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Early Magnetic Resonance Imaging Predicts 30-Month Outcomes after Therapeutic Hypothermia for Neonatal Encephalopathy

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Objective To evaluate the association of therapeutic hypothermia with magnetic resonance imaging (MRI) findings and 30-month neurodevelopment in term neonatal encephalopathy.

Study design Cross-sectional analysis of 30-month neurodevelopment (IQR 19.0-31.4) in a prospective cohort of mild-to-severe neonatal encephalopathy imaged on day 4 (1993-2017 with institutional implementation of therapeutic hypothermia in 2007). MRI injury was classified as normal, watershed, or basal ganglia/thalamus. Abnormal motor outcome was defined as Bayley-II psychomotor developmental index <70, Bayley-III motor score <85 or functional motor deficit. Abnormal cognitive outcome was defined as Bayley-II mental developmental index <70 or Bayley-III cognitive score <85. Abnormal composite outcome was defined as abnormal motor and/or cognitive outcome, or death. The association of therapeutic hypothermia with MRI and outcomes was evaluated with multivariable logistic regression adjusted for propensity to receive therapeutic hypothermia.

Results Follow-up was available in 317 (78%) surviving children, of whom 155 (49%) received therapeutic hypothermia. Adjusting for propensity, therapeutic hypothermia was independently associated with decreased odds of abnormal motor (OR 0.15, 95% CI 0.06-0.40, $P < .001$) and cognitive (OR 0.11, 95% CI 0.04-0.33, $P < .001$) outcomes. This association remained statistically significant after adjustment for injury pattern. The predictive accuracy of MRI pattern for abnormal composite outcome was unchanged between therapeutic hypothermia-treated (area under the receiver operating curve 0.76; 95% CI 0.61-0.91) and untreated (area under the receiver operating curve 0.74; 95% CI 0.67-0.81) infants. The negative predictive value of normal MRI was high in therapeutic hypothermia-treated and untreated infants (motor 96% vs 90%; cognitive 99% vs 95%).

Conclusions Therapeutic hypothermia is associated with lower rates of brain injury and adverse 30-month outcomes after neonatal encephalopathy. The predictive accuracy of MRI in the first week of life is unchanged by therapeutic hypothermia. Normal MRI remains reassuring for normal 30-month outcome after therapeutic hypothermia. *(J Pediatr 2021; ■:1-8)*.

Neonatal encephalopathy affects approximately 3 newborns per 1000 live births, of which hypoxic-ischemic encephalopathy (HIE) affects 1.5 per 1000 live births.[1] Hypoxic-ischemic injury to the developing brain contributes significantly to mortality and long-term morbidity, such that at least 25% of surviving children exhibit long-term neurodevelopmental sequelae ranging from mild to severe, including developmental delay, intellectual disability, cerebral palsy, and epilepsy.[2,3]

Therapeutic hypothermia to 33.5°C for 72 hours, initiated within 6 hours after birth, improves neurodevelopmental outcomes in term newborns with moderate/severe HIE.[4-7] Smaller studies have shown that therapeutic hypothermia is associated with decreased risk of brain injury,[8,9] and the predominant pattern of injury on magnetic resonance imaging (MRI) after hypoxic-ischemic injury is associated with outcome.[10] Three nested studies within randomized-controlled trials (RCTs) that evaluated therapeutic hypothermia have also examined the relationship between therapeutic hypother-

AUROC	Area under the receiver operating curve	NMS	Neuromotor score
BG/T	Basal ganglia/thalamus	NPV	Negative predictive value
EEG	Electroencephalogram	PPV	Positive predictive value
HIE	Hypoxic-ischemic encephalopathy	RCT	Randomized-controlled trial
ICE	Infant Cooling Evaluation	TOBY	Total Body Hypothermia for Neonatal Encephalopathy
MRI	Magnetic resonance imaging	UCSF	University of California–San Francisco
NICHD	National Institute of Child Health and Human Development		

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mia, MRI, and outcomes. The nested substudy of the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) RCT found significant reduction of MRI injury score, but the same rate of death or disability at 18 months in the therapeutic hypothermia and control groups.[11] The nested substudy of the National Institute of Child Health and Human Development (NICHD) RCT found unchanged MRI injury scores after therapeutic hypothermia, but lower rate of death or moderate/severe disability at 18-22 months in the therapeutic hypothermia group than in the control group.[12] The nested substudy of the Infant Cooling Evaluation (ICE) RCT found significant reduction of moderate/severe MRI abnormalities, and that these abnormalities predict death or major disability at 2 years of age.[13] As MRI was available for only a subset of each cohort and the timing of MRI was variable, it remains difficult to reliably assess the predictive value of MRI for outcomes after therapeutic hypothermia.

To enhance our understanding of the relationship between therapeutic hypothermia, pattern of injury on MRI, and motor and cognitive outcomes, and to assess the predictive value of early MRI for these outcomes, we report a large cohort of term newborns with broadly defined neonatal encephalopathy presumed due to HIE prospectively imaged with MRI around day 4 during the pre- and post-therapeutic hypothermia eras. This study aims to evaluate the association of therapeutic hypothermia with MRI injury pattern (watershed and basal ganglia/thalamus [BG/T]) and neurodevelopment at 30 months, and determine the predictive value of injury pattern for outcomes in the setting of therapeutic hypothermia. These findings may assist in counseling families of infants with neonatal encephalopathy regarding the prognostic significance of early MRI and specifically address the question: how reassuring is a normal MRI after therapeutic hypothermia?

Methods

We performed a cross-sectional analysis of the relationship between therapeutic hypothermia, MRI findings, and neurodevelopment in an ongoing prospective cohort of term newborns with mild-to-severe encephalopathy admitted to the University of California–San Francisco (UCSF) Intensive Care Nursery between December 1993 and July 2017.

Participants

Subjects were neonates admitted to the UCSF Intensive Care Nursery with suspected HIE, with one or more of the following: (1) 5-minute Apgar score ≤5, (2) umbilical artery cord blood pH < 7.1, (3) umbilical artery base deficit ≤ −10, or (4) clinical brain dysfunction (abnormal tone, feeding, alertness, respiratory status, or reflexes). Exclusion criteria were evidence of congenital infection, metabolic disease, or anomalies of the brain or other major organ systems. Subjects were enrolled after voluntary informed consent was obtained from parents following a protocol approved by the UCSF Committee on Human Research.

Whole-body hypothermia to 33.5°C for 72 hours was initiated as standard of care at UCSF in 2007, with criteria for therapy as follows: ≥36-week gestational age and ≤6 hours old, clinical evidence of encephalopathy, and 1 of the following: 10-minute Apgar <5, prolonged resuscitation, pH <7 or base deficit <-12 on cord or initial infant blood gas within 1 hour of life. Clinical evidence of encephalopathy included any of the following: lethargy, stupor or coma, hyperalert state, abnormal tone, absent or weak suck, abnormal reflexes, clinical seizures, abnormal amplitude integrated electroencephalogram (EEG) background, and/or electrographic seizures. Prior to therapeutic hypothermia, EEG was obtained at the discretion of the treating physician if there were clinical concerns for seizures. After therapeutic hypothermia was implemented in 2007, continuous video-EEG was obtained through rewarming.

Clinical data were prospectively collected by trained research nurses blinded to imaging. Variables collected included sex, gestational age, birth weight, mode of delivery, Apgar scores at 1, 5, and 10 minutes, pH from umbilical artery or first newborn blood gas within 1 hour of life, and a resuscitation score reflecting amount of intervention required at birth (scored 0-6 with score ≥5 indicating intubation).[14] An encephalopathy score assessing mental status, feeding ability, respiratory support requirement, tone, reflexes, and presence of clinical and/or electrographic seizures, was prospectively assigned on day of life 1 (scored 0-6 with moderate-severe defined as ≥4).[15]

MRI

Each participant had a brain MRI during the first week of life if clinically feasible (median day 4, IQR 3-5 days). Neonates were transported to MRI by a neonatologist and trained research nurses. Imaging was performed with a dedicated neonatal head coil over 1 hour. Standard magnetic resonance sequences were performed on 1.5T (1993-2011) and 3T (2011-2017) GE scanners (GE Healthcare) as previously described.[10,16] Sedation was used at the discretion of the accompanying neonatologist.

A pediatric neuroradiologist blinded to the clinical course classified the extent of injury in the basal ganglia/thalamus (BG/T) (severity score 0-4) and watershed (severity score 0-5) regions on diffusion-, T1- and T2-weighted MRI images using our published scoring system.[10,17] Each subject was assigned a BG/T and watershed score, and these scores were used to categorize injury into predominant injury pattern: normal, watershed, or BG/T. The watershed pattern was assigned when the watershed score was higher than the BG/T score. The BG/T pattern was assigned when the BG/T score was higher than or equal to the watershed score. Any MRI abnormality was defined as BG/T or watershed score ≥1.

Neurodevelopmental Evaluation

Participants underwent follow-up at 12-18 months and/or 24-30 months as part of routine clinical care. The last follow-up available was included in the analysis. Follow-up evaluations included a standardized blinded neurologic examination, neuromotor score (NMS, 0-5),[18,10] and testing with the Bayley

Scales of Infant and Toddler Development, administered by a clinical psychologist blinded to the child's neonatal course, in the child's native language (Spanish or English). Subjects evaluated prior to 2007 were evaluated with the Bayley-II and subjects enrolled thereafter were evaluated with the Bayley-III. Bayley-II mental and psychomotor developmental index scores <70 and Bayley-III motor and cognitive composite scores <85 were classified as abnormal.[19] If Bayley psychomotor developmental index or motor score were unavailable, NMS ≥3 was used to classify abnormal motor outcome. NMS was assigned by an experienced blinded pediatric neurologist with scores ≥3 indicating a functional motor deficit. Composite outcome was defined as abnormal if the subject died, or motor or cognitive outcome was classified as abnormal.

Statistical Data Analyses

Analysis was performed with STATA 16 (StataCorp). Baseline clinical characteristics, MRI findings, and neurodevelopmental outcomes were compared between untreated and therapeutic hypothermia-treated neonates using the Kruskal-Wallis or Student *t* test for continuous variables, and χ^2or Fisher exact test for categorical variables.

Multivariate logistic regression was performed to evaluate the association of therapeutic hypothermia and MRI injury pattern with outcomes, adjusting for quintiles of propensity for receiving therapeutic hypothermia. The propensity score allows an observational study to be designed and analyzed to mimic some of the characteristics of a randomized controlled trial. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics and ensures that the distribution of observed baseline covariates are similar between treated and untreated subjects.[20] Covariates included in the propensity score were baseline characteristics significantly different between the treated and untreated groups that comprise eligibility for therapeutic hypothermia and are likely to influence outcome: Apgar <5 at 10 minutes of life, intubation at resuscitation, pH <7 on initial blood gas, presence of moderate to severe encephalopathy, and presence of clinical and/or electrographic seizures in the first 24 hours of life. Covariates were balanced within each propensity score quintile.

Predictive accuracy was determined by calculating the area under the receiver operating curve (AUROC). Comparisons of predictive accuracy between therapeutic hypothermia-treated and untreated children were made by comparing the confidence intervals of AUROC values. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of injury pattern for abnormal cognitive, motor and composite outcomes were calculated for therapeutic hypothermia-treated and untreated children.

Results

Infant Characteristics

Among 434 term infants with encephalopathy enrolled between 1993 and 2017, 204 (47%) received therapeutic hypothermia (**Table I**). Infants receiving therapeutic hypothermia were more likely to have low 5- and 10-minute Apgar scores ($P < .001$), lower pH on initial blood gas ($P = .005$), and more severe encephalopathy ($P < .001$). Encephalopathy was classified as mild in 31 of 204 (15%) therapeutic hypothermia-treated and 107 of 230 (47%) untreated infants, and moderate to severe in 173 of 204 (85%) therapeutic hypothermia-treated and 123 of 230 (53%) untreated infants. Therapeutic hypothermia-treated infants were less likely to be inborn or have clinical and/or electrographic seizures detected within 24 hours of life ($P = .001$).

MRI Findings

MRI was performed at a median of 4 days of age (IQR 3-5) for both untreated and therapeutic hypothermia-treated infants. Therapeutic hypothermia was associated with decreased rates of MRI-detected brain injury (no injury: 60% vs 27%, watershed: 27% vs 47%, BG/T: 13% vs 27%; $P < .001$) and decreased injury severity within each pattern (both $P < .001$) (**Table I**). Adjusting for quintiles of propensity for receiving therapeutic hypothermia, therapeutic hypothermia was independently associated with decreased relative risk of watershed injury (relative risk reduction 0.27, 95% CI 0.16-0.38, $P < .001$) and BG/T injury (relative risk reduction 0.31, 95% CI 0.21-0.41, $P < .001$) on MRI.

Neurodevelopmental Outcomes

Neurodevelopment was assessed at a median of 30 months (IQR 19.0-31.4) in 317 of 408 (78%) surviving children with neonatal encephalopathy. Outcome data was available for 297 of 409 (73%) surviving children at 12-18 months and for 240 of 408 (59%) surviving children at 24-30 months. Infants who did not return for follow-up had younger mothers and were less likely to have seizures on day 1 of life (**Table II**; available at www.jpeds.com).

Abnormal cognitive and motor outcomes among children with watershed or BG/T injury were significantly less common in the hypothermia group (**Table III**; available at www.jpeds.com). Children treated with therapeutic hypothermia were less likely to have abnormal cognitive (OR 0.10, 95% CI 0.03-0.28), motor (OR 0.16, 95% CI 0.07-0.37), and composite (OR 0.21, 95% CI 0.12-0.37) outcomes. Adjusting for treatment propensity revealed a similar magnitude of effect. These associations were still significant but slightly decreased in magnitude after further adjustment for MRI injury pattern (**Table IV**). Restriction of these analyses to outcomes assessed at 12-18 or 24-30 months yielded similar results.

MRI Pattern and Outcomes

Abnormal MRI was associated with increased odds of abnormal cognitive, motor, and composite outcomes (**Figure**). BG/T-predominant injury on MRI was significantly associated with increased odds of abnormal cognitive (OR 26.2, 95% CI 7.26-94.6) and motor outcome

Table I. Clinical characteristics and MRI findings

Clinical characteristics and MRI findings	No therapeutic hypothermia n = 230	Therapeutic hypothermia n = 204	*P* value
Gestational age ± SD (wk)	39.5 ± 1.8	39.6 ± 1.5	.60
Birthweight ± SD (g)	3349 ± 623	3383 ± 561	.56
Male	132 (57%)	109 (53%)	.41
Maternal age ± SD (y)	30.1 ± 7.0	29.9 ± 6.4	.75
Inborn	95 (42%)	47 (23%)	**<.001**
Meconium	118 (55%)	107 (57%)	.65
Cesarean delivery	124 (54%)	107 (52%)	.69
Apgar score at 5 min of life, median (IQR)	5 (4-7)	4 (2-5)	**<.001**
Apgar score at 10 min of life, median (IQR)	7 (5-8)	6 (4-7)	**<.001**
Intubated at resuscitation*	118 (51%)	122 (60%)	.08
Moderate-severe encephalopathy†	123 (53%)	173 (85%)	**<.001**
pH on initial blood gas ± SD	7.05 ± 0.2	7.00 ± 0.2	**.005**
Seizure detected at <24 HOL	97 (42%)	54 (26%)	**.001**
Death at or before 30 mo of age	17 (7%)	9 (4%)	.19
Median age at MRI, d (IQR)	4 (2-7)	4 (4-5)	.18
MRI pattern of injury			**<.001**
No injury	54 (27%)	108 (60%)	
Watershed pattern	94 (47%)	48 (27%)	
BG/T pattern	54 (27%)	24 (13%)	
Watershed injury severity			**<.001**
None	76 (38%)	125 (69%)	
Mild to moderate (watershed score 1-3)	49 (24%)	40 (22%)	
Severe (watershed score 4-5)	77 (38%)	15 (8%)	
BG/T injury severity			**<.001**
None	114 (56%)	151 (84%)	
Mild to moderate (BG/T score 1-2)	46 (23%)	22 (12%)	
Severe (BG/T score 3-4)	42 (21%)	7 (4%)	

HOL, hours of life.
Bold values indicate statistical significant ($P < .05$).
All subjects in the therapeutic hypothermia group were enrolled in the study in 2007 or later. One hundred ninety-four (84%) subjects in the no therapeutic hypothermia group were enrolled before 2007.
*Resuscitation score ≥5.
†Encephalopathy score ≥4.

(OR 13.5, 95% CI 5.24-34.6). Watershed-predominant injury on MRI was significantly associated with increased odds of abnormal cognitive outcome (OR 7.01, 95% CI 2.00-24.6) but not abnormal motor outcome (OR 2.29, 95% CI 0.89-5.88, $P = .09$) (Table IV). After adjustment for therapeutic hypothermia and propensity for therapeutic hypothermia, all significant associations remained significant, but with lower odds of abnormal outcome.

Predictive Value of MRI

The predictive accuracy of any MRI abnormality for abnormal composite outcome was unchanged between therapeutic hypothermia-treated (AUROC 0.68; 95% CI 0.56-0.81) and untreated (AUROC 0.63; 95% CI 0.57-0.68) infants. Similarly, the predictive accuracy of MRI pattern for abnormal composite outcome was unchanged between therapeutic hypothermia-treated (AUROC 0.76; 95% CI

Table IV. Univariate and multivariate regression for the association of therapeutic hypothermia and MRI pattern of injury with outcomes at 30 months

	Abnormal cognitive outcome		Abnormal motor outcome		Abnormal composite outcome	
Therapeutic hypothermia and MRI pattern of injury	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Therapeutic hypothermia	0.10 (0.03-0.28)	**<.001**	0.16 (0.07-0.37)	**<.001**	0.21 (0.12-0.37)	**<.001**
Therapeutic hypothermia*	0.11 (0.04-0.33)	**<.001**	0.15 (0.06-0.40)	**<.001**	0.19 (0.09-0.37)	**<.001**
Therapeutic hypothermia†	0.23 (0.07-0.74)	**.01**	0.19 (0.06-0.58)	**.004**	0.26 (0.12-0.58)	**.001**
MRI pattern of injury						
Normal	Ref		Ref		Ref	
Watershed	7.01 (2.00-24.6)	**.002**	2.29 (0.89-5.88)	.09	3.72 (1.67-8.28)	**.001**
BG/T	26.2 (7.26-94.6)	**<.001**	13.5 (5.24-34.6)	**<.001**	21.1 (9.17-48.3)	**<.001**
MRI pattern of injury‡						
Normal	Ref		Ref		Ref	
Watershed	6.01 (1.31-27.6)	**.02**	1.55 (0.54-4.46)	.42	2.34 (0.96-5.66)	.06
BG/T	20.3 (4.17-99.3)	**<.001**	9.70 (3.25-28.9)	**<.001**	11.7 (4.57-30.1)	**<.001**

Bold values indicate statistical significant ($P < .05$).
*Adjusted for quintiles of propensity for receiving therapeutic hypothermia; covariates comprising eligibility to receive therapeutic hypothermia included Apgar <5 at 10 minutes of life, intubation at resuscitation, pH less than 7 on initial blood gas, presence of moderate to severe encephalopathy, and presence of seizures in the first 24 hours of life.
†Adjusted for quintiles of propensity for receiving therapeutic hypothermia and MRI pattern of injury.
‡Adjusted for therapeutic hypothermia and quintiles of propensity for receiving therapeutic hypothermia.

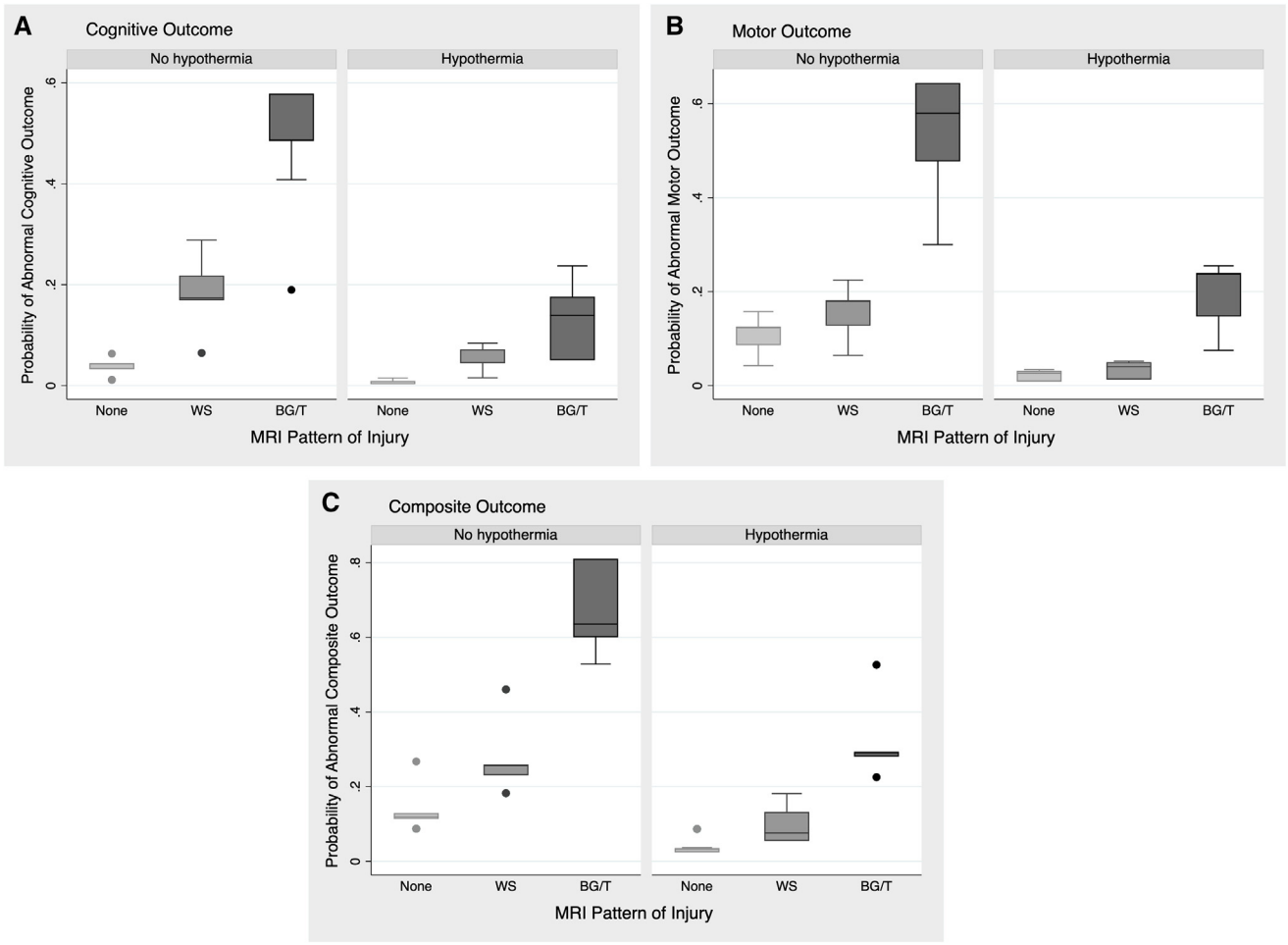

Figure. Box-plot showing the probability of abnormal outcome predicted by the full regression model, which is adjusted for therapeutic hypothermia and quintiles of propensity for receiving therapeutic hypothermia; covariates comprising eligibility to receive therapeutic hypothermia included Apgar <5 at 10 minutes of life, intubation at resuscitation, pH less than 7 on initial blood gas, presence of moderate to severe encephalopathy, and presence of seizures in the first 24 hours of life.

0.61-0.91) and untreated (AUROC 0.74; 95% CI 0.67-0.81) infants.

Detection of any MRI abnormality in untreated infants had a sensitivity of 92% and specificity of 33% for abnormal composite outcome, with PPV of 44% for an abnormal outcome and NPV of 88% for a normal outcome. The specificity of MRI among those with therapeutic hypothermia compared with those without was higher for motor (63% vs 31%) and cognitive (63% vs 34%) outcomes, as was NPV for motor (96% vs 90%) and cognitive (99% vs 95%) outcomes (Table V). The sensitivity and PPV of abnormal MRI for abnormal outcomes was lower among those with therapeutic hypothermia.

Among untreated infants, BG/T-predominant injury had greater specificity than watershed-predominant injury for abnormal cognitive (69% vs 40%) and motor (69% vs 36%) outcomes, and both injury patterns had similar sensitivity for abnormal cognitive (89%) and motor (83% vs 78%) outcomes. Specificity of both injury patterns for abnormal cognitive and motor outcomes and NPV for normal outcomes was increased among those with therapeutic hypothermia (Table V). The sensitivity and PPV of both patterns of injury for abnormal outcomes was lower among those with therapeutic hypothermia.

Discussion

The results of this study demonstrate the association of therapeutic hypothermia with MRI findings and neurodevelopmental outcomes in a prospective cohort of term infants with broadly defined neonatal encephalopathy spanning the era before and after the implementation of therapeutic hypothermia. In summary, we found that therapeutic hypothermia is associated with significantly decreased rates of brain injury and improved outcomes at 30 months after accounting for injury pattern, injury patterns on MRI are significantly associated with outcomes regardless of therapeutic hypothermia, and early MRI remains equally predictive of outcome after therapeutic hypothermia.

Table V. Predictive value of MRI pattern of injury at 30 months

MRI pattern of injury	Sensitivity	Specificity	PPV	NPV
Any MRI abnormality				
Untreated subjects				
Abnormal cognitive outcome	0.94 (33/35)	0.34 (40/119)	0.29 (33/112)	0.95 (40/42)
Abnormal motor outcome	0.89 (33/37)	0.31 (38/122)	0.28 (33/117)	0.90 (38/42)
Abnormal composite outcome	0.92 (59/64)	0.33 (37/112)	0.44 (59/134)	0.88 (37/42)
Therapeutic hypothermia-treated subjects				
Abnormal cognitive outcome	0.75 (3/4)	0.63 (80/127)	0.06 (3/50)	0.99 (80/81)
Abnormal motor outcome	0.50 (3/6)	0.63 (82/131)	0.06 (3/52)	0.96 (82/85)
Abnormal composite outcome	0.73 (11/15)	0.63 (82/130)	0.19 (11/59)	0.95 (82/86)
Watershed injury				
Untreated subjects				
Abnormal cognitive outcome	0.89 (16/18)	0.40 (40/101)	0.21 (16/77)	0.95 (40/42)
Abnormal motor outcome	0.78 (14/18)	0.36 (38/105)	0.17 (14/81)	0.90 (38/42)
Abnormal composite outcome	0.83 (25/30)	0.39 (37/96)	0.30 (25/84)	0.88 (37/42)
Therapeutic hypothermia-treated subjects				
Abnormal cognitive outcome	0.50 (1/2)	0.69 (80/116)	0.03 (1/37)	0.99 (80/81)
Abnormal motor outcome	0 (0/3)	0.68 (82/120)	0 (0/38)	0.96 (82/85)
Abnormal composite outcome	0.33 (2/6)	0.69 (82/119)	0.05 (2/39)	0.95 (82/86)
BG/T				
Untreated subjects				
Abnormal cognitive outcome	0.89 (17/19)	0.69 (40/58)	0.49 (17/35)	0.95 (40/42)
Abnormal motor outcome	0.83 (19/23)	0.69 (38/55)	0.53 (19/36)	0.90 (38/42)
Abnormal composite outcome	0.87 (34/39)	0.70 (37/53)	0.68 (34/50)	0.88 (37/42)
Therapeutic hypothermia-treated subjects				
Abnormal cognitive outcome	0.67 (2/3)	0.88 (80/91)	0.15 (2/13)	0.99 (80/81)
Abnormal motor outcome	0.50 (3/6)	0.88 (82/93)	0.21 (3/14)	0.96 (82/85)
Abnormal composite outcome	0.69 (9/13)	0.88 (82/93)	0.45 (9/20)	0.95 (82/86)

Our first finding that therapeutic hypothermia-treated infants have significantly decreased rates of watershed and BG/T injury and fewer adverse cognitive, motor, and composite outcomes at 30 months supports previous literature and adds that therapeutic hypothermia is associated with both early MRI findings and neurodevelopmental outcomes. The nested sub study of the TOBY RCT reported on the 40% of infants who received MRI (n = 131) at a median age of 8 days (range 2-30), of whom 64 received therapeutic hypothermia.[11] Those with therapeutic hypothermia had reduced injury on MRI, but no significant difference in death or severe disability at 18 months from the untreated group. Likewise, the nested substudy of the NICHD RCT reported on the 65% of infants who received MRI (n = 136) at a mean age of 15 days (SD 12), of whom 73 received therapeutic hypothermia.[12] Although injury on MRI was significantly associated with death or moderate/severe disability at 18-22 months, those with therapeutic hypothermia did not have significantly different injury patterns on MRI. In contrast to the variable timing of MRI in these studies, MRI was obtained around day 4 in the majority of our cohort, at a time when apparent diffusion coefficient values reach their nadir after neonatal HIE.[21] Our study, thus, strengthens the evidence that therapeutic hypothermia is strongly associated with both early MRI findings and developmental outcomes, and illustrates these associations in a real-world context as opposed to a rigorous RCT.

We found that MRI injury pattern in the first week of life was significantly associated with neurodevelopmental outcome among therapeutic hypothermia-treated newborns. Prior studies have reported strong associations of abnormal MRI findings with major disability and mortality following moderate/severe HIE.[11-13] In this cohort, BG/T injury was significantly associated with all adverse outcomes, which is consistent with the previously reported association of BG/T injury with poor outcomes including severe disability and cerebral palsy.[22,23] Watershed-predominant injury was significantly associated with adverse cognitive but not motor outcomes, which is aligned with the predominantly cognitive consequences of watershed injury previously reported.[10,23,24] The significance of these associations was unchanged after adjustment for therapeutic hypothermia, although the CIs for these associations are wide, likely due to the smaller sample sizes within each injury pattern category.

To support prognosis, we calculated the predictive accuracy and value of MRI findings for adverse outcomes among therapeutic hypothermia-treated and untreated infants. The predictive accuracies of MRI findings for outcomes in therapeutic hypothermia-treated and untreated subjects in our cohort were slightly lower than those reported by the TOBY RCT subgroup study (0.84 in therapeutic hypothermia-treated and 0.81 in untreated) and in the magnetic resonance biomarkers in neonatal encephalopathy (MARBLE) study,[25] likely because of our inclusion of a wider spectrum of encephalopathy and MRI injury, but support the finding in the TOBY, NICHD, and ICE studies that therapeutic hypothermia does not change the predictive accuracy of MRI findings.[11-13] The overall sensitivity of any MRI abnormality for abnormal composite outcome in our cohort is comparable with that reported in the NICHD study (90%), and BG/T injury had the highest combined sensitivity/specificity for adverse outcome, as in the ICE study.[12,13] Of

particular clinical relevance is our finding that the predictive accuracy of early MRI is unchanged by therapeutic hypothermia, and normal MRI is highly reassuring for normal outcomes at 30 months (NPV ≥95%).

Our data demonstrate that improved outcomes in the post-hypothermia era are not fully explained by the reduction in the rate of brain injury, or the severity of injury. This suggests there may be effects of therapeutic hypothermia on neurodevelopmental outcome mediated by changes that are not visible on conventional MRI, for example alterations in metabolomics, microstructure, and functional connectivity. Other changes in care that coincided with the implementation of therapeutic hypothermia at our center may have also contributed to better neurodevelopmental outcomes, including standardization of clinical care practices, and implementation of a multidisciplinary model of neonatal neurocritical care that includes emphasis on parent education to support early development, as well as close developmental surveillance and referral to early intervention services for all therapeutic hypothermia-treated infants.[26] Specialized neurocritical care has been shown to improve outcomes following acute brain injury in the adult population,[27] and our data suggest that specialized brain-focused care in critically ill newborns may be similarly beneficial.

The strength of our study is that we have examined MRI findings and neurodevelopmental outcomes in a large prospective cohort of broadly defined neonatal encephalopathy spanning the era before and after therapeutic hypothermia. All infants included in this analysis received a standardized MRI per protocol, and all images were scored by a single reader throughout the course of the study. Our images were also consistently acquired within the first 2 weeks of life when predictive accuracy is greatest,[28] at a median of 4 days, with no differences in MRI timing between treated and untreated infants. This allowed for appropriate comparison, because postnatal age affects MRI findings after HIE.[11] Because our institutional criteria for therapeutic hypothermia are less stringent than the inclusion criteria for the RCTs, 15% of therapeutic hypothermia-treated infants in our study were classified as having mild encephalopathy. Although therapeutic hypothermia has not been proven to be efficacious in the subgroup with mild neonatal encephalopathy, RCTs are planned to address this area of uncertainty (NCT04621279, NCT04176471).

There are limitations to our longitudinal cohort study, including possible selection bias. In our series, there are significant differences in baseline characteristics between treated and untreated subjects, specifically in those that determine receipt of therapeutic hypothermia, and in birth location. This relates in part to changes in the population available for enrollment as therapeutic hypothermia became standard of care and UCSF became a major referral center for therapeutic hypothermia, increasing disease severity and reducing the proportion of inborn infants in our cohort. The propensity score used in our models directly addresses these differences in baseline characteristics by controlling for the likelihood of receiving therapeutic hypothermia, and allows for comparisons between similar subjects within each group. Any residual selection bias due to inclusion of more severely ill infants transferred from outside hospitals in the therapeutic hypothermia treatment group would tend to underestimate the effect of therapeutic hypothermia on outcomes, and is therefore unlikely to change our conclusions. Infants who received therapeutic hypothermia were only enrolled after 2007, and most who did not receive therapeutic hypothermia were enrolled prior to 2007. Unmeasured practice changes in management of neonatal HIE from 1993 to 2017 may be a source of bias.[29-31] One notable change in practice concurrent with implementation of therapeutic hypothermia at our center was routine continuous video EEG monitoring. Although we did not statistically account for this practice difference, seizures are accounted for in the propensity score. Our loss to follow-up of 22% and differences between children with and without follow-up are another source of potential bias. The only clinical difference between these groups was that infants without follow-up had fewer seizures within 24 hours, suggesting they may represent subjects with milder illness. Finally, as the purpose of this study is to assess long-term outcomes, there may have been reduced enrollment of the most severely affected infants with poor prognosis for survival, which could result in underrepresentation of mortality and abnormal composite outcome in our cohort.

An additional limitation involves our outcome measurements, with restructuring of the Bayley roughly coinciding with initiation of therapeutic hypothermia in our cohort. It is widely reported that inherent differences between Bayley-II and Bayley-III preclude their direct comparison, with concerns for underestimation of disability with Bayley-III.[32] To address this, we defined disability using varying cut-offs for these 2 assessments as recommended by multiple studies.[32,33] Our use of NMS to define abnormal motor outcome when Bayley motor evaluation was unavailable also has potential to introduce bias. However, in our cohort, there was good concordance of NMS and Bayley classification of motor abnormality among those subjects with both measures available, with Bayley evaluation tending to classify more subjects as abnormal than NMS. The use of NMS primarily in the untreated group may underestimate motor abnormality in this group and, thus, dampen the apparent effect of therapeutic hypothermia on motor outcome, which is unlikely to change our conclusions. Longer-term outcome data are needed to determine the predictive value of normal MRI at school age and beyond.

In summary, MRI in the first week of life is predictive of 30-month outcome among children who received therapeutic hypothermia, though children with MRI injury who received therapeutic hypothermia are less likely to have adverse outcomes, at least in part due to decreased severity of injury. The predictive accuracy of neonatal MRI is unchanged by therapeutic hypothermia, and normal MRI is reassuring for normal 30-month outcomes after therapeutic hypothermia, with negative predictive values ≥95%. Together, these findings may aid in prognostic counseling

for families of newborns with encephalopathy presumed due to HIE. ■

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References

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev 2010;86:329-38.
2. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2013;2013:CD003311.
3. Pappas A, Shankaran S, McDonald SA, Vohr BR, Hintz SR, Ehrenkranz RA, et al. Cognitive outcomes after neonatal encephalopathy. Pediatrics 2015;135:e624-34.
4. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
5. Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics 2007;119:912-21.
6. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349-58.
7. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-Body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. Arch Pediatr Adolesc Med 2011;165:692-700.
8. Inder TE, Hunt RW, Morley CJ, Coleman L, Stewart M, Doyle LW, et al. Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy. J Pediatr 2004;145:835-7.
9. Rutherford MA. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. Pediatrics 2005;116:1001-6.
10. Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr 2005;146:453-60.
11. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: a nested substudy of a randomised controlled trial. Lancet Neurol 2010;9:39-45.
12. Shankaran S, Barnes PD, Hintz SR, Laptook AR, Zaterka-Baxter KM, McDonald SA, et al. Brain injury following trial of hypothermia for neonatal hypoxic–ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed 2012;97:F398-404.
13. Cheong JLY, Coleman L, Hunt RW, Lee KJ, Doyle LW, Inder TE, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy: substudy of a randomized trial. Arch Pediatr Adolesc Med 2012;166:634-40.
14. Miller SP, Weiss J, Barnwell A, Ferriero DM, Latal-Hajnal B, Ferrer-Rogers A, et al. Seizure-associated brain injury in term newborns with perinatal asphyxia. Neurology 2002;58:542-8.
15. Miller SP, Latal B, Clark H, Barnwell A, Glidden D, Barkovich AJ, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. Am J Obstet Gynecol 2004;190:93-9.
16. Bonifacio SL, Glass HC, VanderPluym J, Agrawal AT, Xu D, Barkovich AJ, et al. Perinatal events and early MRI in therapeutic hypothermia. J Pediatr 2011;158:360-5.
17. Barkovich AJ, Hajnal BL, Vigneron D, Sola A, Partridge JC, Allen F, et al. Prediction of neuromotor outcome in perinatal asphyxia: evaluation of MR scoring systems. Am J Neuroradioal 1998;19:143-9.
18. Hajnal BL, Sahebkar-Moghaddam F, Barnwell AJ, Barkovich AJ, Ferriero DM. Early prediction of neurologic outcome after perinatal depression. Pediatr Neurol 1999;21:788-93.
19. Jary S, Whitelaw A, Walløe L, Thoresen M. Comparison of Bayley-2 and Bayley-3 scores at 18 months in term infants following neonatal encephalopathy and therapeutic hypothermia. Dev Med Child Neurol 2013;55:1053-9.
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 2011;46:399-424.
21. Bednarek N, Mathur A, Inder T, Wilkinson J, Neil J, Shimony J. Impact of therapeutic hypothermia on MRI diffusion changes in neonatal encephalopathy. Neurology 2012;78:1420-7.
22. Rutherford M, Biarge MM, Allsop J, Counsell S, Cowan F. MRI of perinatal brain injury. Pediatr Radiol 2010;40:819-33.
23. de Vries LS, Groenendaal F. Patterns of neonatal hypoxic–ischaemic brain injury. Neuroradiology 2010;52:555-66.
24. Steinman KJ, Gorno-Tempini ML, Glidden DV, Kramer JH, Miller SP, Barkovich AJ, et al. Neonatal watershed brain injury on MRI correlates with verbal IQ at four years. Pediatrics 2009;123:1025-30.
25. Lally PJ, Montaldo P, Oliveira V, Soe A, Swamy R, Bassett P, et al. Magnetic resonance spectroscopy assessment of brain injury after moderate hypothermia in neonatal encephalopathy: a prospective multicentre cohort study. Lancet Neurol 2019;18:35-45.
26. Glass HC, Bonifacio SL, Shimotake T, Ferriero DM. Neurocritical care for neonates. Current Treat Options Neurol 2011;13:574-89.
27. Josephson SA, Douglas VC, Lawton MT, English JD, Smith WS, Ko NU. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management. J Neurosurg 2010;112:626-30.
28. Liu W, Yang Q, Wei H, Dong W, Fan Y, Hua Z. Prognostic value of clinical tests in neonates with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia: a systematic review and meta-analysis. Front Neurol 2020;11:133.
29. Bonifacio SL, McDonald SA, Chock VY, Wusthoff CJ, Hintz SR, Laptook AR, et al. Differences in patient characteristics and care practices between two trials of therapeutic hypothermia. Pediatr Res 2019;85:1008-15.
30. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ, et al. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. Arch Dis Child Fetal Neonatal Ed 2016;101:F149-55.
31. Kapadia VS, Chalak LF, DuPont TL, Rollins NK, Brion LP, Wyckoff MH. Perinatal asphyxia with hyperoxemia within the first hour of life is associated with moderate to severe hypoxic-ischemic encephalopathy. J Pediatr 2013;163:949-54.
32. Anderson PJ, Luca CRD, Hutchinson E, Roberts G, Doyle LW. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med 2010;164:352-6.
33. Lowe JR, Erickson SJ, Schrader R, Duncan AF. Comparison of the Bayley II Mental Developmental Index and the Bayley III Cognitive Scale: are we measuring the same thing? Acta Paediatr Oslo Nor 2012;101:e55-8.

Table II. Follow-up at 30 months among surviving subjects

Clinical characteristics and MRI findings	Follow-up n = 317	No follow-up n = 91	*P* value
Therapeutic hypothermia	155 (49%)	40 (44%)	.41
No MRI injury	127 (43%)	34 (56%)	.19
Watershed pattern injury	119 (40%)	19 (31%)	
BG/T pattern injury	50 (17%)	8 (13%)	
Gestational age ± SD (weeks)	39.5 ± 1.7	39.5 ± 1.8	.74
Birthweight, ± SD (g)	3348 ± 586	3413 ± 617	.31
Male	171 (54%)	52 (57%)	.59
Maternal age ± SD (y)	30.6 ± 6.7	28.2 ± 6.5	**.001**
Inborn	108 (34%)	31 (34%)	1.000
Meconium	176 (59%)	40 (49%)	.11
Cesarean delivery	169 (53%)	46 (52%)	.77
Apgar score at 5 min of life, median (IQR)	4 (3-6)	5 (3-7)	.13
Apgar score at 10 min of life, median (IQR)	6 (4-7)	7 (4-8)	.14
Intubated at resuscitation*	172 (54%)	44 (48%)	.32
Moderate-severe encephalopathy†	224 (71%)	72 (71%)	.92
pH on initial blood gas ±SD	7.03 ± 0.18	7.02 ± 0.19	.50
Seizure detected at <24 HOL	115 (36%)	14 (15%)	**<.001**

Bold values indicate statistical significant ($P < .05$).
*Resuscitation score ≥5.
†Encephalopathy score ≥4.

Table III. Neurodevelopmental outcomes at 30 months by MRI pattern of injury

Neurodevelopmental outcome	MRI pattern of injury	No therapeutic hypothermia n = 162	Therapeutic hypothermia n = 155	*P* value
Abnormal cognitive outcome	No injury	2 (5%)	1 (1%)	.23
	Watershed pattern	16 (21%)	1 (3%)	**.01**
	BG/T pattern	17 (49%)	2 (15%)	**.04**
	Total	35 (22%)	4 (3%)	**<.001**
Abnormal motor outcome	No injury	4 (10%)	3 (4%)	.16
	Watershed pattern	14 (17%)	0 (0%)	**.006**
	BG/T pattern	19 (53%)	3 (21%)	**.045**
	Total	37 (23%)	6 (4%)	**<.001**
Abnormal composite outcome	No injury	5 (12%)	4 (5%)	.13
	Watershed pattern	25 (30%)	2 (5%)	**.002**
	BG/T pattern	34 (68%)	9 (45%)	.07
	Total	64 (36%)	15 (9%)	**<.001**

Bold values indicate statistical significant ($P < .05$).
Bayley-II Mental Developmental Index and Psychomotor Developmental Index <70 and Bayley-III motor and cognitive scores <85 were classified as abnormal. Composite outcome was defined as abnormal motor or cognitive outcome or death.
Denominator for the total proportion with abnormal composite outcome includes 179 untreated and 164 therapeutic hypothermia-treated infants.