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Quantitative Cranial Magnetic Resonance Imaging in Neonatal Hypoxic-Ischemic Encephalopathy

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Abstract

The volume of acute injury detected by diffusion-weighted imaging and quantitative brain growth on serial cranial magnetic resonance imaging was not previously used to predict neurodevelopmental outcomes in infants with neonatal hypoxic-ischemic encephalopathy treated with head cooling. Our longitudinal study involved 16 head-cooled term infants with hypoxic-ischemic encephalopathy who underwent early and follow-up cranial magnetic resonance imaging and follow-up neurologic evaluations, out of 105 infants who received therapeutic hypothermia. The volume of acute injury was measured on initial cranial magnetic resonance imaging, using diffusion-weighted images. Total brain volumes were measured in both early and follow-up magnetic resonance imaging studies. Acute injury volume in the corpus callosum $>0.5 \text{ cm}^3$ was associated with developing epilepsy (odds ratio, 20; 95% confidence interval, 1.01-1059.6; $P=0.013$). Follow-up whole brain volume was reduced in those with unfavorable outcomes (i.e., epilepsy, cerebral palsy, and delayed developmental milestones), compared with infants without all three outcomes. Although acute brain injury volume and brain growth measurements may be useful predictors of outcomes in neonatal hypoxic-ischemic encephalopathy, the evolution of brain injury in these infants has yet to be fully understood and should be studied prospectively.

Introduction

Neonatal hypoxic-ischemic encephalopathy occurs in 1-2 per 1000 term infants in developed countries [1,2]. Brain hypoxia and ischemia, at or around the time of birth, result in the initiation of a complex biochemical cascade leading to neuronal cell death. This hypoxic-ischemic process occurs over several hours to days, and when therapeutic hypothermia is applied within 6 hours of birth, it was demonstrated to attenuate brain injury and improve survival without severe neurodevelopmental disability [3]. Head cooling constituted the first proven therapy for the treatment of moderate neonatal hypoxic-ischemic encephalopathy, and was approved by the Food and Drug Administration in 2006.

The proper timing for initial and follow-up cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy treated with hypothermia was identified in 2005 by the National Institute of Child Health and Human Development as an important

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understudied topic [4]. Deep gray matter and watershed patterns of injury are commonly observed on cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy [5]. In a study of uncooled infants with hypoxic-ischemic encephalopathy, deep gray matter injury and a diffuse injury pattern on conventional cranial magnetic resonance imaging were strong predictors of unfavorable prognoses [6]. Diffusion-weighted imaging can also be useful in determining the extent of acute injury, because regions exhibiting restricted diffusion often develop permanent changes at the time of follow-up imaging. Studies of follow-up cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy have been performed, and the findings have been associated with neurodevelopmental outcomes. However, acute brain injury on magnetic resonance imaging in head-cooled infants has not been compared with follow-up imaging to assess brain growth [7,8].

Volumetric cranial magnetic resonance imaging is an additional tool that may improve our understanding of the impact of injury and the effects of therapeutic hypothermia on the developing brain. Quantitative cranial magnetic resonance imaging volumes have been used in preterm and term infants to describe brain development. This technique may also be useful in evaluating brain injury [9-11]. A single-center, randomized controlled trial of infants with hypoxic-ischemic encephalopathy treated with whole-body cooling demonstrated no significant difference in initial total brain volumes between cooled and noncooled infants [12]. However, a slightly larger volume of subcortical white matter in infants who received hypothermia was identified on initial cranial magnetic resonance imaging [12]. Initial brain volumes would be expected to be normal, because anatomic injury, and therefore reduced volumes on magnetic resonance imaging, take time to develop after injury. Initial or follow-up volumetric magnetic resonance imaging has not been studied in infants with hypoxic-ischemic encephalopathy treated with head cooling. Further, the quantification of acute brain injury volumes using diffusion-weighted imaging has not previously been examined, and may provide an important indicator of long-term neurodevelopmental impairment.

The objectives of this study were to: (1) demonstrate a detailed technique for measuring acute perinatal brain injury volume, using cranial magnetic resonance diffusion-weighted imaging in newborns treated with head cooling; (2) compare early and follow-up brain volumes in infants with hypoxic-ischemic encephalopathy who underwent head cooling to evaluate brain growth; and (3) examine associations between these magnetic resonance imaging findings and neurodevelopmental outcomes in newborns with hypoxic-ischemic encephalopathy treated with head cooling who received follow-up clinical evaluation. We hypothesized that quantitative measures of acute brain injury and brain growth in infants with hypoxic-ischemic encephalopathy treated with head cooling would be helpful in predicting unfavorable neurodevelopmental outcomes.

Methods

Subjects

This was a retrospective study of all infants with hypoxic-ischemic encephalopathy treated with head cooling at Arkansas Children's Hospital from 2000-2010 who had received initial cranial magnetic resonance imaging at 7 days of age, follow-up cranial magnetic resonance imaging, and a follow-up neurologic evaluation. Infants with hypoxic-ischemic encephalopathy were enrolled in the CoolCap Trial from 2000-2004 [3]. Infants born between 2004 and 2006 were enrolled in the CoolCap Continuation Trial after informed consent (all infants were cooled), and infants since December 2006 have been head-cooled with equipment approved by the Food and Drug Administration. Infants received head cooling if they were born at 36 weeks of gestational age and demonstrated at least one of

several findings: a 10-minute Apgar score 5, the continued need for resuscitation at 10 minutes after birth, acidosis within 60 minutes of birth (pH <7.00 or base deficit 16 mmol/L), evidence of moderate-to-severe encephalopathy according to physical examination or clinical seizures, and an abnormal amplitude-integrated electroencephalogram recording 1-6 hours after birth. Infants were cooled using the CoolCap device (Natus Medical, Inc., San Carlos, CA) to a rectal temperature of $34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for 72 hours, and then gradually rewarmed for 4 hours. This study received Institutional Review Board approval.

Data collected from each infant included demographics, early clinical features, the dates of the initial and follow-up cranial magnetic resonance images, and the date of most recent neurologic follow-up (with the findings of the neurologic evaluation closest to the time of the follow-up cranial magnetic resonance imaging). Infants were defined as demonstrating a "history of seizures" if they manifested seizures during their first 72 hours of age. Unfavorable neurodevelopmental outcomes were defined as the presence of epilepsy (persistent seizures, and still receiving antiepileptic drugs at the time of follow-up evaluation), cerebral palsy (abnormal motor tone), delayed developmental milestones (delay in developmental milestones for the infant's age), or any combination of these abnormalities observed during follow-up neurologic assessment. Infants who did not receive clinical follow-up cranial magnetic resonance imaging at 2 months of age and a follow-up neurologic evaluation were excluded.

Cranial Imaging

All infants underwent initial cranial magnetic resonance imaging (including diffusion-weighted imaging) using a 1.5 T scanner (General Electric Healthcare or Philips Medical Systems, Bothell, WA) as part of the usual standard of clinical care. Follow-up cranial magnetic resonance imaging was also performed using a 1.5 T scanner on infants identified as clinically in need of follow-up imaging. Pediatric neuroradiologists interpreted the cranial magnetic resonance images. The magnetic resonance imaging report in the medical record was reviewed to assess acute injury to the basal ganglia and thalamus on the initial cranial magnetic resonance imaging, and focal or global areas of cerebral atrophy or encephalomalacia on the follow-up cranial magnetic resonance imaging.

Quantitative Brain Measurement

Using the initial and follow-up clinical scans, brain measurements were performed on serial axial diffusion-weighted images (only for initial cranial magnetic resonance imaging), axial T₁ magnetic resonance images, and sagittal T₁ magnetic resonance images, using the standard clinical scanning protocol, i.e., a slice width ranging from 3.0-5.0 mm and an interslice gap from 0-2.5 mm. The quantification of cross-sectional areas on individual slices was performed using axial T₁ images that were input into a personal computer-based system as converted digital images. Images were digitized using a DT 2858 Frame Grabber (Data Translation, Wellesley, MA). Tracings and area calculations were based on the digital images of the whole brain and corpus callosum. The anatomic boundary of the corpus callosum for the tracings was previously described [13-15]. The margins of acute brain injury, corresponding to the absolute area of restricted diffusion on the axial diffusion-weighted cranial magnetic resonance images, were marked by a pediatric neurologist (S.B.M.) before tracing (Fig 1). The presence of hypointensity on apparent-diffusion coefficient images was used to verify that the regions were sustaining acute injury and not T₂ shine-through. Follow-up cranial magnetic resonance images were measured similarly, except acute injury volumes from diffusion-weighted images were not performed. Commercial image-analysis software (Image-Pro Plus, Media Cybernetics, Bethesda, MD) was used. Data from individual slices were compiled, using a customized algorithm (G.B.S.) that incorporates slice thickness, intergap size, number of slices, and external calibration

standardization to render a final volumetric estimate for each structure/space measured. Head circumference was measured during both the initial and follow-up cranial magnetic resonance images by tracing the outer border of the scalp at the level of the maximum occipital projection, using an axial T₁ magnetic resonance imaging slice. Volumetric estimates using this technique are highly reproducible [14]. The volumes of acute injury in the whole brain and corpus callosum, the whole brain volumes, and the volumes of the corpus callosum were compared between infants with and without unfavorable neurodevelopmental outcomes.

Statistical Analysis

Summary statistics were estimated for demographic and clinical data, with continuous variables summarized as means and standard deviations, and categorical data summarized as frequencies and percentages of totals. The Fisher exact test was used to estimate differences between those with and without injury in the thalamus and/or basal ganglia, and the presence of any unfavorable outcome or all three unfavorable neurodevelopmental outcomes (i.e., epilepsy, cerebral palsy, and delayed developmental milestones). Logistic regression was used to determine if any association existed between acute brain injury volume (either whole brain or corpus callosum) and any single unfavorable neurodevelopmental outcome or the presence of all three. Because of the limited sample size, exact logistic regression was used to verify statistical significance [16]. Outcome classification, using varying acute injury volume thresholds, was examined using receiver operating characteristic analysis, with the area under the receiver operating characteristic curve determining the optimal threshold for outcome discrimination [17].

To evaluate brain growth over time, a general linear model was used to estimate whole brain volume as a function of the infant's age (in days) at measurement. The general linear model accounted for the correlation inherent with repeated observations on the same infant. Moreover, restricted cubic splines were used to associate an infant's age with brain volume, thereby relaxing the strict linear relationship usually imposed by linear regression [18]. The resulting estimation accommodates the known nonlinear relationship between age and brain growth. Brain volume at follow-up magnetic resonance imaging subsequently compared the model estimation with volumes outside the 95% and 99% confidence intervals, identified as outliers within the sample. Associations between outlier follow-up volumes and the neurologic outcomes of epilepsy, cerebral palsy, and delayed developmental milestones, and between infants with and without all three unfavorable outcomes, were estimated. During estimations of changes in whole brain volume over time, one infant's follow-up findings were determined to constitute an outlier, because that infant's duration of follow-up involved more than three times the average duration of follow-up. Whereas model estimation was performed excluding the outlier observation, model prediction and subsequent outcome assessments were performed using the outlier. A sensitivity analysis, including the outlier in the model estimation, was performed, but it did not change the inference of the outcome analysis. Statistical analysis was performed using STATA, version 12.1 (STATA, College Station, TX).

Results

Sixteen of 105 (15%) infants with hypoxic-ischemic encephalopathy who received head cooling met the study inclusion criteria by undergoing both initial and clinically indicated follow-up cranial magnetic resonance images and a follow-up neurologic evaluation. Selected characteristics of the study population are presented in Table 1. Four infants (25%) demonstrated all three unfavorable neurodevelopmental outcomes, and five infants (31%) exhibited none during the follow-up neurologic evaluation (Table 1). The mean (with

standard deviation) follow-up duration was 925 days (standard deviation, 796 days; median, 556 days; interquartile range, 255-1556 days).

Initial Cranial Magnetic Resonance Imaging

The mean day of age for the initial cranial magnetic resonance imaging was 4.6 days (standard deviation, 0.8 days). Eight of 16 infants (50%) had sustained an injury to the thalamus or basal ganglia or both. In three of the four infants with all three unfavorable neurodevelopmental outcomes, injury to the basal ganglia was observed (Table 1). Thalamic injury was not associated with any outcome. Injury to the basal ganglia was associated with cerebral palsy ($P = 0.019$) and the presence of all three unfavorable neurodevelopmental outcomes ($P = 0.027$).

The mean initial whole brain volume was 395.6 cm^3 (standard deviation, 64.6 cm^3), the mean corpus callosum volume was 1.93 cm^3 (standard deviation, 0.80 cm^3), and the mean head circumference was 35.6 cm (standard deviation, 2.7 cm). Measured acute brain injury volumes and percent volumes of injury in the whole brain and corpus callosum are reported in Table 2. The percent volume injuries in the whole brain and corpus callosum were highly associated ($r^2 = 0.791$; $P < 0.001$).

Acute brain injury volume in the corpus callosum was associated with epilepsy, according to exact logistic regression (odds ratio, 24.1; $P < 0.030$), but not cerebral palsy or delayed developmental milestones. Receiver operating characteristic analysis (Table 3) determined that an injury threshold of 0.5 cm^3 achieved the best discrimination between those with and without epilepsy (area under the curve = 0.802). Using this threshold in a 2×2 cross tabulation, acute brain injury volume in the corpus callosum of $>0.5 \text{ cm}^3$ was associated with epilepsy (odds ratio, 20; 95% confidence interval, 1.01-1059.6; $P = 0.013$). Whole brain acute injury volume did not predict unfavorable neurodevelopmental outcomes.

Follow-Up Cranial Magnetic Resonance Imaging

Follow-up cranial magnetic resonance imaging was performed on mean day 286 of age (standard deviation, 224 days; median, 227 days; interquartile range, 189-306 days). Nine of 16 (56%) demonstrated focal or bilateral areas of atrophy or encephalomalacia, and four (25%) demonstrated normal follow-up cranial magnetic resonance images. Three of the four infants with all three unfavorable neurodevelopmental outcomes manifested cerebral atrophy. The mean follow-up whole brain volume was 745 cm^3 (standard deviation, 157 cm^3), the mean corpus callosum volume was 4.2 cm^3 (standard deviation, 1.9 cm^3), and the mean head circumference was 42.3 cm (standard deviation, 3.3 cm).

Whole-Brain Follow-Up Volumes And Association With Neurodevelopmental Outcomes

The estimations of whole brain volume (cm^3) and the 95% and 99% confidence intervals, based on the general linear model using restricted cubic splines, are depicted in Fig 2, along with the unfavorable neurodevelopmental outcomes during follow-up cranial magnetic resonance imaging. Infant 8, who received follow-up cranial magnetic resonance imaging on day 1072 of age and exhibited all three unfavorable neurodevelopmental outcomes, was excluded in the model estimation because of his age at follow-up cranial magnetic resonance imaging (representing an outlier), but was included in the outcome analysis. Infants with whole brain volumes below the lower 99% confidence interval boundary yielded an odds ratio of 33 to manifest all three unfavorable neurodevelopmental outcomes (95% confidence interval, 2.32-469.03; $P = 0.008$), compared with those above the lower boundary. Those infants with whole brain volumes above the upper 99% confidence interval boundary

yielded an odds ratio of 15 to manifest none of the measured outcomes (95% confidence interval, 1.21-185.46; $P = 0.029$), compared with those below the upper boundary.

The mean difference in head circumference from initial to follow-up cranial magnetic resonance imaging was 6.6 cm (standard deviation, 2.8 cm). Differences in head growth, using the measurement of head circumference, were not associated with unfavorable outcomes.

Discussion

Volumetric cranial magnetic resonance imaging provides quantitative information about brain injury, and can be used to help predict prognoses in infants with hypoxic-ischemic encephalopathy who are treated with hypothermia. We report on a detailed technique of measuring the volume of areas of acute brain injury on diffusion-weighted cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy treated with head cooling, and correlated this technique with both early and follow-up brain volumes and unfavorable neurodevelopmental outcomes. Our study produced two main conclusions of clinical importance.

First, a volume of acute brain injury in the corpus callosum of $>0.5 \text{ cm}^3$ was associated with the development of epilepsy. To our knowledge, this study is the first to report that a specific volume of injury to the corpus callosum greatly increases the risk of epilepsy in head-cooled infants with hypoxic-ischemic encephalopathy. The blood to the corpus callosum is provided mostly via the pericallosal arteries and other small arterioles, producing a fairly constant supply that is relatively resistant to ischemia compared with other brain structures. In newborn hypoxic-ischemic encephalopathy, however, a significant degree of hypoxia and ischemia appear to overcome the resistance to corpus callosum injury. Although not classically recognized as an epileptogenic structure, injury to the corpus callosum, by way of its complex brain connections, likely represents a more severe and global brain injury, thus increasing the risk for epilepsy. This idea is consistent with our observation that the percent injury in the corpus callosum in our study sample was highly associated with the percent injury in the whole brain. In a previous study of infants with hypoxic-ischemic encephalopathy treated with head cooling, 10 of 34 infants who demonstrated restricted diffusion in the corpus callosum on initial cranial magnetic resonance imaging tended to exhibit poorer neurodevelopmental outcomes and more severe encephalopathy [19]. Because our study sample included infants with hypoxic-ischemic encephalopathy who also manifested clinical indications for follow-up magnetic resonance images and neurologic assessments, our study infants represent an especially affected group of survivors at increased risk for unfavorable outcomes. Our results are consistent with a study of children with new-onset epilepsy, in whom diffusion abnormalities in the corpus callosum were observed [20]. We suggest that the corpus callosum is a vulnerable brain structure in those with epilepsy and significant amounts of brain injury after neonatal hypoxic-ischemic encephalopathy. This knowledge may help clinicians counsel families about prognoses in neonatal hypoxic-ischemic encephalopathy.

A second important finding was brain volume growth at $<99\%$ confidence interval during follow-up cranial magnetic resonance imaging. This finding was observed in infants with unfavorable neurodevelopmental outcomes, compared with brain volume at $>99\%$ confidence interval, as observed in most of our infants who did not manifest epilepsy, cerebral palsy, or delayed developmental milestones. This study is the first, to the best of our knowledge, to evaluate brain volumes on serial magnetic resonance images in infants with hypoxic-ischemic encephalopathy. Our observations of infants with reduced follow-up brain volumes more commonly developing unfavorable neurodevelopmental outcomes are

consistent with the known effects of severe brain injury on the developing brain and subsequent neurologic impairment. Reduced brain volumes at follow-up, and thus a reduced rate of cerebral growth, represent a form of cerebral atrophy, because the brain is supposed to experience substantial growth during early childhood [21]. The mean timing of follow-up cranial magnetic resonance imaging was 9.5 months, which represents a period when brain atrophy and reduced brain volumes over time after neonatal hypoxic-ischemic encephalopathy should be apparent. Although it would be ideal if early magnetic resonance imaging could predict outcomes, no specific volume or location of injury was associated with impaired follow-up whole brain volumes.

Infants who clinically seemed the most affected with all three unfavorable outcomes were also more likely to have sustained an injury to the basal ganglia ($P = 0.027$) according to initial cranial magnetic resonance imaging, and brain atrophy reported at the time of follow-up cranial magnetic resonance imaging. Our findings are consistent with those in previous studies [5,22].

The change in head circumference over time, unlike the change in brain volume, was not associated with unfavorable outcomes. This observation was surprising, because a simple free and noninvasive measurement of head circumference was not predictive of underlying brain growth. Thus, head growth, as determined by a subsequent head circumference, may be falsely reassuring.

Although all initial cranial magnetic resonance images were performed when diffusion-weighted imaging changes were evident, large variability was observed in the measured acute brain injury volumes. Diffusion-weighted images can be abnormal within hours of a hypoxic injury, and changes typically last up to 7 days. However, they may be most evident 1–4 days after an acute perinatal brain injury [23,24]. Our study, depending on the exact timing of the injury and the timing of the initial cranial magnetic resonance imaging, may have overestimated or underestimated the true volume of injury for each infant, which can be considered a limitation of our retrospective study and our method. For infants with very severe injury, in whom the signal intensity of the brain parenchyma is diffusely abnormal, the boundary between normal and abnormal signals may be hard to judge, increasing the difficulty in accurately tracing the region of acute brain injury.

Hypoxic-ischemic encephalopathy is diagnosed in newborns who at birth clinically experience asphyxia, defined as a blood pH <7.00 , along with elevated carbon dioxide and low oxygen levels. After the initial hypoxic-ischemic event, a primary energy failure causes a small amount of necrotic cell death. The subsequent secondary energy failure leads to the majority of neuronal cell death through apoptosis, when an accumulation of excitotoxins and mitochondrial failure occur. The severity of the secondary energy failure is most correlated with poor neurodevelopmental outcomes [25]. Therapeutic hypothermia works by reducing both necrotic and apoptotic cell death, preventing mitochondrial failure, and limiting the cellular toxicity produced by cytokines and excitotoxins during the period when most of the cellular death would occur [26]. The two accepted methods of therapeutic hypothermia for newborn hypoxic-ischemic encephalopathy include selective head cooling with mild systemic hypothermia (as performed at our center) and whole-body cooling [3,27]. In both methods, cooling is initiated within 6 hours of birth, and is continued for 72 hours.

This study was limited by its retrospective design and by the inclusion of the perceived sickest infants with neonatal hypoxic-ischemic encephalopathy. A small percentage of our infants cooled over the last 10 years met the inclusion criteria, despite the large number of infants treated with therapeutic hypothermia at our institution. According to our standard practice, infants undergo cranial magnetic resonance imaging after head cooling when they

are stable enough for transfer to the radiology suite, which usually occurs within the first 7 days of age. Some infants, however, were unable to undergo cranial magnetic resonance imaging within this period. After hospital discharge, infants are examined in the high-risk newborn clinic, and only infants with seizures or evidence of other neurologic conditions are followed by pediatric neurologists. Therefore, the infants in this study comprise those with a high incidence of unfavorable neurodevelopmental outcomes. Moreover, our outcome measurement was limited because the assessment in the medical record documenting epilepsy, cerebral palsy, or delayed developmental milestones by a pediatric neurologist was not standardized, and reflects an impression about the infant during follow-up evaluation. Standardized scores to document developmental delay were not obtained for all infants included in the study, so that outcome measures could not be correlated with a standard score of infant development. Follow-up cranial magnetic resonance images were also ordered at different time points. Our institution has now adopted a standard clinical practice plan for all infants with hypoxic-ischemic encephalopathy that includes a set timing for follow-up cranial magnetic resonance imaging, neurology, and neurodevelopmental assessment.

Considering these limitations, we expect that the volumes of acute brain injury in our study infants are greater than the volumes of injury in all of our 105 cooled infants, provided they were measured. Because infants with unfavorable neurodevelopmental outcomes usually exhibit larger acute brain injury volumes and would be more likely to receive pediatric neurology care, our study infants represent a clinically distinct and more severe subgroup of all infants with hypoxic-ischemic encephalopathy treated with hypothermia. Likewise, follow-up brain volumes and brain growth in our study infants were likely different in comparison with all of our cooled infants. Despite these limitations, the data produced striking preliminary findings with valuable clinical meaning.

The volumetric measurement of cranial magnetic resonance imaging appears to be a useful tool for improving the prognostic ability of routine cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy. Measuring volumes of acute brain injury is easy, and can help identify those infants at highest risk for long-term neurodevelopmental disabilities, and especially epilepsy when acute injury to the corpus callosum is evident. Reduced brain volume on follow-up magnetic resonance imaging was associated with unfavorable neurodevelopmental outcomes. Our findings support the benefits of both early and follow-up cranial magnetic resonance imaging in infants with hypoxic-ischemic encephalopathy. Future studies are needed to elucidate the most informative time to obtain cranial magnetic resonance images, assess the utility of acute brain injury volumes, and evaluate the impact of early injury on subsequent brain growth and neurodevelopmental trajectory in infants with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia, to understand the usefulness of these methods.

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Figure 1.

Axial diffusion-weighted cranial magnetic resonance image from a head-cooled infant with hypoxic-ischemic encephalopathy (study identification number 1) demonstrates the technique used to measure polygonal regions of acute brain injury (areas of restricted diffusion) on initial cranial magnetic resonance imaging and the corresponding areas in cm^2 (PG1-PG7) and the internal measurement scale (dashed arrow) using Image-Pro Plus (Media Cybernetics, Bethesda, MD).

Figure 2.

Estimated whole brain volumes and 95% and 99% confidence intervals (CI) by age at follow-up magnetic resonance imaging (MRI) are associated with the presence of none, one or two, or all three unfavorable neurodevelopmental outcomes (excluding infant 8, who demonstrated all three unfavorable outcomes).

Table 1

Characteristics of the study sample

ID	GA (weeks)	BW (g)	Male	Apgar score <3*	pH [‡]	GMI [§]	SZ	EP	CP	DD
1	38	2700	No		6.9	T	Yes	No	No	No
2	38	4236	Yes	Yes	7.3		Yes	Yes	No	Yes
3	39	2955	No	No		BG	Yes	Yes	Yes	Yes
4	40	3090	No	Yes	6.7	T	Yes	Yes	No	No
5	38	2072	Yes	Yes	6.7		Yes	Yes	No	Yes
6	41	3445	Yes	Yes	7.0		Yes	Yes	Yes	Yes
7	36	2646	No			BG and T	Yes	Yes	Yes	Yes
8	39	3350	Yes	Yes	7.1	BG and T	Yes	Yes	Yes	Yes
9	39	2900	Yes	Yes	7.0		Yes	No	Yes	Yes
10	36	3000	No	Yes	7.1		Yes	No	No	No
11	36	2310	Yes	Yes	7.0	T	No	No	No	No
12	41	3750	No	No	7.2	T	Yes	No	Yes	Yes
13	36	3185	No	No	6.9		Yes	No	No	Yes
14	38	3700	Yes	No	6.8		Yes	No	No	No
15	39	3390	Yes	Yes	7.0	BG and T	Yes	No	Yes	Yes
16	39	3093	Yes	Yes	7.4		No	No	No	No
Mean (S.D.) [‡]	38.3 (1.7)	3114 (545)	9 (56%)	10 (71%)	7.0 (0.2)	8 (50%)	14 (88%)	7 (44%)	7 (44%)	10 (63%)

Abbreviations: BG = Basal ganglia

BW = Birth weight

CP = Cerebral palsy

DD = Delayed developmental milestones

EP = Epilepsy

GA = Gestational age

GMI = Gray matter injury

ID = Study number

S.D. = Standard deviation

SZ = Seizures

T = Thalamus

* APGAR <3, refers to 5-minute Apgar score.

⁷ Mean (S.D.) or N (%) is reported.

⁸ Initial arterial pH, when available.

⁸ If absent, no gray matter injury was evident.

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Table 2
Whole brain, corpus callosum, and acute brain injury volumes

ID	DOL	Whole Brain Volume (cm ³)			Corpus Callosum Volume (cm ³)		
		Total	Injury [*]	Percent Injury [†]	Total	Injury [*]	Percent Injury [†]
1	4	444.8	47.7	10.7	2.48	0.33	13.9
2	5	436.5	88.3	20.2	0.87	0.60	69.0
3	3	350.7	5.5	1.6	2.87	0.52	18.1
4	5	410.8	131.3	32.0	1.36	1.29	94.9
5	6	308.8	16.1	5.2	2.39	1.12	46.9
6	4	478.7	227.2	47.5	1.43	1.38	96.5
7	6	348.7	0.5	0.1	1.06	0	0
8	5	463.9	31.9	6.9	1.76	0	0
9	5	358.4	0	0	1.74	0	0
10	4	332.1	19.9	6.0	1.31	0.22	16.8
11	5	270.2	5.6	2.1	1.57	0.53	33.8
12	5	437.8	97.5	22.3	0.99	0.37	37.4
13	4	343.3	0	0	2.23	0	0
14	4	437.1	0	0	3.13	0	0
15	4	472.0	0.8	0.2	2.09	0.06	2.9
16	4	436.3	0.3	0.1	3.63	0	0
Mean (S.D.)	4.6 (0.8)	395.6 (64.6)	42.0 (64.2)	9.7 (13.9)	1.93 (0.80)	0.40 (0.48)	26.9 (33.7)

Abbreviations: DOL = Day of age during magnetic resonance imaging

ID = Study number

S.D. = Standard deviation

^{*} Injury refers to volume of acute injury from diffusion-weighted cranial magnetic resonance imaging.

[†] Percent Injury refers to the volume of injury divided by the total volume for the whole brain or corpus callosum.

Table 3
Corpus callosum injury volume threshold determination for epilepsy

Corresponding ID *	Cut Point (cm ³)	Sensitivity (%)	Specificity (%)	Correctly Classified (%)	ROC	95% CI
7, 8, 9, 13, 14, and 16	0	100	0	43.75	0.500	0.500-0.500
15	0.06	71.4	44.4	56.25	0.635	0.385-0.885
10	0.22	71.4	55.6	62.50	0.635	0.385-0.885
1	0.33	71.4	66.7	68.75	0.746	0.515-0.977
12	0.37	71.4	77.8	75.00	0.746	0.515-0.977
3	0.52	71.4	88.9	81.25	0.802	0.591-1.000
11	0.53	57.1	88.9	75.00	0.730	0.504-0.956
2	0.60	57.1	100	81.25	0.786	0.588-0.984
5	1.12	42.9	100	75.00	0.714	0.516-0.912
4	1.29	28.6	100	68.75	0.643	0.462-0.824
6	1.38	14.3	100	62.50	0.571	0.431-0.711

Abbreviations: CI = Confidence interval

ID = Study number

ROC = Receiver operating characteristic curve

* For each cut point (volume of acute injury in the corpus callosum), the corresponding study ID listed is the study ID for that cut point. All study IDs in the list are greater than or equal to that specified cut point.