

ORIGINAL ARTICLE

Abnormal Brain Development in Newborns with Congenital Heart Disease

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ABSTRACT

BACKGROUND

Congenital heart disease in newborns is associated with global impairment in development. We characterized brain metabolism and microstructure, as measures of brain maturation, in newborns with congenital heart disease before they underwent heart surgery.

METHODS

We studied 41 term newborns with congenital heart disease — 29 who had transposition of the great arteries and 12 who had single-ventricle physiology — with the use of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) before cardiac surgery. We calculated the ratio of *N*-acetylaspartate to choline (which increases with brain maturation), the ratio of lactate to choline (which decreases with maturation), average diffusivity (which decreases with maturation), and fractional anisotropy of white-matter tracts (which increases with maturation). We compared these findings with those in 16 control newborns of a similar gestational age.

RESULTS

As compared with control newborns, those with congenital heart disease had a decrease of 10% in the ratio of *N*-acetylaspartate to choline ($P=0.003$), an increase of 28% in the ratio of lactate to choline ($P=0.08$), an increase of 4% in average diffusivity ($P<0.001$), and a decrease of 12% in white-matter fractional anisotropy ($P<0.001$). Preoperative brain injury, as seen on MRI, was not significantly associated with findings on MRS or DTI. White-matter injury was observed in 13 newborns with congenital heart disease (32%) and in no control newborns.

CONCLUSIONS

Term newborns with congenital heart disease have widespread brain abnormalities before they undergo cardiac surgery. The imaging findings in such newborns are similar to those in premature newborns and may reflect abnormal brain development in utero.

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IN THE UNITED STATES, SEVERE CONGENITAL heart disease is a common cause of childhood morbidity, occurring in 6 to 8 infants per 1000 live births.¹ Although most forms of congenital heart disease are now amenable to early surgical repair, deficits that impair widespread neurodevelopmental domains are identified in up to half of childhood survivors: fine motor skills, visuospatial skills, and cognition, including memory, attention, and higher-order language skills.²⁻⁵ Despite the importance of these functional impairments at a public health level, the underlying basis of the deficits is largely unknown.

Although studies of brain injury in newborns with congenital heart disease have focused largely on factors related to surgery and cardiopulmonary bypass, a substantial percentage of children are found to have cognitive impairments regardless of the type of cardiopulmonary-bypass treatment.^{2,3,6} Indeed, more than half of newborns with congenital heart disease have neurologic abnormalities before surgery.⁷ Although magnetic resonance imaging (MRI) shows focal brain injuries acquired before or after heart surgery,⁸⁻¹⁰ the extent of these lesions may not account for global impairments in development that are seen later in childhood.

Advanced MRI techniques, such as magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI), now provide an unprecedented window into neonatal brain development *in vivo*. MRS measures regional brain biochemistry. Of the compounds measured by MRS, *N*-acetylaspartate and lactate are useful in assessing metabolic changes associated with brain development and injury. Levels of *N*-acetylaspartate, an acetylated amino acid found in high concentrations in neurons, increase with advancing cerebral maturity.¹¹ Although lactate levels are elevated with disturbances in the delivery of cerebral energy substrates and oxidative metabolism,¹² elevated lactate levels are observed in premature newborns in the absence of overt brain injury.¹¹ Changes in metabolite ratios are predictive of neurodevelopmental outcomes after hypoxia-ischemia — for example, higher ratios of *N*-acetylaspartate to choline and lower ratios of lactate to choline are associated with better outcomes.¹³

DTI characterizes the three-dimensional spatial distribution of water diffusion in each voxel of the MRI scan,¹⁴ providing a sensitive measure of regional brain microstructural development.

With increasing maturity, average diffusivity decreases,^{14,15} presumably owing to a decrease in water content and to the development of membranes in neuronal and glial cells, changes that restrict water diffusion.^{14,16} In gray matter of the cerebral cortex, fractional anisotropy, a measure of the directionality of water diffusion, is high early in the third trimester,^{17,18} reflecting the radial organization of the cerebral cortex, and becomes undetectable by term.^{17,18} However, fractional anisotropy increases with the maturation of white matter, particularly with the maturation of the oligodendrocyte lineage and early events of myelination.^{15,19,20}

White-matter injury is the characteristic pattern of brain injury in premature newborns.^{21,22} Yet full-term infants with congenital heart disease have a strikingly high incidence of white-matter injury.^{10,23-25} We hypothesized that this shared selective vulnerability reflects impaired brain development, possibly caused by impaired cerebral oxygen delivery *in utero*.²⁶⁻²⁸ There is increasing evidence in support of this hypothesis, particularly in newborns with two forms of congenital heart disease: transposition of the great arteries and single-ventricle physiology, especially the hypoplastic left heart syndrome. To investigate whether brain development is impaired before neonatal cardiac surgery and whether such impairment might be the basis for widespread developmental deficits in newborns with congenital heart disease, we studied a prospective cohort of term newborns with transposition of the great arteries and single-ventricle physiology, using MRI techniques to measure brain development, as represented by microstructure and metabolism, and compared these infants with a group of normal term newborns.

METHODS

PATIENTS

Between September 2001 and July 2005, we screened newborns with transposition of the great arteries or single-ventricle physiology who had been born in or transferred to the University of California, San Francisco, Children's Hospital for inclusion in our study. Neonates were excluded if their gestational age at birth was less than 36 weeks or if there was a suspected congenital infection or a genetic malformation syndrome.

We prospectively studied 16 normal term neo-

nates with the same methods, permitting direct comparison of brain development. Term newborns with no signs of perinatal illness or major malformations (e.g., congenital heart disease) were enrolled as normal control subjects through a complementary study.²⁹ All of the infants were admitted to our hospital's well-baby nursery after an examination by the attending pediatrician showed no abnormalities.

Preoperative clinical data were prospectively collected from the medical records and reviewed by a pediatric intensivist who was unaware of the neuroimaging findings.⁹ We calculated the overall severity of illness in newborns with congenital heart disease with the use of the Score for Neonatal Acute Physiology–Perinatal Extension (SNAP-PE), in which scores range from 0 to 70, with higher scores indicating a greater severity of illness.³⁰

Newborns were enrolled after their parents had provided informed written consent. The ethics review board of our institution approved the study protocol.

MRI STUDIES

Preoperatively, MRI studies were performed as soon as the baby could be safely transported to the MRI scanner with the use of a specialized MRI-compatible isolette, which included a dedicated neonatal head coil.³¹ A repeat MRI scan was obtained postoperatively in 36 of 41 newborns with congenital heart disease. No adverse events occurred with this protocol. A neuroradiologist who was unaware of all clinical information except for age and cardiac diagnosis scored each MRI scan for acquired focal, multifocal, or global changes, as reported previously.^{8,9}

THREE-DIMENSIONAL MRS IMAGING

Three-dimensional MRS imaging (MRSI) with specialized lactate editing overcomes the limitations of conventional, single-voxel MRS with the use of a point-resolved spectroscopic sequence to acquire spatially resolved MRS data over most of the brain with a spatial resolution of 1 cm³.^{32,33} The lactate-editing MRSI technique allows the detection of lactate, independent of lipid, in addition to *N*-acetylaspartate, choline, and creatine. All spectra were analyzed off-line with the use of automated routines developed by our group,^{32,34,35} with voxels (1 cm³) centered bilaterally on seven anatomical regions of gray and white matter with

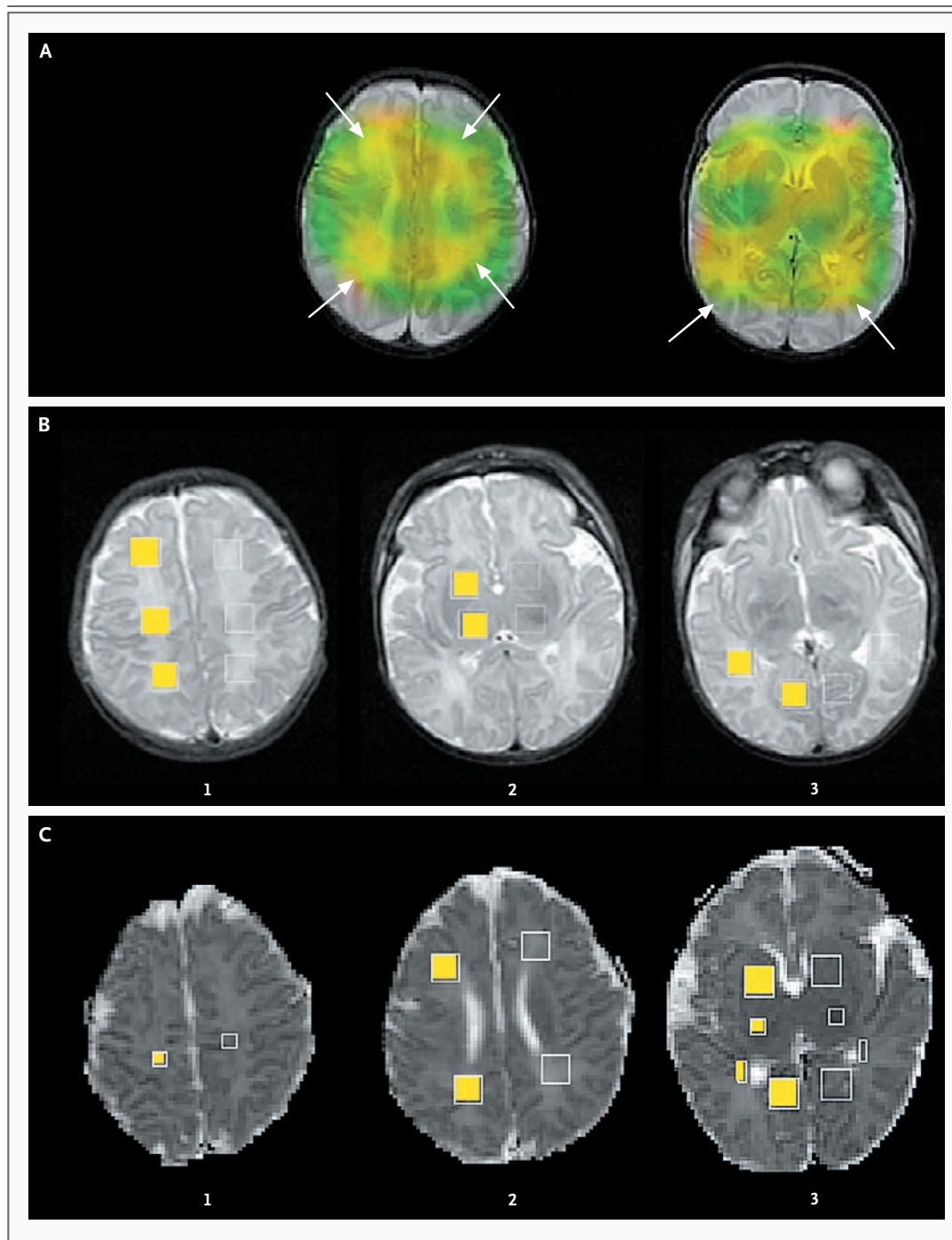
Figure 1 (facing page). Magnetic Resonance Spectroscopic Images in a Newborn with Transposition of the Great Arteries.

In Panel A, a metabolite map shows lactate (red color) laid over choline (green); more intense yellow and orange indicate a higher ratio of lactate to choline. Elevated ratios of lactate to choline are diffusely distributed but are most prominent in the periventricular white matter (arrows). In Panel B, proton spectra are measured bilaterally from the following 1-cm³ regions of interest (clear boxes) overlaid on T₂-weighted images (with yellow boxes for orientation only): frontal, periorlandic, and posterior white matter (image 1); basal ganglia and thalamus (image 2); and optic radiations and the calcarine region (image 3). In Panel C, diffusion tensor imaging shows water-diffusion measures bilaterally from the following regions of interest (measuring 5 mm × 5 mm × 3 mm unless otherwise noted): periorlandic white matter (image 1), posterior and frontal white matter (image 2), and basal ganglia, thalamus, optic radiations (3 mm × 10 mm × 3 mm), and the calcarine region.

the use of prespecified anatomical references (Fig. 1). Each voxel is reviewed to ensure an adequate ratio of signal intensity to noise (SNR), or peak height divided by noise height, with ratios reported only for voxels with a choline SNR of more than 5 (seen in all newborns with congenital heart disease and in 14 control newborns).^{32,35} Since absolute quantitation of individual metabolite concentrations is not possible with this MRSI technique, ratios of *N*-acetylaspartate and lactate to choline were calculated bilaterally in each region.

DTI

DTI was performed with the use of a sequence developed by our group specifically for neonatal brain imaging. Images were acquired in 4.8 minutes with the use of a multirepetition, single-shot echo planar sequence with six gradient directions, with a diffusion weighting of 700 seconds per square millimeter (*b* value) and an image without diffusion weighting. The sequence resulted in an in-plane resolution of 1.4 mm, as reported previously.^{17,35,36} The diffusion tensor describes an ellipsoid in space, with size, shape, and orientation given by the “maximum,” “intermediate” and “minimum” eigenvalues and their corresponding eigenvectors. The maximum eigenvalue reflects axial diffusion, such as that parallel to organized white-matter tracts. In contrast, the intermediate and minimum eigenvalues reflect radial diffusion, perpendicular to white-matter tracts. Average dif-



fusivity reflects the mean of these eigenvalues, expressed as 10^{-3} millimeters squared per second, whereas fractional anisotropy reflects their variance (higher fractional anisotropy with increasing variance).

We then generated parametric maps for average diffusivity, fractional anisotropy, and the three

eigenvalues.^{17,35-37} Average diffusivity was calculated for the same regions assessed by MRSI, with fractional anisotropy calculated from white-matter regions. Given the high spatial resolution, some regions of interest were smaller than those used for MRSI (Fig. 1) to separate white and gray matter as much as possible.³⁶

STATISTICAL ANALYSIS

We compared clinical variables in newborns with congenital heart disease and in control newborns with the use of the Mann–Whitney U test for continuous data, Cuzick’s test for ordinal variables,³⁸ and Fisher’s exact test for categorical variables, using Stata Software, version 9 (Stata). Unadjusted mean values for ratios of *N*-acetylaspartate and lactate to choline, average diffusivity, and fractional anisotropy are presented for newborns with congenital heart disease and control newborns. We used linear regression for repeated measures (generalized estimating equations) to compare ratios of *N*-acetylaspartate and lactate to choline, average diffusivity, and fractional anisotropy (as outcomes) in newborns with congenital heart disease, as compared with the values in control newborns (as predictors), accounting for multiple regions of interest in each infant and adjusting for gestational age at the time that MRI was performed.³⁹ Region-specific effects were explored by inclusion of an interaction term. We then tested the effect of cardiac lesions with the control newborns as the reference group and with infants who had transposition of the great arteries and those who had single-ventricle physiology as comparison groups.

Among newborns with congenital heart disease, we explored whether preoperative brain injury (as seen on MRI), SNAP–PE rating, or critical illness (requiring mechanical ventilation or inotropes) predicted the ratios of *N*-acetylaspartate and lactate to choline, average diffusivity, and fractional anisotropy, using linear regression for repeated measures and adjusting for age at the time of MRI and region of interest. A log-transformed outcome variable was used in all regressions. We calculated the relative percent differences in ratios of *N*-acetylaspartate and lactate to choline, average diffusivity, and fractional anisotropy between newborns with congenital heart disease and control newborns by the exponentiation of the mean differences of the log-transformed values from the regression model.⁴⁰ All reported *P* values are two-sided and have not been adjusted for multiple testing.

RESULTS**CLINICAL CONDITION AND MRI**

Of the 58 eligible newborns with congenital heart disease, the parents of 41 infants (71%) provided

consent for participation in the study. Of these newborns, 29 had transposition of the great arteries, and 12 had single-ventricle physiology, with associated aortic-arch obstruction in 10 newborns. As compared with control newborns, those with congenital heart disease had a slightly lower gestational age at birth (median difference, approximately 3 days) (Table 1), although they underwent MRI at a similar gestational age. Newborns with congenital heart disease were also smaller in weight, length, and head circumference. Although 5-minute Apgar scores were lower in newborns with congenital heart disease, none had a score of less than 6. Although this cohort of patients by definition is cyanotic and most of the newborns required stabilization with prostaglandins and mechanical ventilation before surgery, congenital heart disease had been diagnosed prenatally in a number of the infants, none had preoperative cardiac arrest, and only a minority required inotropic support. Most of the newborns no longer required mechanical ventilation at the time that preoperative MRI was performed (Table 1).

Acquired brain injury was common in newborns with congenital heart disease (Table 2). Preoperative strokes and white-matter injuries were focal, and 11 of 13 were acute and associated with reduced water diffusion. None of the newborns had the basal nuclei or watershed patterns of injury that are characteristic of global hypoxia–ischemia in term newborns. All control newborns had normal MRI scans.

BRAIN METABOLISM AND MICROSTRUCTURE

The mean ratio of *N*-acetylaspartate to choline, averaged across all of the brain regions, was 0.60 in newborns with congenital heart disease and 0.66 in control newborns; the mean ratio of lactate to choline was 0.11 and 0.10, respectively (Table 3). In the multivariate models, newborns with congenital heart disease had a significantly lower mean ratio of *N*-acetylaspartate to choline (a reduction of 10%) than did control newborns (*P*=0.003), whereas the difference in the mean ratio of lactate to choline (an increase of 28%) was not significant (*P*=0.08) (Table 3). The percent difference in the ratio of *N*-acetylaspartate to choline, for example, reflects a difference of 10% in the adjusted mean ratio of *N*-acetylaspartate to choline in newborns with congenital heart disease (0.59), as compared with the adjusted mean value in control newborns (0.65).

Table 1. Demographic and Clinical Characteristics of the Newborns.

| Variable | Control Newborns* (N = 16) | Newborns with Congenital Heart Disease (N = 41) | P Value |
|--|-------------------------------|---|---------|
| Male sex — no. (%) | 13 (81) | 29 (71) | 0.52 |
| Cesarean delivery — no. (%) | 1 (6) | 10 (24) | 0.15 |
| Gestational age at birth — wk | | | |
| Median | 39.6 | 39.1 | 0.01 |
| Interquartile range | 39.2–40.5 | 38.2–40.0 | |
| Gestational age at preoperative MRI — wk | | | 0.13 |
| Median | 40.3 | 39.7 | |
| Interquartile range | 40.0–41.0 | 38.9–40.9 | |
| Age at preoperative MRI — days | | | 0.22 |
| Median | 7 | 5 | |
| Interquartile range | 4–9 | 3–6 | |
| Birth weight — g | | | 0.04 |
| Median | 3638 | 3300 | |
| Interquartile range | 3360–4075 | 3000–3580 | |
| Birth length — cm | | | 0.01 |
| Median | 52.0 | 50.5 | |
| Interquartile range | 51.0–54.0 | 47.5–52.5 | |
| Birth head circumference — cm | | | 0.002 |
| Median | 35.5 | 34.0 | |
| Interquartile range | 35.0–37.0 | 33.5–35.5 | |
| Apgar score at 5 minutes† | | | 0.002 |
| Median | 9 | 8 | |
| Interquartile range | 9–9 | 8–9 | |
| Resuscitation score‡ | | | 0.42 |
| Median | 2 | 2 | |
| Interquartile range | 1–2 | 1–4 | |
| SNAP–PE rating§ | | | |
| Median | — | 16 | |
| Interquartile range | — | 12–21 | |
| Heart lesion — no. (%) | — | | |
| Transposition of the great arteries | — | 29 (71) | |
| Single-ventricle physiology | — | 12 (29) | |
| Prenatal diagnosis — no. (%) | — | 7 (17) | |
| Preoperative mechanical ventilation — no. (%) | — | 30 (73) | |
| Mechanical ventilation at time of preoperative MRI — no. (%) | — | 15 (37) | |
| Inotropic support — no. (%) | — | 14 (34) | |
| Prostaglandin E ₁ — no. (%) | — | 36 (88) | |
| Cardiac arrest — no. (%) | — | 0 | |
| Balloon atrial septostomy — no. (%) | — | 19 (46) | |

* Dashes indicate that the variables either were not measured in control newborns or are conditions for which such newborns were not at risk.

† Apgar scores range from 0 to 10, with lower scores indicating a worse clinical condition.

‡ The resuscitation score is based on interventions that are administered at birth, ranging from 1 (no intervention) to 6 (endotracheal intubation and epinephrine).⁹

§ The Score for Neonatal Acute Physiology–Perinatal Extension (SNAP–PE), a measure of the overall severity of illness, ranges from 0 to 70, with higher scores indicating more severe illness.²⁹

Table 2. Classification and Timing of Injury, as Seen on MRI.*

| Type of Injury | No. of Newborns | White-Matter Injury | Stroke | Intraventricular Hemorrhage | Total with Injury |
|-------------------------------------|-----------------|---------------------|------------------|-----------------------------|-------------------|
| | | | number (percent) | | |
| Preoperative injury | | | | | |
| Transposition of the great arteries | 29 | 3 (10) | 9 (31) | 2 (7) | 12 (41) |
| Single-ventricle physiology | 12 | 1 (8) | 1 (8) | 0 | 2 (17) |
| New postoperative injury | | | | | |
| Transposition of the great arteries | 28 | 7 (25) | 0 | 0 | 7 (25) |
| Single-ventricle physiology | 8 | 2 (25) | 3 (38) | 0 | 4 (50) |
| Total no. of newborns | 41 | 13 (32) | 13 (32) | 2 (5) | 25 (61) |

* Some newborns had multiple types of injury in a single study.

Table 3. Comparison of Brain Development in Newborns with Congenital Heart Disease and in Control Newborns, as Seen on Magnetic Resonance Spectroscopic Imaging (MRSI) and Diffusion Tensor Imaging (DTI).

| Variable | Control Newborns (Unadjusted Analysis) | Newborns with Congenital Heart Disease (Unadjusted Analysis) | Adjusted Difference* % (95% CI) | P Value |
|--|--|--|------------------------------------|---------|
| MRSI | | | | |
| Mean ratio of <i>N</i> -acetylaspartate to choline | 0.66 | 0.60 | -10 (-15 to -3) | 0.003 |
| Transposition of the great arteries | | | -10 (-16 to -4) | |
| Single-ventricle physiology | | | -9 (-18 to 3) | |
| Mean ratio of lactate to choline | 0.10 | 0.11 | 28 (-3 to 68) | 0.08 |
| Transposition of the great arteries | | | 32 (0 to 77) | |
| Single-ventricle physiology | | | 17 (-16 to 62) | |
| DTI | | | | |
| Average diffusivity† | 1.28 | 1.35 | 4 (2 to 7) | <0.001 |
| Transposition of the great arteries | | | 4 (2 to 7) | |
| Single-ventricle physiology | | | 5 (2 to 8) | |
| Mean fractional anisotropy | 0.21 | 0.18 | -12 (-18 to -6) | <0.001 |
| Transposition of the great arteries | | | -11 (-16 to -5) | |
| Single-ventricle physiology | | | -14 (-19 to -7) | |

* Analyses were adjusted for gestational age at the time of MRI and for brain region. The percent differences were calculated by exponentiation of the mean differences of the log-transformed values from the regression model.⁴⁰ The values are the relative differences between newborns with congenital heart disease and control newborns. Values for each cardiac anatomical diagnosis are presented below the main effect.

† Average diffusivity is calculated as the mean of the eigenvalues.

The mean value for average diffusivity, averaged across all of the brain regions, was 1.35 in newborns with congenital heart disease and 1.28 in control newborns, and the mean value for white-matter fractional anisotropy was 0.18 in newborns with congenital heart disease and 0.21 in control newborns (Table 3). In the multivariate models, newborns with congenital heart disease had a significant increase of 4% in average diffusivity and a significant decrease of 12% in white-matter fractional anisotropy ($P < 0.001$ for both comparisons).

Although the decrease in the ratio of *N*-acetylaspartate to choline and the increase in average diffusivity in newborns with congenital heart disease, as compared with values in control newborns, were not homogeneous across regions (test for interaction, $P < 0.001$), these effects were each seen in six of seven regions (Fig. 2). The reduction in white-matter fractional anisotropy in newborns with congenital heart disease, as compared with that in control newborns, was homogeneous across regions, and the interaction was not significant ($P = 0.37$). The findings were similar when the cardiac-lesion subgroups were compared with the control newborns (Table 3).

ABNORMAL WHITE MATTER IN NEWBORNS WITH HEART DISEASE

Newborns with transposition of the great arteries and those with single-ventricle physiology had a level of fractional anisotropy that was lower than that in control newborns, a finding that was independent of white-matter region and age. This difference was associated with an increase of 6% in intermediate eigenvalues ($P = 0.001$) and an increase of 9% in minimum eigenvalues ($P < 0.001$).

EFFECT OF PREOPERATIVE BRAIN INJURY

Among newborns with congenital heart disease, the presence of preoperative brain injury, as seen on MRI, was not significantly associated with the decrease of 5% in the ratio of *N*-acetylaspartate to choline ($P = 0.13$), with the decrease of 17% in the ratio of lactate to choline ($P = 0.08$), with the increase of 2% in average diffusivity ($P = 0.10$), or with the decrease of 5% in fractional anisotropy ($P = 0.11$). When the comparison with control newborns was limited to newborns with congenital heart disease who did not have preoperative brain injury, those with congenital heart disease had a reduction of 8% in the ratio of *N*-acetylaspartate

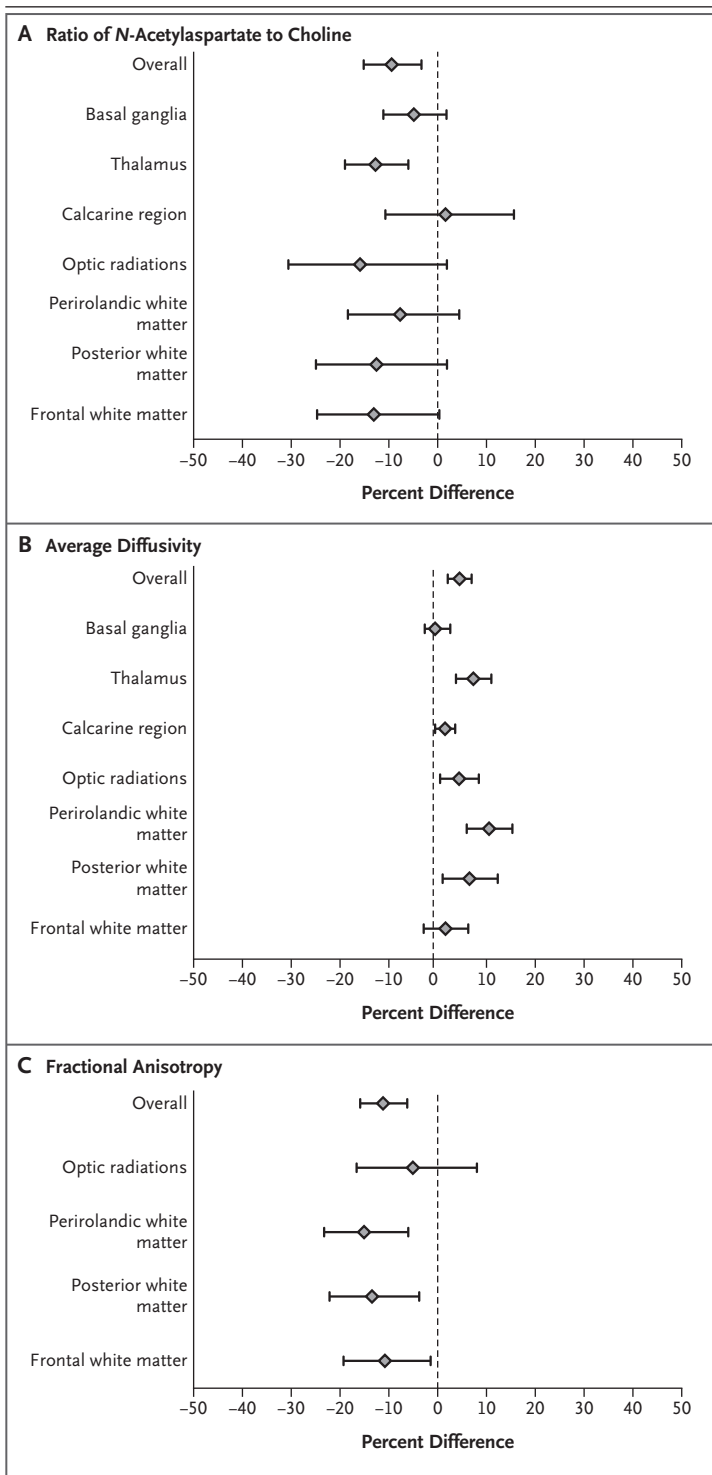


Figure 2. Differences in Ratios of *N*-Acetylaspartate to Choline, Average Diffusivity, and Fractional Anisotropy in Newborns with Congenital Heart Disease, as Compared with Control Newborns.

The mean difference, with 95% confidence intervals, is plotted for the overall effect and each region of interest.

to choline ($P=0.04$), an increase of 38% in the ratio of lactate to choline ($P=0.02$), an increase of 4% in average diffusivity ($P=0.008$), and a decrease of 10% in fractional anisotropy ($P<0.001$).

Even when regions with signal abnormalities on MRI scans or diffusion images were removed from the analysis, the pattern of differences between newborns with congenital heart disease and control newborns remained similar, with a decrease of 10% in the ratio of *N*-acetylaspartate to choline ($P=0.003$), an increase of 28% in the ratio of lactate to choline ($P=0.08$), an increase of 4% in average diffusivity ($P<0.001$), and a decrease of 11% in fractional anisotropy ($P<0.001$).

EFFECT OF PREOPERATIVE ILLNESS

Among newborns with congenital heart disease, the presence of critical illness (requiring mechanical ventilation or inotropes) was not significantly associated with an increase of 1% in the ratio of *N*-acetylaspartate to choline ($P=0.80$), a decrease of 5% in the ratio of lactate to choline ($P=0.64$), a decrease of less than 1% in average diffusivity ($P=0.90$), and an increase of 2% in fractional anisotropy ($P=0.53$). In addition, when the comparison with control newborns was limited to newborns with congenital heart disease who did not require mechanical ventilation or inotropic support, those with congenital heart disease had a decrease of 10% in the ratio of *N*-acetylaspartate to choline ($P=0.04$), an increase of 31% in the ratio of lactate to choline ($P=0.02$), an increase of 5% in average diffusivity ($P=0.008$), and a decrease of 12% in fractional anisotropy ($P<0.001$).

Increases in the SNAP-PE rating, indicating an increased severity of illness, were associated with higher ratios of lactate to choline, with an increase of 2% per unit increase in the SNAP-PE rating ($P=0.007$). In contrast, increases in SNAP-PE ratings were not significantly associated with lower ratios of *N*-acetylaspartate to choline (<1% increase per unit increase in the SNAP-PE rating, $P=0.86$), with average diffusivity (<1% increase per unit increase in the SNAP-PE rating, $P=0.10$), or with fractional anisotropy (<1% decrease per unit increase in the SNAP-PE rating, $P=0.47$).

DISCUSSION

Newborns with transposition of the great arteries and single-ventricle physiology have brain abnormalities before they undergo cardiac surgery,

as evidenced by altered brain metabolism and microstructure shortly after birth. Advanced MRI can quantify brain development and injury at a time when intervention for brain protection may be possible, allowing for incorporation of these data into the development and assessment of new clinical interventions for this population.

The discovery of abnormal brain microstructure and metabolism shortly after birth in newborns with congenital heart disease is consistent with mounting evidence that these newborns have impaired brain development in utero, possibly related to impaired cerebral oxygen and substrate delivery prenatally.²⁶⁻²⁸ In newborns with transposition of the great arteries and single-ventricle physiology, especially the hypoplastic left heart syndrome, the brain receives lower levels of oxygen-saturated blood from the right ventricle as a consequence of disordered fetal circulation.²⁸ Despite cerebral vasodilation in human fetuses with transposition of the great arteries and hypoplastic left heart syndrome,^{26,27} at autopsy, 55% of newborns with hypoplastic left heart syndrome are microcephalic, and 21% have an immature cortical mantle.⁴¹ With the increasing diagnosis of congenital heart disease in utero, methods to intervene and improve fetal circulation, such as fetal aortic valvuloplasty, are being studied.⁴² Information regarding brain maturation may be important in considering when to perform these interventions.

We identified impaired brain metabolism and microstructure in a cohort of newborns with congenital heart disease, even in the absence of visible injury on MRI and in uninvolved regions. These impairments were widespread and did not conform to the pattern of brain injury that is typical of hypoxia-ischemia in term newborns.⁴³ However, with a complex interplay between brain injury and abnormal brain development, brain injury may itself disturb brain development. Preoperative brain injury in term newborns with congenital heart disease is associated with subsequently impaired development of the corticospinal tract.⁴⁴ Data from our cohort suggest that abnormal brain development precedes surgery and some acquired injuries.

Our study was limited by a lack of comparison with other critically ill newborns who did not have heart disease. Thus, we are unable to exclude the possibility that some of the measured effects reflect changes that are generic to critically ill

newborns. The analyses examining the effects of preoperative brain injury and the severity of illness on the MRSI and DTI measures were relatively underpowered, yet they showed smaller effect sizes than those observed in comparisons of newborns with congenital heart disease with control newborns. Future improvements in MRI spatial resolution may allow for detection of specific regional differences underlying the vulnerability of newborns with congenital heart disease to white-matter injury. In addition, fetal MRI holds promise for determining the precise onset of the brain changes observed shortly after birth in such newborns.

The findings of lower ratios of *N*-acetylaspartate to choline, higher average diffusivity, and lower white-matter fractional anisotropy in newborns with congenital heart disease are similar to findings in premature newborns at an earlier age, and the MRS metabolite ratios are similar to those in premature newborns approximately 1 month before full term.^{15,32,45} The pattern of white-matter injury in premature newborns is attributed to cell populations that are vulnerable to ischemia, inflammation, and oxidative stress.⁴⁶⁻⁴⁸ Though predominant injury to neurons would be the expected response to these insults in term newborns with congenital heart disease,⁴³ white-matter injury, the pattern of injury that is typical in premature newborns, occurs frequently.^{10,23-25}

Our findings suggest that white-matter vulnerability in term newborns with congenital heart

disease is related to impaired brain development that is detected preoperatively, shortly after birth. The increase in white-matter radial diffusion (perpendicular to axon tracts) in newborns with congenital heart disease, as in premature newborns, suggests an abnormality of cells associated with axons forming white-matter tracts, such as oligodendrocyte progenitors or glia.^{19,49} The dramatic difference in brain development in newborns with congenital heart disease, as compared with other term neonates, and the pattern of brain injury suggest that new and specific neuroprotective strategies may be needed in this population. Furthermore, the state of brain maturation before cardiac surgery may influence the choice of brain protective strategy.

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