Early Versus Late Brain Magnetic Resonance Imaging after Neonatal Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia

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Objective To evaluate the agreement in brain injury findings between early and late magnetic resonance imaging (MRI) in newborn infants with hypoxic–ischemic encephalopathy treated with therapeutic hypothermia and to compare the ability of early vs late MRI to predict early neurodevelopmental outcomes.

Study design This was a prospective longitudinal study of 49 patients with hypoxic–ischemic encephalopathy who underwent therapeutic hypothermia and had MRI performed at both <7 and ≥7 days of age. MRIs were reviewed by an experienced neuroradiologist and assigned brain injury severity scores according to established systems. Scores for early and late MRIs were assessed for agreement using the kappa statistic. The ability of early and late MRI scores to predict death or developmental delay at 15-30 months of age was assessed by logistic regression analyses.

Results Agreement between the early and late MRI was substantial to near perfect ($k > 0.75$, $P < .001$) across MRI scoring systems. In cases of discrepant scoring, early MRI was more likely to identify severe injury when compared with late MRI. Early MRI scores were more consistently predictive of adverse outcomes compared with late MRI.

Conclusions The results of this study suggest that a single MRI performed in the first week after birth is adequate to assess brain injury and offer prognostic information in this high-risk population. *(J Pediatr 2021;232:73-9)*.

Although the introduction of therapeutic hypothermia following neonatal hypoxic–ischemic encephalopathy (HIE) has greatly reduced the risk of death and disability, nearly one-half of all newborn infants suffering from moderate-to-severe HIE still suffer from death and neurodevelopmental delay.[1-4] Methods for assessing the extent and severity of brain injury in the subacute period following therapeutic hypothermia are necessary to serve as early end points to assess therapeutic effectiveness of current and future early neuroprotective interventions, and perhaps to direct the need for additional adjuvant therapies. In addition, early and accurate predictors of later neurodevelopmental outcomes are needed to determine prognosis and counsel families appropriately after HIE.

Magnetic resonance imaging (MRI) of the brain following therapeutic hypothermia is the mainstay of assessing subacute brain injury in clinical care.[5] Severity of brain injury on MRI shows good prognostic value for early childhood neurodevelopmental outcomes.[6-12] In addition, the location and extent of MRI lesions can specify outcome phenotypes. Specifically, basal ganglia and thalamic lesions have been associated with long-term motor outcomes,[9,11,12] whereas watershed lesions have been associated with verbal and intellectual outcomes.[10] The timing of MRI of the brain, however, remains controversial.[13]

Current guidelines proposed by the American College of Obstetrics and Gynecology suggest performing 2 MRIs of the brain in the neonatal period following therapeutic hypothermia.[14] These guidelines are based on the notion that early MRI (at 1-4 days) indicates the timing of injury, but later MRI (between 7-21 days) more fully defines the extent of the injury. However, disagreement exists regarding whether both are necessary and which is more valuable in determining injury and prognosis. Although some studies suggest there is no difference between early and late MRI scans,[15] others propose that a late MRI is necessary to appropriately predict prognosis.[16] Conversely, other studies report that the early MRI shows a greater specificity for brain injury than the late MRI and is sufficient to determine prognosis.[6]

Given the absence of clear evidence on the optimal timing of MRI of the brain after neonatal HIE, the primary objective of this study was to determine the agreement between early and late MRI of the brain after therapeutic hypothermia

BSITD-III	Bayley Scales of Infant Toddler Development–3rd Edition
HIE	Hypoxic–ischemic encephalopathy
MRI	Magnetic resonance imaging
NICHD	National Institute of Child Health and Human Development

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in newborn infants with HIE. A secondary purpose was to determine whether either MRI reliably predicted outcomes at 15-30 months.

Methods

This was a prospective longitudinal cohort study performed in a level 4 neonatal intensive care unit at Children's National Hospital. Enrollment occurred from April 2012 to June 2016. Infants included in the study were eligible for and underwent therapeutic hypothermia for moderate-severe HIE according to institutional protocol. All included infants had gestational ages of at least 35 weeks, had birth weights >1800 g, and evidence of perinatal depression according to the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network protocol (including Apgar score ≤5 at 10 minutes, prolonged resuscitation [chest compressions, mechanical ventilation, intubation] at 10 minutes, or metabolic acidosis including umbilical cord or infant blood gas within the first hour after birth).[1] Moderate-severe encephalopathy was defined using the worst examination before 6 hours of life according to modified Sarnat clinical staging.[1,17] All included patients received 72 hours of hypothermia, initiated within 6 hours of birth, with a target temperature of 33.5 ± 0.5 C. Infants who underwent therapeutic hypothermia but did not have 2 MRI scans of the brain after rewarming and before hospital discharge were excluded.

MRI

MRIs of the brain were performed according to institutional protocol developed for newborn infants with suspected hypoxic–ischemic injury. All infants treated with therapeutic hypothermia were assessed by MRI as soon as possible after rewarming (target 4-6 days of age) and again at a target age of 10-12 days or discharge if earlier. Infants did not undergo MRI if deemed medically unstable by the clinical team. Infants were not scanned twice if discharged at age <7 days. All scans were performed on a 3-Tesla scanner (Discovery MR750; GE Healthcare) using a 32-channel receive-only head coil (MR Instruments, Inc). Standard anatomical sequences included 3D T1-weighted spoiled gradient recalled, double-acquisition axial FSE T2 proton density, axial T2 propeller (in cases of patient motion), axial T2-star weighted susceptibility imaging, coronal T1 fluid-attenuated inversion recovery propeller, axial pseudocontinuous arterial spin labeling, and axial 30-direction diffusion tensor imaging with generation of apparent diffusion coefficient maps off-line.

MRIs of the brain were reviewed by an experienced neuroradiologist, who assigned an individual basal ganglia, watershed, and basal ganglia/watershed score according to Barkovich et al.[9] In addition, images were scored according to the NICHD scoring system.[8] The neuroradiologist was blinded to the patient outcomes when reviewing MRI scans. For each scan, T1, T2, and apparent diffusion coefficient were reviewed for overall scoring of injury and both scoring systems were applied based on the pattern/extent of injury described for each system (ie, irrespective of sequence where signal abnormality was observed).

Neurodevelopmental Follow-Up

Surviving infants underwent clinical neurodevelopmental follow-up at 15, 21, and 30 months of age per institutional protocol. Infants were assessed with the Bayley Scales of Infant-Toddler Development-3rd Edition (BSITD-III) by a certified developmental psychologist who was blinded to neonatal brain MRI scores.[18] The BSITD-III is a scale commonly used to assess developmental progress in young children that measures cognitive, language (receptive and expressive), and motor (gross and fine motor) domains. A composite score of 100 is the normative mean, with an SD of 15. Given reports of overestimation of developmental performance with the BSITD-III, significant neurodevelopmental delay was defined as a BSITD-III cognitive composite score <85 or a motor composite score <85.[19-21] The latest available developmental assessment was used for analysis.

Statistical Analyses

Descriptive statistics included means (SDs) and medians (ranges) for continuous variables, as well as counts (percentages) for categorical data. Agreement between early and late MRI scores was assessed with the weighted kappa statistic. The ability of MRI scores to predict significant neurodevelopmental delay was assessed with logistic regression analyses. Secondary exploratory models were developed controlling for clinical confounders including encephalopathy grade (moderate vs severe), Apgar score at 5 minutes, and socioeconomic status (public vs private insurance). Models were compared using the C-statistic (area under the curve, where values close to 1 represent perfect model prediction) and Akaike information criterion (where lower values represent greater quality of the model).[22] In addition, the relationship between MRI scores and individual BSITD-III cognitive, language, and motor scores were assessed with Spearman correlation analyses. A P value < .05 was considered statistically significant. Statistical analysis was performed using SAS, 9.4 (SAS Institute).

Results

Of the 110 infants admitted for therapeutic hypothermia during the study period, 92 were enrolled. Of those enrolled in the study, 15 patients died before MRI, 26 had only 1 MRI (n = 13 early and n = 13 late), and 2 had both MRIs in the early window, leaving 49 infants who met the eligibility criteria of 2 MRIs of the brain at <7 days and ≥7 days. **Table I** (available at www.jpeds.com) shows the baseline characteristics and clinical presentation of the studied infants which was typical of infants with moderate (n = 43) and severe (n = 6) encephalopathy. These baseline and clinical characteristics, as well as the distribution of MRI severity scores, did not significantly differ from the excluded population of babies with HIE who did not undergo MRI in both windows of interest (P > .05). The

median age for the early MRI was 4 days (range 2-6) and the median age for the late MRI was 10 days (range 7-25).

Neurodevelopmental outcomes were available for 30 patients (61%) assessed at a median age of 28 months (range 13-36). Significant neurodevelopmental delay was observed in 6 (20%) patients. The patients lost to follow-up had greater birth weights and presenting pH compared with the study population with known outcomes but were otherwise similar with regards to baseline and clinical characteristics, as well as distribution of MRI severity scores ($P > .05$; Table I).

Agreement Between Early and Late MRI

Early and late basal ganglia scores demonstrated substantial agreement with k = 0.772 ($P < .001$), whereas early and late watershed and basal ganglia/watershed scores both demonstrated almost-perfect agreement with k = 0.883 ($P < .001$) and k = 0.8063 ($P < .001$), respectively. There was also substantial agreement between the early and late NICHD scores with k = 0.766 ($P < .001$).

Table II summarizes the changes that were observed between the early and late MRI scores. Although the majority demonstrated no change between serial scans, MRI scores more often decreased between the early and late scans as opposed to increasing over time, suggesting fading or pseudonormalization of injury by the second time point (Figure).

Association Between MRI Score and Neurodevelopmental Outcome

Logistic regression model results are summarized in Table III. Early and late basal ganglia and basal ganglia/watershed scores, and early NICHD MRI scores were associated with significant neurodevelopmental delay at 15-30 months of age ($P < .05$). Neither the early nor the late watershed score was significantly predictive of outcome. Evaluation of model statistics suggested that early basal ganglia, basal ganglia/watershed, and NICHD scores had area under the curves >0.8. Based on Akaike information criterion, other than late basal ganglia score, which performed slightly better than early basal ganglia score, early MRI scores were better predictors of neurodevelopmental delay than late scores. These results were similar after adjusting for clinical covariates.

The relationships between MRI scores and BSITD-III cognitive, language, and motor composite score are summarized in Table IV. Early MRI basal ganglia and basal ganglia/watershed scores as well as early and late NICHD scores were associated with cognitive scores ($P < .05$). Early MRI NICHD as well as late MRI basal ganglia and NICHD were associated with language scores ($P < .05$). None of the MRI scores were significantly associated with the continuous motor composite score.

Discussion

Lifelong injury following neonatal HIE remains a significant problem, associated with high physical, psychological, and financial burden of disease. Ongoing and future studies require outcomes that can be assessed in the neonatal period to provide early assessment of treatment effect. In addition, detailed early prognostication can help guide care following discharge and enable appropriate counseling of families. Although MRI serves as the putative subacute biomarker of brain injury in neonatal HIE, optimal timing of MRI after therapeutic hypothermia remains controversial. In this cohort, we found substantial agreement between early and late MRI across several established scoring systems. Furthermore, although both early and late MRI scans were associated with prediction of later neurodevelopmental outcomes, these data suggest that the information provided by the early MRI is sufficient, and possibly more reliable, for establishing prognosis and counseling families. Given the substantial agreement between serial MRI scans and limited evidence for additive prognostic value, the practice of serial MRI in babies with HIE may add unnecessary cost in a condition in which cost of care is known to be high.[23]

Our study evaluated agreement between early and late MRI using well-established scoring systems in 49 newborn infants with HIE treated with therapeutic hypothermia. Previously, Wintermark et al reported preliminary findings on serial MRI in 12 newborn infants with HIE treated with therapeutic hypothermia. These authors used the scoring system of Barkovich et al in infants who underwent 2-4 MRI scans in the first month after birth, and they concluded that early MRI at day 2-3 of life demonstrated injuries seen in later scans.[24] Similarly, Agut et al compared sequential MRI in a small cohort of 15 infants with HIE and found no significant differences between the early and late scans.[25] In a study of 43 infants with HIE, Boudes et al compared early MRI performed during therapeutic hypothermia, with late MRI performed after the completion of therapeutic hypothermia.[26] Although the investigators found that MRI performed during therapeutic hypothermia was sufficient to assess the extent of brain injury, performing MRI during therapeutic hypothermia has practical challenges. Skranes et al studied a cohort of 41 newborn infants with HIE treated with therapeutic hypothermia and compared early MRI (4 days) with late MRI (11 days) using different scoring methods than were used in this study.[27] Another large cohort of 89 infants with neonatal encephalopathy (including

Table II. MRI score changes between early and late scan (n = 49)

Measurements	Paired difference late – early, mean ± SD	Increase	No change	Decrease	*P* value (paired comparison)
Basal ganglia score	−0.18 ± 0.73	2.0%	85.7%	12.3%	.083
Watershed score	−0.08 ± 0.48	4.1%	87.8%	8.1%	.252
Basal ganglia/watershed score	−0.04 ± 0.71	4.1%	85.7%	10.2%	.688
NICHD score	−0.14 ± 0.94	10.2%	75.5%	14.3%	.290

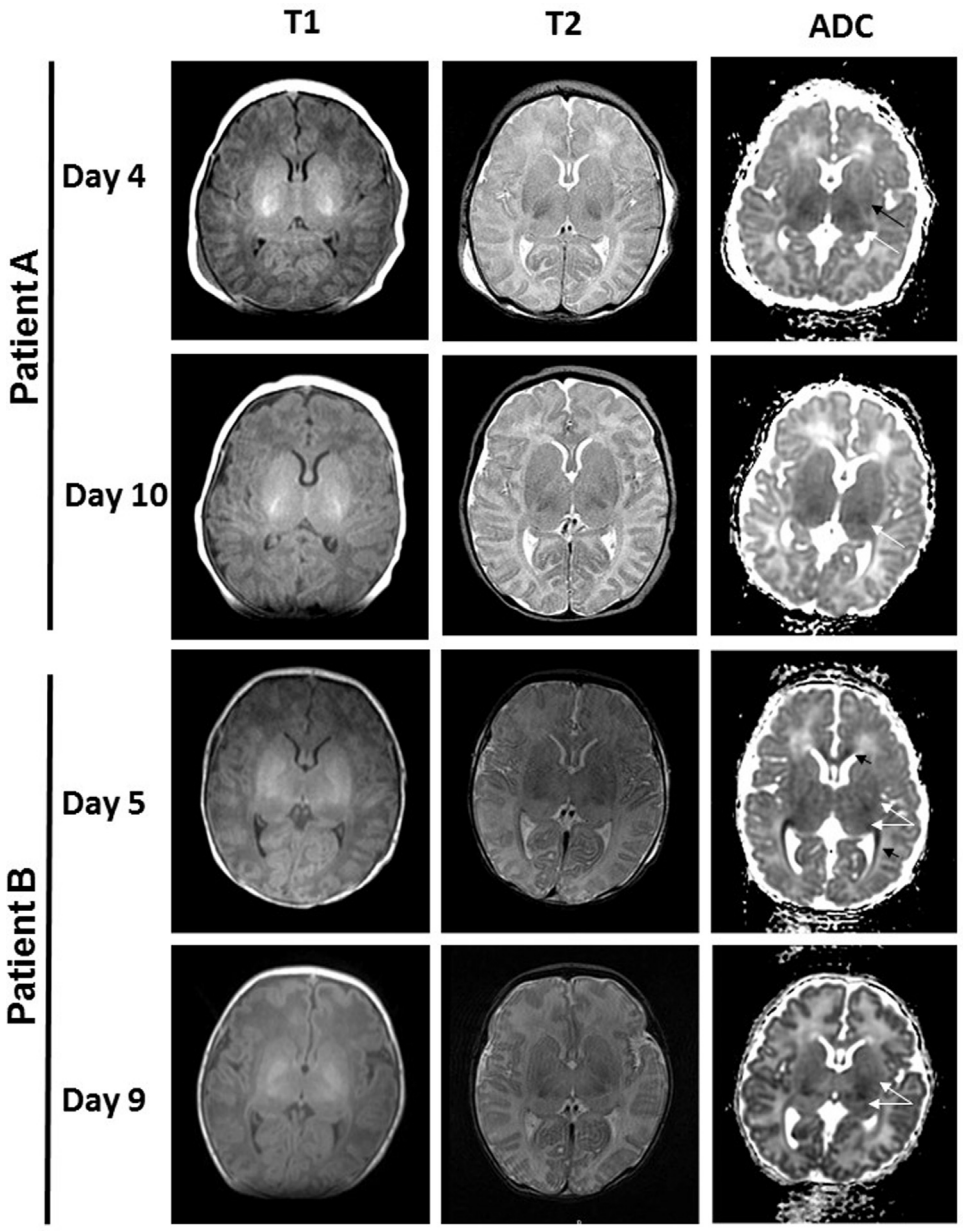

Figure. Exemplar cases with discordant scores between early and late scans. T1, T2, and diffusion-weighted images are shown. In patient A, basal ganglia score was greater on day 4 (basal ganglia score = 3, signifying signal abnormality in the thalamus [*white arrow*] and basal ganglia [*black arrow*]) compared with day 10 (basal ganglia score = 1, signifying signal abnormality in the thalamus only [*white arrow*]). Similarly in patient B, basal ganglia injury was more apparent on day 5 (basal ganglia score = 4, signifying extensive involvement with signal abnormality in the thalamus and basal ganglia [*white arrows*] and white matter tracts [*black arrows*]) compared with day 9 (basal ganglia score = 2, signifying less extensive signal abnormality in the thalamus and basal ganglia [*white arrows*]). *ADC*, apparent diffusion coefficient.

43 who were cooled) was reported by Chakkarapani et al and likewise the authors observed substantial agreement between early (3-6 days) and late (10-14 days) MRI.[16] One other study compared predictive abilities of early vs late MRI for developmental outcomes in infants with HIE. Using a visual analysis system to classify MRIs as normal vs abnormal in 33 infants with HIE, Charon et al reported that both early (<7 days) and late (≥7 days) MRIs yielded 100% sensitivity for adverse outcome at median age 24 months but that early MRI had a greater specificity than late MRI (96.3% vs 89.3%).[6] Our findings are consistent with these previous reports suggesting that findings on early and late MRI substantially agree and that early MRI provides a fuller picture of the extent of injury that can be used to most accurately predict early cognitive and motor outcomes. It should be noted, however, that although one early MRI is likely sufficient for clinicians in most circumstances, a second image may be warranted in a setting in which the MRI quality is suboptimal for confident

Table III. Prediction of developmental delay by MRI score (n = 30)

Variable names	OR (95% CI)	β	SE	*P* value	AUC (C-statistic) (95% CI)	R-square	% Concordant	AIC	aOR*	*P* value
Early basal ganglia	2.63 (1.22-5.69)	0.968	0.393	**.014**	0.819 (1.22-5.96)	0.36	73.6	26.24	3.31 (1.26-8.66)	**.015**
Late basal ganglia	3.20 (1.31-7.80)	1.163	0.455	**.011**	0.788 (1.31-7.80)	0.43	64.6	24.50	3.14 (1.31-7.51)	**.010**
Early watershed	1.44 (0.89-2.35)	0.367	0.249	.141	0.628 (0.89-2.35)	0.11	44.4	31.85		
Late watershed	1.50 (0.91-2.47)	0.404	0.254	.112	0.646 (0.91-2.47)	0.13	45.8	31.47		
Early basal ganglia/watershed	2.84 (1.24-6.51)	1.043	0.424	**.014**	0.816 (1.24-6.51)	0.37	72.9	26.14	2.98 (1.26-7.06)	**.013**
Late basal ganglia/watershed	2.56 (1.13-5.79)	0.940	0.416	**.024**	0.792 (1.13-5.79)	0.30	70.1	27.72	2.43 (1.07-5.51)	**.033**
Early NICHD	2.41 (1.10-5.30)	0.881	0.401	**.028**	0.816 (1.10-5.30)	0.34	74.3	26.74	2.68 (1.11-6.47)	**.029**
Late NICHD	1.79 (0.99-3.24)	0.582	0.303	.055	0.771 (0.99-3.24)	0.22	68.8	29.59		

AIC, Akaike information criterion; *AUC*, area under the curve; β, regression coefficient.
P-values in bold denote statistically significant predictors.
*Adjusted for encephalopathy grade, encephalopathy grade (moderate vs severe), Apgar score at 5 minutes, and socioeconomic status (public vs private insurance).

interpretation or if findings are incongruent with the clinical picture.

Although the agreement between early and late MRI in our study was substantial, the data also provide insights into the evolution of specific changes that occurred from early to late scores to better understand how visualization of injury by MRI progresses over the first weeks of life. Late MRI scores were more likely to decrease compared with early scores. That early scores were overall slightly more predictive of later outcomes suggests that imaging in the second week of life may be capturing potential pseudonormalization of injury on diffusion-weighted images, whereas signal abnormalities on T1- and T2-weighted images may be less apparent or not fully evolved, affecting the sensitivity of assessment of tissue injury by MRI at this time point. Previous reports have suggested that the time course of pseudonormalization is delayed in the setting of therapeutic hypothermia, with pseudonormalization occurring after 10 days in cooled infants compared with day 6-8 in controls.[28] Thus, it would be expected that brain injury may continue to be visible on diffusion-weighted imaging throughout the first postnatal week in cooled infants. We recognize that both the Barkovich et al[9] and NICHD[8] systems did not include analysis of diffusion-weighted images and were described for application to T1 and T2-weighted images beyond the first week of life. Thus, our reported predictive abilities cannot be directly compared with the source publications. However, our goal was to extend the application of these commonly used systems to pragmatic timepoints to provide data to refine optimal timing of MRI in clinical practice.

Although the aim of our study was to assess the ability of MRI at alternative time points to predict later neurodevelopmental adverse outcomes categorically, we also evaluated individual BSITD-III composite scores as continuous measures to assess the association of MRI findings with individual developmental domains. Although the relationship with MRI scores and BSITD-III cognitive composite scores largely mirrored our primary analyses, it was of interest that we did not observe any significant correlations between MRI and BSITD-III motor composite scores. This may be due to a relatively narrow distribution of scores across a small sample size or may reflect the limitations of the Bayley motor composite as a reliable measure of motor function.[29-31] We did not have systematic capture of concurrent neurologic examination for identification and classification of cerebral palsy to augment our assessment of the association between neonatal brain injury by MRI and later motor performance.

There were some limitations to this study. There is an inherent selection bias in this cohort of patients, as those who did not receive 2 MRIs of the brain were excluded. Sicker patients may have been too medically unstable for early MRI or may not have survived to the second MRI time point, and healthier infants may have been discharged before obtaining a second MRI, limiting the MRIs available for analysis and potentially selecting out extreme phenotypes in our cohort. We used a single experienced reader for MRI scoring in our study based on the high intraobserver reliability (k = 0.85-1) reported for scoring system used,[9] as well as previous experience using multiple readers with high reliability in our earlier studies.[32,33] Whereas our results may be dependent on the reliability of scoring, previous large studies have relied on a single central scorer for MRI in this population.[8] A large portion of the study cohort was lost to follow-up, limiting the data available to analyze the correlation between MRI scores and early

Table IV. Spearman correlation between BSITD-III and MRI scores (n = 30)

Variable names	Cognitive composite score	*P* value	Language composite score	*P* value	Motor composite score	*P* value
Early basal ganglia	−0.400	**.039**	−0.357	.067	−0.225	.258
Late basal ganglia	−0.278	.160	−0.506	**.007**	−0.180	.368
Early watershed	−0.359	.066	−0.162	.419	−0.197	.326
Late watershed	−0.256	.198	−0.130	.519	−0.228	.252
Early basal ganglia/watershed	−0.478	**.012**	−0.301	.127	−0.157	.433
Late basal ganglia/watershed	−0.309	.117	−0.358	.067	−0.122	.544
Early NICHD	−0.530	**.004**	−0.485	**.010**	−0.254	.201
Late NICHD	−0.474	**.013**	−0.395	**.041**	−0.213	.286

P-values in bold denote statistically significant predictors.

neurodevelopmental outcome and the ability to control for all of the possible confounders in this study. Furthermore, because clinical follow-up was used in this study, there was a large age range at neurodevelopmental assessment. We used any available developmental assessment to optimize the sample size and power for the study, leading to a relatively wide age range used in these analyses which was not ideal. Although studies of outcomes after HIE routinely assessed and reported outcomes at 18 months,[1,2,4] additional studies are needed to assess predictive abilities for later school ages. These factors limit our ability to draw robust conclusions about the relationship between MRI and neurodevelopmental outcome. Although our study involved a relatively large cohort of infants who underwent serial MRI to assess agreement between early and late scans, a future study with more complete follow-up may be helpful to confirm our findings with regards to optimal timing for developmental prognosis.

We found substantial agreement across multiple MRI scoring systems between early (<7 days) and late (≥7) MRI in newborn infants with HIE following therapeutic hypothermia. Although both early and late MRI showed predictive value for later significant developmental delay, early MRI scores generally demonstrated better predictive ability compared with late MRI scores. These data support that a single MRI performed in the first week after birth is sufficient to assess the degree and extent of subacute brain injury after neonatal HIE. ■

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50 Years Ago in *The Journal of Pediatrics*

Albumin Synthesis in Children: Still a Relevant Biomarker

Walker WA, Ulstrom R, Lowman J. Albumin synthesis rates in patients with hypoproteinemia. J Pediatr 1971;78:812-20.

Walker et al undertook a detailed analysis of hepatic albumin synthesis rates in 3 groups of children, namely, those with excessive gastrointestinal or renal protein losses, those with advanced liver disease, and hospitalized controls. Using isotopic labelling of the precursor amino acid methionine, the authors determined that children with protein losses could rapidly increase synthetic capacity, in contrast to controls as well as those with limited liver synthetic function.

Documenting this extra capacity for hepatic albumin synthesis was an important piece in the puzzle supporting the role of nutritional support in states of protein loss (eg, nephrosis, colitis, and other catabolic illnesses). Moreover, this work anticipated a critical safety breakthrough, namely the administration of nonradioactive isotopes for nutritional assessment. The use of stable isotopes in children has become widespread, even among neonates.[1] When ventilated premature infants, for example, are administered a continuous infusion of amino acids with dextrose, the rate of albumin synthesis (as measured by ^{13}C-leucine incorporation) is substantially higher compared with infants receiving only intravenous glucose.[2] Moreover, low serum albumin alone continues to be an important prognostic sign for overall survival, intensive care unit length of stay, and other important morbidities in numerous pediatric populations.[3,4]

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Table I. Comparison of study population with and without follow-up data

Characteristics	Overall study population (n = 49)	Subjects with outcome data (n = 30)	Lost to follow-up (n = 19)	*P* value*
Gestational age, wk, mean ± SD	38.6 ± 1.5	38.4 ± 1.6	39 ± 1.1	.148
Birth weight, kg, mean ± SD	3.24 ± 0.75	3.06 ± 0.58	3.51 ± 0.92	.039
Sex, n (% male)	25 (51)	14 (47)	11 (58)	.561
Apgar				
1 min	1 (0-5)	1 (0-5)	1 (0-5)	.602
5 min	4 (0-8)	4 (0-8)	4 (0-7)	.442
10 min	5 (0-9)†	5 (1-9)‡	6 (0-8)§	.290
Presenting pH	6.96 (6.6-7.4)†	6.9 (6.6-7.3)¶	7.1 (6.6-7.4)**	.015
Presenting base deficit	18.1 (3-30)	18.6 (6-30)	16 (3-25)	.141
Encephalopathy grade, n (% severe)	6 (12)	4 (13)	2 (11)	1.000
Public insurance, n (%)	24 (49)	12 (40)	12 (63)	.148
Distribution of early MRI scores				
Basal ganglia				.471
0	32 (65.3)	18 (60)	14 (74)	
1	4 (8.2)	3 (10)	1 (5)	
2	4 (8.2)	4 (13)	0 (0)	
3	6 (12.2)	3 (10)	3 (16)	
4	3 (6.1)	2 (7)	1 (5)	
Watershed				.405
0	32 (65.3)	18 (60)	14 (74)	
1	4 (8.2)	3 (10)	1 (5)	
2	5 (10.2)	2 (7)	3 (16)	
3	0 (0)	0 (0)	0 (0)	
4	7 (14.3)	6 (20)	1 (5)	
5	1 (2)	1 (3)	0 (0)	
Basal ganglia/watershed				.701
0	28 (57.2)	16 (53)	12 (63)	
1	6 (12.2)	5 (17)	1 (5)	
2	5 (10.2)	3 (10)	2 (11)	
3	9 (18.4)	5 (17)	4 (21)	
4	1 (2)	1 (3)	0 (0)	
NICHD				.949
0	20 (41)	11 (37)	9 (47)	
1A	6 (12)	4 (13)	2 (11)	
1B	5 (10)	3 (10)	2 (11)	
2A	8 (16)	6 (20)	2 (11)	
2B	8 (16)	5 (17)	3 (16)	
3	2 (4)	1 (3)	1 (5)	
Distribution of late MRI scores				
Basal ganglia				.369
0	35 (71)	21 (70)	14 (74)	
1	3 (6)	2 (7)	1 (5)	
2	5 (10)	4 (13)	1 (5)	
3	4 (8)	1 (3)	3 (16)	
4	2 (4)	2 (7)	0 (0)	
Watershed				.675
0	34 (70)	19 (63)	15 (79)	
1	3 (6)	2 (7)	1 (5)	
2	4 (8)	2 (7)	2 (11)	
3	1 (2)	1 (3)	0 (0)	
4	6 (12)	5 (17)	1 (5)	
5	1 (2)	1 (3)	0 (0)	
Basal ganglia/watershed				.480
0	29 (59)	16 (54)	13 (69)	
1	5 (10)	4 (13)	1 (5)	
2	6 (12)	5 (17)	1 (5)	
3	8 (16)	4 (13)	4 (21)	
4	1 (2)	1 (3)	0 (0)	
NICHD				.831
0	22 (45)	13 (44)	9 (47)	
1A	7 (14)	4 (13)	3 (16)	
1B	3 (6)	1 (3)	2 (10.5)	
2A	7 (14)	5 (17)	2 (10.5)	
2B	9 (18)	6 (20)	3 (16)	
3	2 (2)	1 (3)	1 (5)	

(*continued*)

Table I. Continued

Characteristics	Overall study population (n = 49)	Subjects with outcome data (n = 30)	Lost to follow-up (n = 19)	*P* value*
BSITD-III composite scores				
Motor	n/a	93 ± 17	n/a	
Cognitive	n/a	91 ± 20	n/a	
Language	n/a	90 ± 19	n/a	

n/a, not available.
Data presented as median (range) unless otherwise specified.
*Comparison between patients with and without developmental follow-up.
†Data available for 46.
‡Data available for 29.
§Data available for 17.
¶Data available for 27.
**Data available for 19.