Published in final edited form as:

J Perinatol. 2009 February ; 29(2): 143–149. doi:10.1038/jp.2008.184.

Volumetric and Anatomic MRI for Hypoxic-Ischemic Encephalopathy: Relationship to Hypothermia Therapy and Neurosensory Impairments

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Abstract

Objective—To relate volumetric MRI findings to hypothermia therapy and neurosensory impairments.

Study Design—Newborns ≥ 36 weeks' gestation with hypoxic-ischemic encephalopathy who participated in the NICHD hypothermia randomized trial at our center were eligible. We determined the relationship between hypothermia treatment and usual care (control) to absolute and relative cerebral tissue volumes. Further, we correlated brain volumes with death or neurosensory impairments at 18 to 22 months.

Results—Both treatment groups were comparable before randomization. Total brain tissue volumes did not differ in relation to treatment assignment. However, relative volumes of subcortical white matter were significantly larger in hypothermia-treated than control infants. Furthermore, relative total brain volumes correlated significantly with death or neurosensory impairments. Relative volumes of the cortical gray and subcortical white matter also correlated significantly with Bayley Scales psychomotor development index.

Conclusion—Selected volumetric MRI findings correlated with hypothermia therapy and neurosensory impairments. Larger studies utilizing MRI brain volumes as a secondary outcome measure are needed.

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The authors have no conflicts of interest to disclose.

Keywords

hypoxia-ischemia, brain; hypothermia, induced; magnetic resonance imaging; cerebral palsy; outcome assessment

INTRODUCTION

Neonatal encephalopathy resulting from suspected acute hypoxic-ischemic perinatal events affects 1–2 near-term and term newborns per 1000 births in the developed world.1,2,3 Up to 40% of infants with moderate hypoxic-ischemic encephalopathy (HIE) and 100% of those with severe HIE either die or develop neurosensory impairments, including cerebral palsy, mental retardation, and deafness.4 Until recently, treatment for this disorder was primarily supportive. Randomized therapy with selective head or systemic induced hypothermia therapy has been administered to more than 700 newborns with HIE. 5,6,7,8,9,10 The National Institute of Child Health and Human Development (NICHD) whole-body hypothermia trial9, demonstrated a 28% relative reduction in death or moderate or severe disability at 18 to 22 months in hypothermia-treated infants compared with control infants. Although how hypothermia confers neuroprotection is not fully understood, hypothermia reduces cerebral metabolism, inhibits glutamate release, preserves high energy phosphates, reduces neuronal nitric oxide production, preserves endogenous antioxidants, and ameliorates apoptotic neuronal death in experimental models.11,12

Qualitative anatomic MRI studies have helped elucidate the potential short-term effects of hypothermia on the extent and pattern of cerebral injury following HIE13,14 and in predicting neurosensory disability.15,16 However, quantitative volumetric MRI – an emerging tool to assess subtle neuroanatomic treatment effects17–may provide complementary information to anatomic MRI scans by objectively assessing regional or global cerebral atrophy, a common sequelae of HIE,15,18 and improving prediction of neurosensory impairments.19,20 In this pilot investigation, we determined the feasibility and reliability of using volumetric MRI to investigate the effects of systemic hypothermia therapy on regional brain volumes for neonates with HIE and to establish whether MRI brain volumes correlate with neurosensory outcomes. We hypothesized that encephalopathic newborns randomized to whole-body hypothermia therapy8,9 will have larger total brain tissue volumes than those randomized to the usual care. We further hypothesized that total brain volumes will correlate with death or neurosensory impairments at 18 to 22 months of age.

METHODS

Subjects

All infants at our institution who were enrolled in the NICHD Neonatal Research Network whole body hypothermia trial8,9 were eligible for this substudy. All of the following criteria were required for enrollment in the trial: gestational age ≥36 weeks; NICU admission with a diagnosis of neonatal depression, asphyxia or encephalopathy; signs of acute perinatal asphyxia (cord or neonatal gas within the first hour with pH of ≤7.0 and/or base deficit of

≥16 mmol per L; if pH was between 7.01 and 7.15 or a base deficit was between 10 and 15.9 mmol per L, or a blood gas was not available, additional history of an acute perinatal event and an Apgar score at 10 minutes of ≤5 or need for assisted ventilation at birth was required); and seizures or moderate or severe encephalopathy by standardized neurological examination. Of the 24 eligible infants, 10 subjects, 5 each in the hypothermia-treatment and control (usual care) groups, were excluded: 4 because of early death (3 receiving hypothermia treatment and 1 control); 3 (all controls) because they were discharged home without receiving a brain MRI; 2 because of incomplete MRI scans (1 hypothermia-treated and 1 control); and 1 due to poor image quality resulting from significant motion artifacts (hypothermia-treated). Of the 14 infants assessed, 8 were randomized to hypothermia treatment and 6 to the control usual care arm within 6 hours after birth. Seven of the 8 infants in the hypothermia arm were systemically cooled to a core temperature of 33.5°C and one from the pilot trial8 was cooled to 34.5°C with a cooling blanket (Blanketrol II Hyper-Hypothermia System, Cincinnati Sub-Zero). Hypothermia was maintained for 72 hours at this temperature, followed by gradual re-warming over a 6-hour period (0.5°C per hour) until the core temperature reached 36.5°C. Core temperature was monitored with an esophageal probe and skin temperature with a probe placed on the abdominal wall. Infants in the control group were cared for on overhead radiant warmers and their abdominal-wall skin and esophageal temperatures recorded every 4 hours. While informed consent was obtained for each infant in the hypothermia trial, a separate institutional review board approval was obtained for this substudy.

Anatomic MRI Acquisition and Analysis

Standard anatomic MRI and diffusion-weighted images were obtained with a GE-LX or GE-Horizon 1.5 Tesla scanner (General Electric, Milwaukee, WI). Axial T2 scans (TE 85; TR 4500; slice thickness 4 mm; gap 2mm). One of the authors (EBM), blinded to clinical history and treatment assignment, interpreted all anatomic MRI scans using a modified HIE MRI scoring system based on studies by Barkovich et al21 and Mercuri et al22 (0=normal; 1=abnormal signal in either basal ganglia (putamen, caudate, and globus pallidus), thalamus, or cortex; 2=abnormal signal in cortex and either basal ganglia or thalamus; OR abnormal signal in entire cortex; 3=abnormal signal in cortex, basal ganglia and thalami; 4=abnormal signal in entire cortex, basal ganglia, and thalamus). Degree of myelination/signal intensity of the posterior limb of the internal capsule23 and presence of other abnormalities such as brain atrophy and vascular territory infract were also assessed.

Volumetric MRI Analysis

The primary anatomical references used were the Haines atlas of neuroanatomy24 Bayer and Altman atlas of human central nervous system development 25 and 2 online human atlases.26,27 Axial T2-weighted images were imported into Analyze 7.0 software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) for manual and semi-automated whole brain segmentation and volume rendering. We estimated brain volumes for the 2mm gap using Analyze. After standardization of image intensity, readily identifiable structures were manually segmented based on predefined algorithms, including pixel intensity and known spatial neuroanatomical boundaries, in the following order: brain stem, fourth ventricle, cerebellum, amygdala, corpus callosum, thalamus, lenticular nucleus,

caudate nucleus, and third ventricle (Figure 1B). The lateral ventricles, subcortical/periventricular white matter, cortical gray matter, and extra-axial CSF were segmented last using semiautomated algorithms (Figure 1C).

The ventricles, cerebellum, corpus callosum, cortical gray matter, subcortical white matter, and extra-axial CSF were identified and segmented as previously described.17 The brain stem was defined by its central location and anterior placement to the cerebellum and fourth ventricle. The amygdalae were bound by the hippocampi inferiorly, the lateral ventricles inferior-laterally, and the mamillary bodies superiorly.28,29 The thalamic nuclei were defined as anterior to the posterior commissure, floor of the lateral ventricles posteriorly, posterior limb of the internal capsule medially, and third ventricle laterally. The lenticular nuclei were bounded by the internal capsule laterally and external capsule medially. The caudate nuclei were located lateral to the anterior horn of the lateral ventricle, lateral and ventral to the anterior limb of internal capsule and anterior to the lenticular nucleus. The inferior boundaries of the caudate head began at the level of the anterior commissure and the most inferior aspect of the third ventricle.30,31

Subcortical gray matter was defined as comprising thalamic, lenticular (putamen and globus pallidum), amygdalae, and caudate nuclei. Total intracranial volume was defined as all brain tissue and CSF spaces combined. Total brain tissue volume was defined as the total intracranial volume minus all CSF spaces. One of the authors (CNG), blinded to clinical history and group treatment assignment, segmented all the MR images.

Volumetric MRI Reliability

Regional and global brain segmentation for all 14 MRI scans was repeated by the same author (CNG) a fourth time and results compared to the third iteration to determine the intraobserver correlation coefficients for all segmented brain regions. Interobserver correlation coefficients were determined by comparing segmentation performed by CNG to segmentation performed by another experienced evaluator in a separate group of 10 preterm subjects scanned at term-equivalent age utilizing the same methodology and landmark definitions.

Data Collection and Neurosensory Assessment

Research nurses using prespecified definitions and data forms collected clinical data prospectively.9 Anatomic brain MRI was recommended at 44 weeks postmenstrual age or at discharge home, whichever occurred first. Data on vision and audiometric characteristics were obtained from parental report and standardized neurologic and developmental testing were performed by trained and certified examiners blinded to intervention status at 18 to 22 months of age.9 An assessment of neuromotor disability was based on the presence of cerebral palsy, and functional disability was graded according to the Gross Motor Function Classification System (GMFCS; range 1–5)32 (level 1 includes children who walk independently with some gait abnormalities; level 5 includes those who require adult assistance to move). Cognitive outcomes were assessed by using Bayley Scales of Infant Development II.33 Moderate disability was defined as a Bayley Mental Development Index (MDI) scores 1 to 2 SD below the mean score (i.e., 70 to 84) in addition to one or more of

the following: a GMFCS grade of level 2, hearing impairment with no amplification, or a persistent seizure disorder. Severe disability was defined as any of the following: MDI score more than 2 SD below the mean score (i.e., below 70), a GMFCS grade of level 3 to 5, hearing impairment requiring hearing aids, or blindness.9

Statistical Analysis

Baseline variables known or suspected to affect the primary outcome were compared in the hypothermia-treated and control groups using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. To control for the effects of small and statistically nonsignificant group differences in head circumference and/or postmenstrual age at MRI, we also tested relative brain volumes (absolute volume divided by total intracranial volume). Therefore, all analyses examined the effect of absolute and relative regional brain volumes. Outcomes were analyzed by Fisher's exact test or the Mann-Whitney U test as appropriate. Correlations of relative brain volumes with the Bayley subscales were assessed using Spearman rank correlation (ρ). The analyses were conducted using NCSS (version NCSS 2004; NCSS, Kaysville, Utah) statistical software. Intraobserver and interobserver correlation coefficients were calculated using SPSS software (version 10.0.7; June 2000; SPSS, Inc. Chicago, IL). Multiple secondary analyses were conducted to identify significant relationships and to generate new hypotheses. A P value of <0.05 was considered significant. All reported P values are 2 sided and uncorrected for multiple comparisons.34

RESULTS

Subjects

Before randomization, the 8 hypothermia-treated infants and 6 usual care control infants were comparable with respect to important baseline variables (P = NS; Table 1). While only large differences would be statistically significant with the modest number of infants studied, with the exception of cord pH, there was no overall tendency for the hypothermia group to be lower risk than the usual care group. Median postmenstrual age at MRI scan was also comparable in hypothermia-treated infants (41.0 weeks; 95% CL: 38.6–43.3) and control infants (40.4 weeks; 95% CL: 38.7–45.9) (P=0.60). An MRI scan was performed within 10 days of life in 4 infants in the usual care and 3 in the hypothermia group.

Perinatal Variables and Total and Regional Brain Volumes

As expected, head circumference, gestational age, and postmenstrual age at MRI scan all correlated with total brain intracranial volume (correlation coefficients=0.55 to 0.67; P=0.008 to 0.05). These covariates were comparable in our two treatment groups. Potential residual scaling effects were controlled by including relative regional brain volumes in the analysis (absolute volume divided by total intracranial volume).

Hypothermia and Anatomic MRI Outcomes

Three of the eight hypothermia-treated infants and three of the six controls had abnormal anatomic brain MRIs before discharge home (P=NS). Two of the three hypothermia-treated infants with abnormal MRI scans had cortical lesions with sparing of the basal ganglia/

thalamus and the third had cortex-sparing lesions in the basal ganglia/thalamus. Among the control infants, one infant had isolated basal ganglia/thalamic lesions, one had cortical lesions only, and the third had severe lesions to the basal nuclei and cerebral cortex.

Volumetric MRI Reliability

The intraobserver correlation coefficients ranged from 0.80 to 0.83 for the amygdalae, thalamic and caudate nuclei and 0.90 to 0.99 for all the other segmented structures and tissue classes. The interobserver correlation coefficient for the lenticular nucleus was 0.88, 0.89 for the corpus callosum, and 0.93 to 1.00 for all the other segmented structures and tissue classes.

Hypothermia and Regional Brain Volumes

Table 2 presents the absolute and relative brain tissue volumes. Although hypothermia-treated infants had larger absolute total brain tissue volumes, our primary outcome, this difference was not statistically significant. There was no significant difference in relative total brain tissue volumes either. We did however observe significantly larger relative subcortical white matter volumes in hypothermia-treated infants as compared to control infants (P=0.02).

Hypothermia, MRI and Neurosensory Outcomes

Mortality and neurosensory outcome data at 18–22 months were available for all 14 infants. Bayley Scales testing however was not performed for two infants (evaluator unavailable). These two infants (one from each treatment arm) had normal hearing, vision, and motor function on standardized neurological exam. One hypothermia treated infant died after nursery discharge but before follow-up. Of the 11 infants with a complete standardized neurosensory examination (median age 19 months; 95% CL: 18–28), six were diagnosed as having severe neurosensory impairments, and the other five had mild to no impairments. In our small sample, treatment assignment did not correlate with death or moderate or severe neurosensory impairments (4 of 7 hypothermia-treated infants and 3 of 5 controls; P=NS).

Anatomic MRI findings prior to nursery discharge were strongly associated with death or neurosensory impairments: all five infants with abnormal anatomic MRI scans either died or developed severe neurosensory impairments (sixth infant with an abnormal MRI did not receive a Bayley exam); of the seven infants with normal MRI scans (eighth infant with a normal MRI did not receive a Bayley exam), five were developing normally at ≥ 18 months and two developed severe impairments (P=0.03). These two infants with a normal MRI and severe impairments were both treated with hypothermia, did not have a history of seizures, demonstrated a normal standardized neurological exam at discharge and normal clinical anatomic MRI readings as well. One of these MRI scans was performed at 21 days of life and the second at 5 days of life (122 hours post-birth). In the latter of these two cases, diffusion weighted images did demonstrate restricted diffusion in the left occipital periventricular white matter, however no signal changes were evident on T1 or T2 weighted scans. At 18–22 months, both these infants had a normal motor exam and PDI score at 2 years of age, but Bayley MDI scores two standard deviations below the mean (<70). Overall,

anatomic MRI findings did not significantly correlate with Bayley MDI (P=0.18) or PDI scores (P=0.21).

Relative total brain tissue volumes were significantly associated with death or neurosensory impairments (P=0.048). Similarly, relative total CSF volumes also correlated with such adverse outcomes (P=0.048). However, there was no relationship between absolute total brain tissue volumes or total CSF volumes and adverse outcomes. Neither absolute or relative subcortical white matter nor cortical gray matter significantly correlated with death or disability (P=NS). Relative cortical gray matter and subcortical white matter combined volume showed a nonsignificant trend toward correlation with death or neurologic disability (P=0.11). No other cerebral regions correlated with death or neurosensory disability. The two hypothermia infants with a normal anatomic MRI that developed severe cognitive delays had absolute and relative total brain tissue volumes close to the median for the hypothermia group.

Last, we observed a significant correlation between relative cortical gray matter and subcortical white matter combined volume and Bayley PDI (ρ=0.69; P=0.02). No significant relationship existed between relative cortical gray matter and subcortical white matter combined volume and Bayley MDI (ρ=0.36; P=0.28). Similarly, relative volumes of total brain tissue did not significantly correlate with PDI (ρ=0.51; P=0.11) or MDI scores (ρ=0.43; P=0.19). None of the other regional volumes correlated with Bayley II MDI or PDI scores.

DISCUSSION

In a single center substudy of the NICHD randomized controlled trial of systemic hypothermia, we demonstrated the feasibility and reliability of measuring regional brain volumes in infants with HIE. We did not observe significantly larger total brain tissue volumes in infants randomized to hypothermia as compared to usual care. Except for subcortical white matter, hypothermia was not associated with significantly larger absolute or relative volumes in the multiple regions assessed. This absence of differences may reflect the small sample size or multiple small baseline differences between the groups favoring the usual care group. Alternatively, systemic hypothermia may exert beneficial effects primarily through preservation of subcortical/periventicular white matter, a vulnerable region that is often injured in infants with HIE. We also observed a significant correlation between qualitative and quantitative measure of brain injury on MRI and death or neurosensory impairments at ≥ 18 months of age. While volumetric MRI did not appear to provide an incremental benefit over anatomic MRI in prediction of neurosensory impairments, our study lacked the power to detect smaller differences in diagnosis. Additionally, because half of the subjects had their MRI scans within 10 days post-birth, we may not have captured the full extent of the cerebral atrophy that follows perinatal hypoxia-ischemia.15,18

To our knowledge, this is the first study to use volumetric brain MRI to assess the effect of hypothermia therapy on regional and global cerebral volumes in term infants with HIE and to correlate such volumes with their neurosensory impairments. Volumetric MRI may yield information complementary to that of qualitative MRI and volumetric sequences can be

readily incorporated into routinely performed anatomic MRI scans. Moreover, because brain volumes are a continuous outcome measure, significant group differences can be readily detected, even with small sample sizes. For these reasons, investigators should consider including volumetric analyses along with qualitative MRI assessments. We were able to reliably segment not only the three major tissue classes but also smaller subcortical structures commonly involved in hypoxic-ischemic injury. Atrophy and cellular loss, an important pathologic feature of cerebral injury following hypoxia-ischemia,15,35 can be more objectively assessed using 3-dimensional quantitative analyses than with qualitative assessments using conventional MRI.

We were able to measure brain volumes using the existing NICHD hypothermia study anatomic brain MRI data and commercially available segmentation software. While this type of analysis can be performed on regular T_2-weighted MRI scans, ideally spoiled gradient thin isotropic contiguous slices are required to accurately assess brain volumes for smaller structures. Because the anatomic MRI scans we analyzed were performed with a 2 mm gap, brain volumes for this gap were estimated using the Analyze software. While this should have adequately compensated for the slice gap for larger structures and tissue classes, the reliability of volume measurements for smaller structures may not be as robust. This limitation may have masked true differences in volumes for vulnerable structures such as the lenticular nucleus and thalamus. Furthermore, our small sample size lacked the power to detect smaller yet meaningful differences in volumes. However, because the primary intervention was randomized, our findings are not subject to some of the limitations inherent in observational studies.

Unlike Inder and colleagues,13 we observed selective neuroprotection of the subcortical white matter rather than cortical gray matter after systemic hypothermia therapy. Their study13 also observed more frequent isolated basal ganglia injury in hypothermia-treated infants than in controls. In contrast, Rutherford and colleagues14 in an observational study, reported significantly fewer lesions in the basal ganglia and thalamus after whole-body or selective head cooling than in unmatched controls with HIE. In our small randomized study, we observed no qualitative or quantitative differences in basal nuclei injury. Similar but larger quantitative studies, including volumetric MRI and diffusion tensor imaging, performed at discharge and at neurodevelopmental follow-up are required to delineate the regional effects of hypothermia therapy.

As in several previous HIE studies,15,16 we observed a strong relationship between structural lesions detected by anatomic MRI and neurosensory impairments at ≥ 18 months of age. Similarly, total brain tissue volume correlated with this important adverse outcome. Relative cortical gray matter and subcortical white matter combined volumes also correlated significantly with Bayley PDI scores. To our knowledge, only one other study has correlated in vivo brain volumes, as measured by volumetric MRI at term equivalent age, with neurosensory outcomes at ≥ 18 months of age.20 That pilot investigation of preterm infants and term controls demonstrated a significant correlation between several hemispheric white and cortical gray matter regional volumes with Bayley MDI and PDI scores. One larger cohort study related brain volumes in preterm infants to object working memory at 2 years but not motor or sensory impairments as in our study.36 Our study provides preliminary

evidence that volumetric MRI is also a significant predictor of neurosensory outcomes in term infants with HIE. Advanced quantitative MR imaging is emerging as a valid tool to assess the short-term neurologic effects of neonatal interventions17 and facilitate prediction of neurosensory outcomes.

CONCLUSIONS

In a single-center, substudy of the NICHD randomized whole-body hypothermia trial, we demonstrated that volumetric brain MRI is a feasible and reliable surrogate measure predictive of neurosensory impairments. Larger multi-center studies are needed to fully reveal the potential benefits and limitations of volumetric MRI for assessing the effects of neuroprotective interventions for infants with HIE. In centers where it is feasible to reliably assess quantitative MRI, we recommend that future randomized trials of neuroprotection assess in vivo brain volumes as a secondary outcome measure in all or a representative sample of treated infants.

Acknowledgements

This work was supported in part by National Institutes of Health grant 5K23NS048152 to Nehal Parikh. We thank the NICHD Neonatal Research Network for access to hypothermia study data.

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Figure 1. Panel A

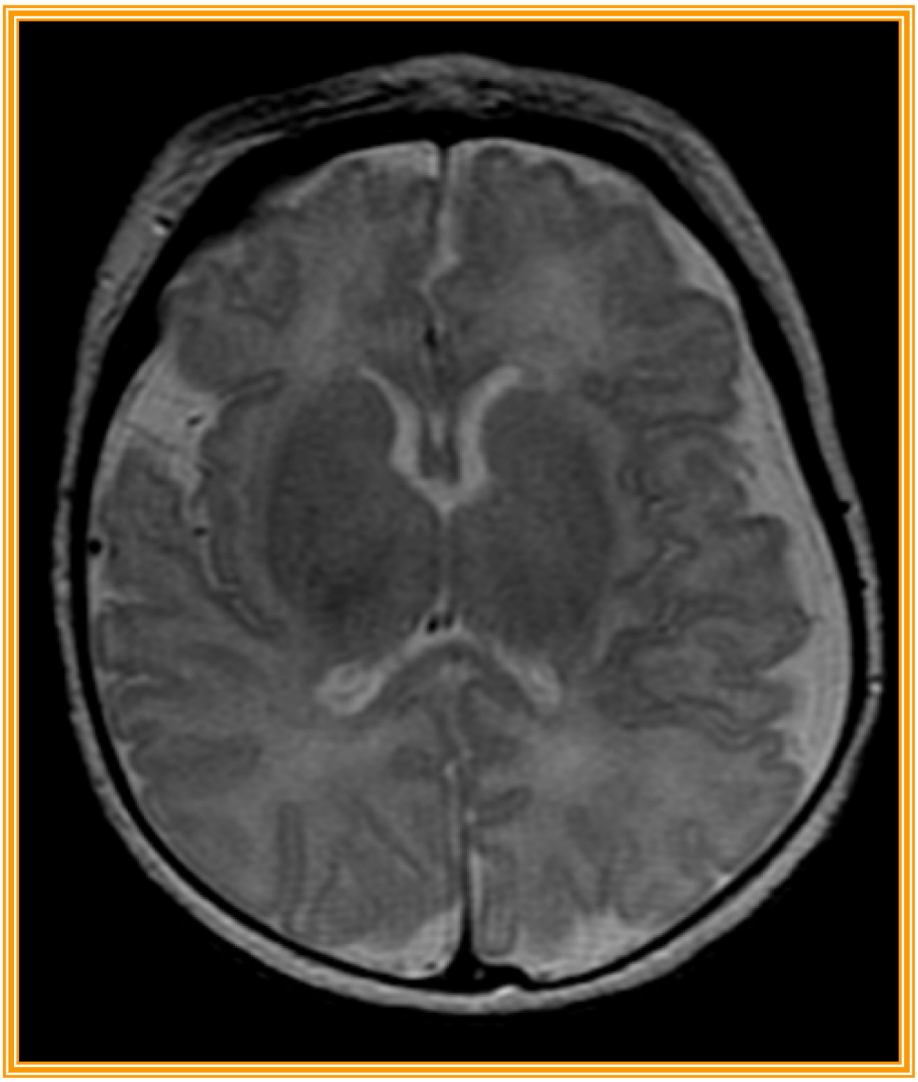

Figure 1. Panel B

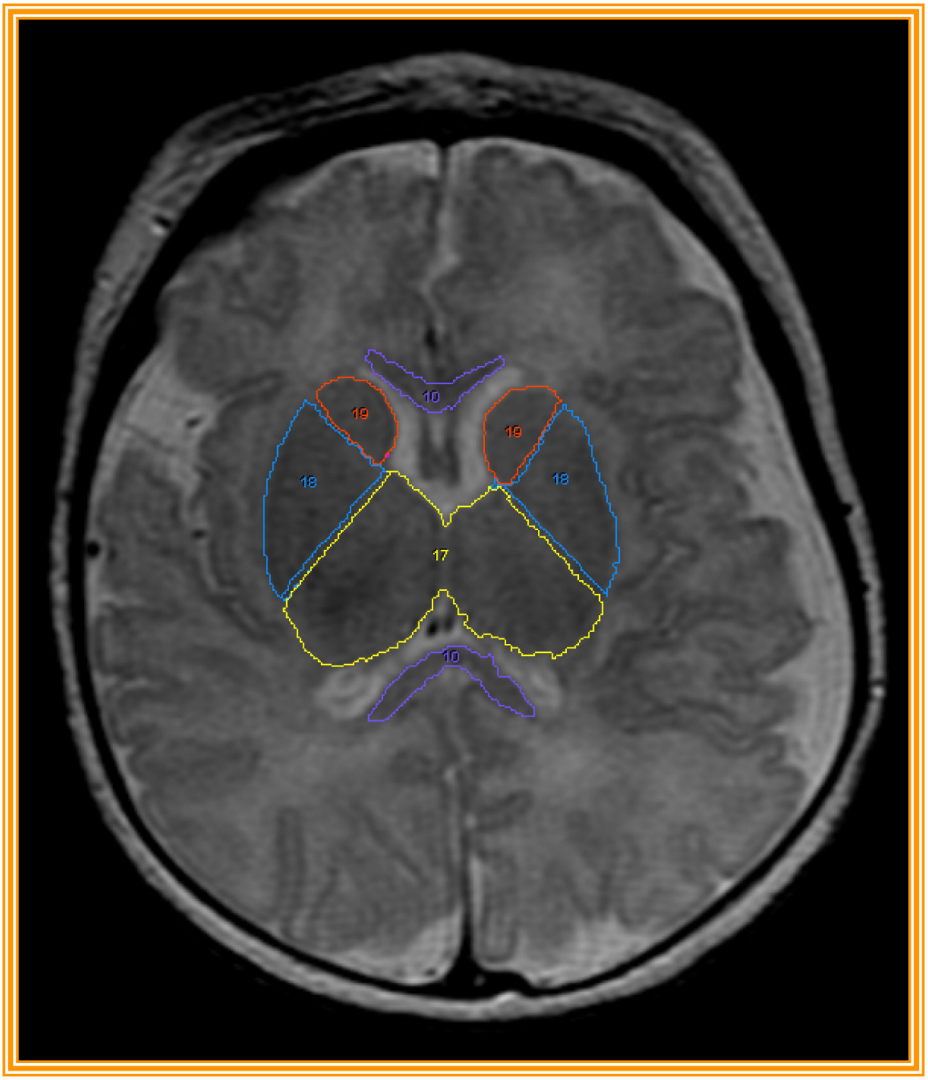

Figure 1. Panel C

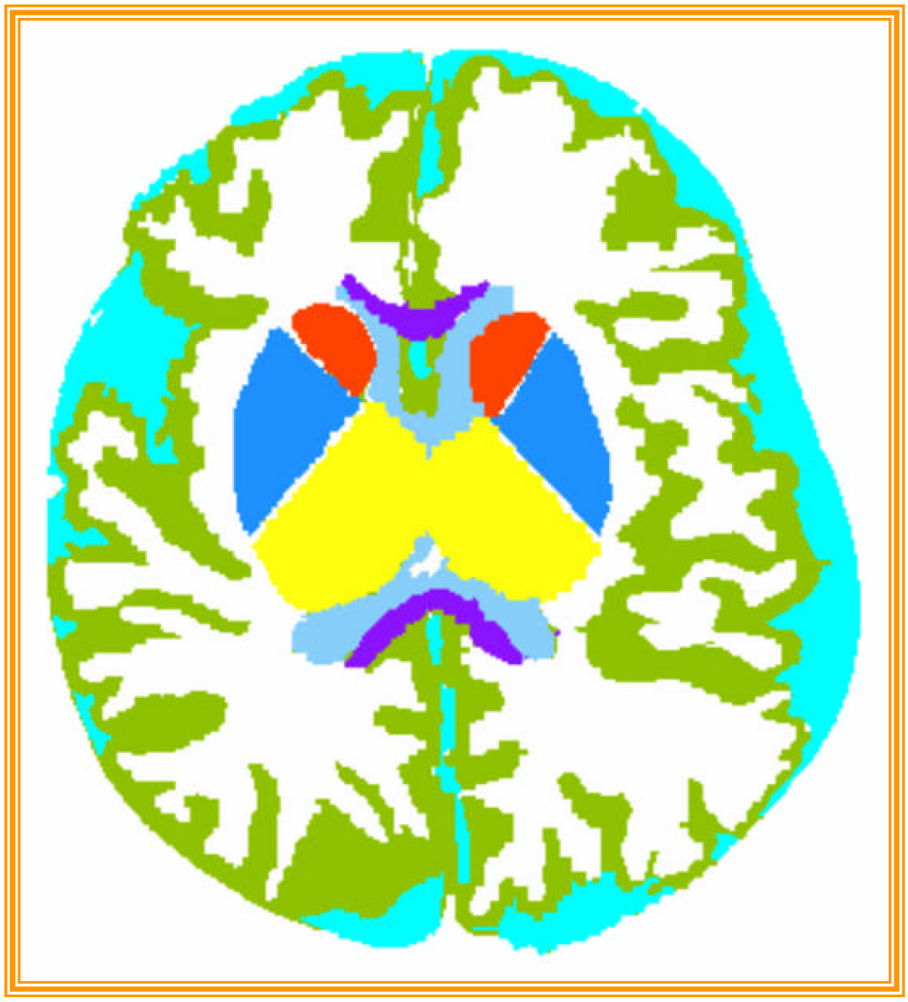

FIGURE 1. Representative example of brain volume segmentation and labeling methodology for an axial T2-weighted brain MRI

A. Unsegmented T2- weighted mid-brain MRI slice.

B. Manual segmentation and labeling of smaller subcortical structures: 10-corpus callosum; 17-thalamus; 18-lenticular nucleus; 19-caudate nucleus

C. Fully segmented mid-axial slice. Representative pixels were individually sampled from the lateral ventricles (light blue), subcortical white matter (white), and cortical gray matter (green) and segmented using a semi-automatic segmentation tool. Extra-axial CSF (cyan) spaces were sampled and labeled last, based on location and clear regional intensity differences.

TABLE 1

Baseline Characteristics of Hypothermia-Treated and Usual Care Control Infants

Variables	Hypothermia-Treated (N = 8)	Controls (N = 6)
Gestational age, wk*	38.5 (36 – 40)	39.5 (37 – 41)
Birth weight, g*	3288 (2775 – 3850)	3415 (2385 – 4885)
Head circumference, cm*	34.3 (32.5 – 35.5)	35.0 (33.0 – 37.0)
Male, n (%)	5 (63%)	3 (50%)
Non-Caucasian, n (%)	7 (88%)	6 (100%)
Chest compressions at birth	4 (50%)	1 (17%)
Resuscitation at 10 minutes	6 (75%)	4 (67%)
Apgar score (5 min)*	3 (0 – 6)	3.5 (1 – 5)
Apgar score (10 min)*	4 (0 – 5)	5 (3 – 7)
Cord pH*	6.96 (6.57 –7.25)	6.77 (6.63 – 7.18)
Outborn	3 (38%)	1 (17%)
Moderate encephalopathy, n (%)	6 (75%)	5 (83%)
Severe encephalopathy, n (%)	2 (25%)	1 (17%)

*Median and 95% CL

TABLE 2

Absolute and Relative Brain Tissue Volumes (Median and 95% CL) in Hypothermia-Treated and Control Infants

Tissue Class	Hypothermia-Treated (N=8)	Control (N=6)	*P* Value
Total brain tissue, total			
Absolute volume, mL	373.1 (314.0 – 396.5)	348.1 (216.2 – 448.6)	0.34
Relative volume, %	84.3 (78.1 – 87.4)	84.2 (46.8 – 89.8)	0.85
Subcortical white matter			
Absolute volume, mL	152.7 (119.3 – 173.0)	134.8 (119.4 – 188.8)	0.18
Relative volume, %	35.2 (33.2 – 36.6)	33.5 (29.6 – 34.9)	0.02
Cortical gray matter			
Absolute volume, mL	157.7 (146.1 – 170.3)	163.4 (27.4 – 190.2)	0.45
Relative volume, %	35.9 (32.5 – 40.4)	39.2 (5.9 – 43.7)	0.57
Subcortical gray matter*			
Absolute volume, mL	18.7 (16.4 – 22.3)	18.0 (12.4–25.5)	0.75
Relative volume, %	4.2 (4.0 – 5.0)	4.5 (2.7 – 5.3)	0.66
Corpus callosum			
Absolute volume, mL	1.0 (0.6–1.6)	1.0 (0.2 – 1.9)	0.75
Relative volume, %	0.2 (0.1 – 0.4)	0.2 (0.1 – 0.5)	0.95
Brain stem			
Absolute volume, mL	8.3 (6.3 – 8.6)	7.8 (7.2 – 9.3)	0.85
Relative volume, %	1.8 (1.5 – 2.0)	1.9 (1.6 – 2.2)	0.75
Cerebellum			
Absolute volume, mL	25.2 (18.4 – 27.5)	25.5 (21.5 – 34.1)	0.85
Relative volume, %	5.8 (4.9 – 6.1)	6.1 (5.4 – 6.3)	0.14
Total cerebrospinal fluid			
Absolute volume, mL	67.4 (45.2 – 89.5)	66.8 (39.4 – 245.7)	0.95
Relative volume, %	15.7 (12.2 – 19.1)	15.8 (10.2 – 53.2)	0.85
Total intracranial volume			
Absolute volume, mL	437.3 (359.2 – 486.0)	419.5 (357.4 – 562.2)	0.66

*Comprising caudate, amygdalae, thalamic, and lenticular nuclei