropy compared to control infants.

DISCUSSION

This pilot study demonstrates the usefulness of the quantitative MRI technique of DTI with tract-based spatial statistics as a way to thoroughly evaluate the white matter in newborns with CHD and is the first study, to our knowledge, in this population. This technique is better able to detect white matter changes, which may have been missed using DTI with region of interest analysis and changes that are not seen with conventional brain MRI. The study found that fractional anisotropy values in CHD newborns with preoperative brain injury were lower in many major white matter tracts compared to CHD newborns without preoperative brain injury and compared to control infants. Given that much of the injury seen in these infants was small and focal; these findings demonstrate that the distribution of white matter changes are more extensive than is appreciated based on conventional imaging. It can therefore be hypothesized that infants with small focal areas of brain injury by conventional brain MRI that also have multiple white matter tracts involved when imaged with DTI tract-based spatial statistics, would be at higher risk for long-term motor and cognitive/behavioral deficits.

A previous report using DTI with region of interest analysis in CHD infants found that white matter injury was observed in CHD infants compared with control infants.[15] We demonstrated the same finding using tract-based spatial statistics analysis comparing CHD infants to control infants and also showed a difference between CHD infants with and without brain injury based on conventional brain MRI. The region of interest method has been a long accepted technique for DTI analysis, but has limitations which may impact results including dependency on operator skill, need for accurate placement of measurement area, reproducibility between operators, and it is fairly time-consuming.[8] While region of interest analysis may be a sensitive method to detect white matter abnormalities, the selection of region of interest is inevitably subjective. The definition of white matter regions may vary across different observers, or even vary at different time of measurements by the same observer. On the other hand, tract-based spatial statistics can provide a non-subjective voxel-wise comparison of white matter in the whole brain.[18] Therefore, DTI with tract-based spatial statistics analysis may be a more sensitive MRI tool to thoroughly assess the white matter in at risk newborns, since conventional MRI may underestimate the amount of affected white matter, and tract-based spatial statistics is more objective than the region of interest approach.

The cause of early brain injury in CHD newborns is multi-factorial making it difficult to identify a single reason for a particular infant. Potential risk factors include genetics, birth weight, CHD type, prenatal cerebral blood flow, hypoxemia, and demographics.[27] Brain injury in newborns with CHD is similar to preterm newborn brain injury, with injury to the white matter a prominent injury type. CHD newborns also may have relative brain immaturity.[1, 2] Tract-based spatial statistics has been successfully used in several studies of brain injury in preterm newborns and also in newborns with encephalopathy.[12, 19, 20, 28] Newborns with CHD may have chronic hypoxemia and poor tolerance to changes at birth with some degree of neonatal encephalopathy.[29] In our study infants, Apgar scores were lower in those with preoperative brain injury compared to those without preoperative brain injury (Table 1). In a DTI study using tract-based spatial statistics in preterm newborns with

CHD, widespread microstructural changes were found in the white matter tracts compared to term newborns without CHD.[30] The finding that fractional anisotropy values were higher in all major areas postoperatively, mean of 18(13) days from preoperative MRI, showed that the technique used to analyze the data worked well.[31] It was expected that there would be an increase in fractional anisotropy values from the preoperative to the postoperative periods as the brain matures. This study was not able to determine if the increase in fractional anisotropy from the preoperative to the postoperative brain MRI was less in infants with preoperative brain injury compared to infants without preoperative brain injury. Based on a similar study evaluating maturation of the pyramidal tracts in newborns with CHD, lower fractional anisotropy postoperatively may be expected in infants with preoperative brain injury.[16]

Brain maturity using the validated Total Maturation Score in our study infants, mean of 11.95(1.72) correlating with a postmenstrual age of 38–39 weeks, was similar to other studies of CHD newborns.[1, 2, 23] Our study found a difference in fractional anisotropy values between infants with Total Maturation Score ≤12 vs. Total Maturation Score >12, but, due to low sample size, lacked sufficient power to survive correction for multiple comparisons. This difference, therefore, may simply be due to a slight age difference, but does confirm that the maturation scoring system is reliable as fractional anisotropy values increased with increasing brain maturity. This study is limited by the small sample size and that not every infant was able to have postoperative brain MRI. Two infants who had preoperative brain injury did not have postoperative MRI. One was discharged soon postoperatively and was unable to have MRI scheduled prior to discharge, and the other infant died postoperatively and was not ever stable enough for the postoperative research MRI. An additional infant had postoperative brain MRI, but the DTI dataset was not able to be analyzed. This may explain the loss of significance in the fractional anisotropy values between the brain injury and no brain injury groups at the time of the postoperative brain MRI. MRIs also occurred at slightly different postnatal ages since the timing was dependent upon the surgery date and postoperatively, was dependent upon the infants' clinical stability. Importantly though, compared groups were equivalent for postmenstrual age at MRI since fractional anisotropy values increase with age.

The quantitative brain MRI technique of DTI tract-based spatial statistics in newborns with CHD offers a detailed insight into brain white matter changes. Brain injury, even small focal changes in the white matter, may be associated with more diffuse changes to the brains' white mater tracts. These findings can be used to predict long-term neurodevelopmental outcome. Larger studies evaluating how CHD in newborns with and without brain injury affects the developing white matter, using specialized MRI techniques such as DTI with tract-based spatial statistics analysis, are needed to determine how these tools can best be used clinically and for research.

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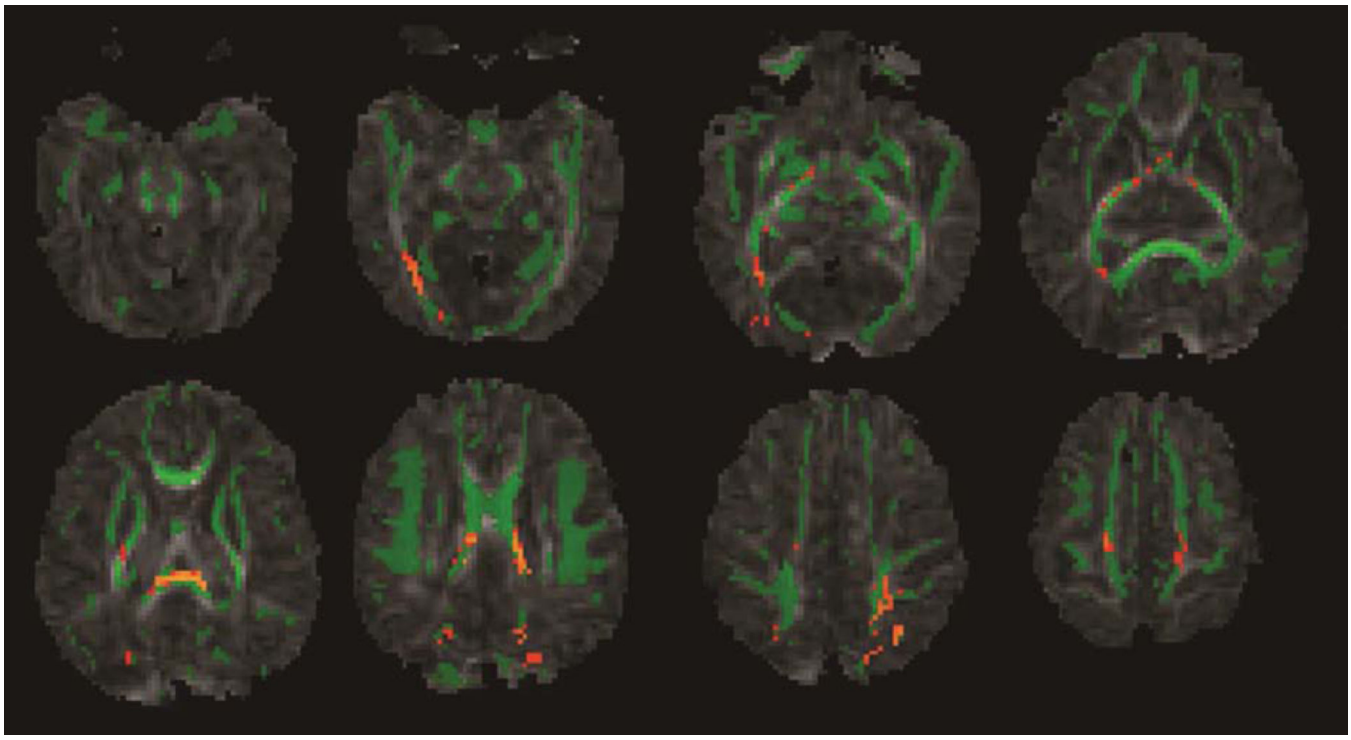

Figure 1.

Mean fractional anisotropy skeleton (green) of 19 CHD infants overlaid on fractional anisotropy maps from preoperative brain MRIs. Yellow/orange color represents brain regions with lower fractional anisotropy values (P <0.05, corrected) in CHD infants with preoperative brain injury compared to CHD infants without preoperative brain injury.

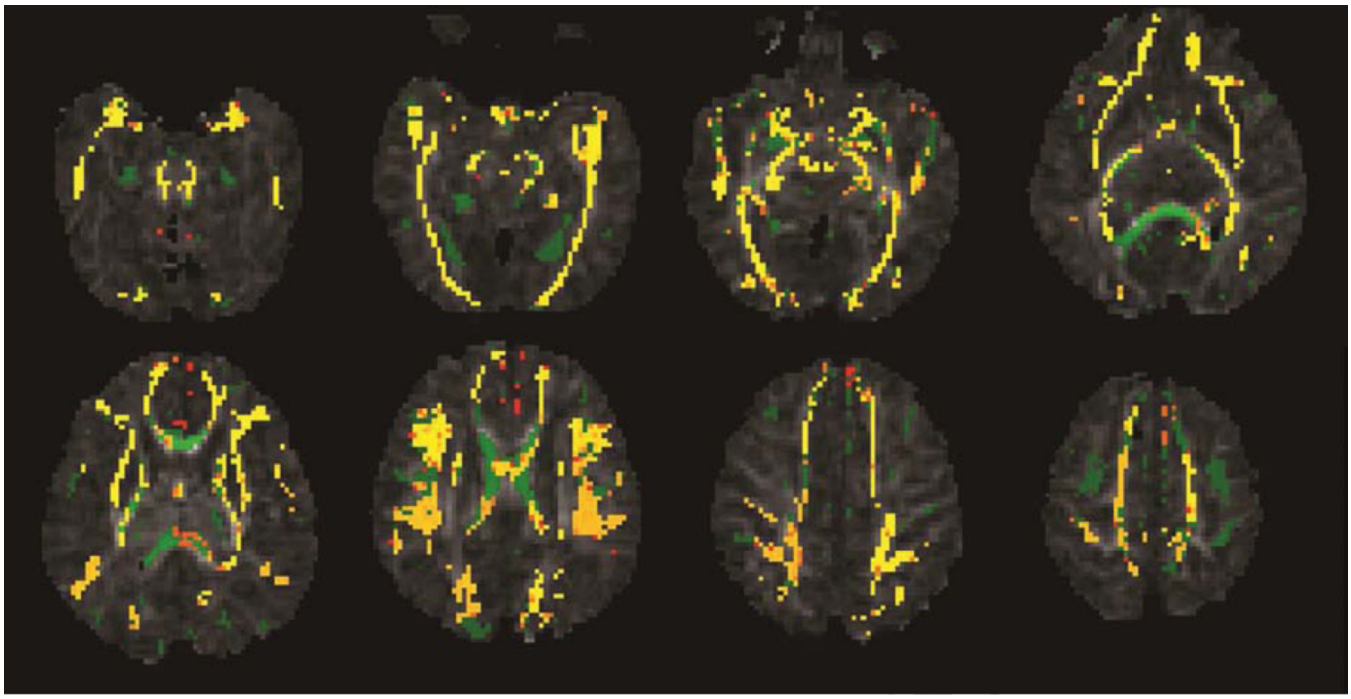

Figure 2.

Mean fractional anisotropy skeleton (green) of 16 CHD infants overlaid on fractional anisotropy maps. Yellow/orange color represents regions with lower fractional anisotropy values (P <0.05, corrected) in the preoperative MRI compared to the postoperative MRI. Almost all major white matter tracts had increased fractional anisotropy values by the time of the postoperative brain MRI.

Table 1

Characteristics of Study Infants by Preoperative Brain Injury

	n †	No Brain Injury* *n* = 9	Brain Injury* *n* = 10	Combined* *n* = 19	Equivalence§
Birth gestational age (weeks)	19	38 **39** 39	37 **37** 38	37 **38** 39	E
Birth weight (grams)	19	3076 **3418** 3460	2663 **3192** 3494	2769 **3360** 3488	NE
Apgar Score 1-min	19	8 **8** 9	4.5 **7** 7	7 **8** 8	NE
Apgar Score 5-min	19	8 **9** 9	7.2 **8** 8	8 **8** 9	NE
Age at MRI 1 (days)‡	19	6 **8** 13	6 **7** 8	6 **8** 10.5	NE
Postmenstrual age MRI 1 (weeks)	19	39.71 **39.86** 40.14	37.75 **38.50** 40.00	38.50 **39.71** 40.21	E
Age at Surgery (days)	19	6.0 **8.0** 13.0	8.0 **8.0** 13.8	6.0 **8.0** 13.5	NE
Age at MRI 2 (days)‡	16	18 **19** 35	26 **34** 36	18 **32** 36	NE
Postmenstrual age MRI 2 (weeks)	16	40.7 **41.6** 43.3	40.3 **42.3** 43.2	40.7 **42.1** 43.4	E
Days between MRI 1 and MRI 2‡	16	8.0 **12.0** 29.0	13.0 **27.0** 30.0	9.5 **14.5** 29.0	E

Abbreviations:
MRI = magnetic resonance imaging
E = equivalent
NE= non-equivalent
Specific notes:

* a **b** c represent the lower quartile a, the median b, and the upper quartile c for continuous variables

† *n* is the number of non–missing values

‡ MRI 1 = Preoperative brain MRI; MRI 2 = Postoperative brain MRI

§ Tests used: Equivalence testing (E = equivalent assuming a 20% margin[25, 26]; NE = non-equivalent)

Table 2

Infant CHD Type, Preoperative Brain Injury, and Neurologic Examination

Infant	CHD Type	RACHS*	Preoperative Brain Injury	Focal Infarct	White Matter Injury†	CHD MRI Injury Score‡	Preoperative Neurologic exam§
1	Hypoplastic left heart syndrome	4	Yes	MCA (left, right)	–	6	Limited
2	d-Transposition of the great arteries	3	Yes	–	Minimal	4	Limited
3	Pulmonary atresia with intact ventricular septum	3	Yes	MCA (left)	–	4	Normal
4	d-Transposition of the great arteries, double outlet right ventricle, pulmonary artery stenosis	3	Yes	ACA (right) MCA (left)	–	2	Normal
5	Tetralogy of Fallot, pulmonary artery stenosis	3	No	–	–	1	Normal
6	Coarctation of aorta	2	No	–	–	3	Normal
7	Hypoplastic left heart syndrome	3	Yes	–	Minimal	5	Normal
8	d-Transposition of the great arteries	4	No	–	–	0	Normal
9	Hypoplastic left heart syndrome, coarctation of aorta	6	No	–	–	3	Abnormal
10	d-Transposition of the great arteries	3	Yes	–	Minimal	3	Normal
11	d-Transposition of the great arteries, hypoplastic left heart syndrome	3	No	–	–	4	Limited
12	Hypoplastic left heart syndrome	3	Yes	ACA (right) MCA (right)	–	6	Abnormal
13	d-Transposition of the great arteries	4	Yes	ACA (left)	Minimal	6	Abnormal
14	d-Transposition of the great arteries	3	No	–	–	0	Abnormal
15	d-Transposition of the great arteries	4	Yes	–	Moderate	3	Normal
16	Double outlet right ventricle, pulmonary artery stenosis	3	Yes	PCA (right)	–	1	Normal
17	Hypoplastic left heart syndrome	3	No	–	–	0	Normal
18	Heterotaxy syndrome	NA	No	–	–	0	Normal
19	d-Transposition of the great arteries	3	No	–	–	0	Normal

Abbreviations:

RACHS = Risk Adjustment for Congenital Heart Surgery category[21]
ACA = anterior cerebral artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
Specific Notes:

*RACHS-1 category: A consensus-based method for CHD surgical risk. “1” is the lowest score associated with the least amount of risk of in-hospital mortality and “6” is the highest.[21] Not all surgeries for CHD have a RACHS-1 category.

† White matter injury; Minimal is less than or equal to 3 areas of T1 signal abnormality on brain MRI measuring less than 2 mm in size, Moderate is greater than 3 areas of T1 signal abnormality or the areas measure greater than 2mm but less than 5% of the hemisphere involved.[1, 4, 32]

‡ CHD MRI Injury Score: A detailed score based on conventional brain MRI for newborns with CHD in which distribution/severity of brain injury is quantified for 11 types of MRI findings. “0” represents a completely normal brain MRI.[4]

§ Neurologic examination included an assessment of level of consciousness, cranial nerves, motor strength, tone, muscle stretch reflexes, and newborn reflexes. A normal exam was complete and had normal findings in all areas for age. An abnormal exam was complete, but with at least one abnormal finding for age, and a limited exam was an examination that was performed, but was felt to not be complete due to infant’s level of sedation or medical complexity at the time of the exam.